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THE USE OF PROCEDURAL SEDATION IN CHILDREN

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DEDICATION

DEDICATED WITH LOVE TO MY PARENTS, MY HUSBAND, MY CHILDREN AND ALL MY FAMILY MEMBERS IN SAUDI ARABIA.

ABSTRACT

The use of sedation for diagnostic and therapeutic procedures in children is common and leads to considerable debate. Evaluating this subject is complicated by differences in the methods and the outcomes used for sedation assessment in children reported in the literature which are large. This thesis used systematic literature reviews, a prospective study and a national survey to evaluate several aspects of paediatric sedation.

A systematic review of the safety and effectiveness of chloral hydrate in three categories of procedural sedation was conducted. For painless procedural sedation, chloral hydrate was more effective for shorter imaging procedures, such as CT scanning. The incidence of adverse events was 1,951 occurring in 14439 patients (13.5%), with hypoxia the most frequent. Moderate hypoxia (SpO2 85%–90%) was seen in 281 cases of 14439 patients (1.9%) of children.

For painful procedural sedation, the success rate of chloral hydrate was variable (35%–100%). Hypoxia was the most common adverse event, occurring in 95 of 1810 patients (5.2%). Most (66 cases/1810 patients, 3.6%) were mild however moderate hypoxia occurred in 29 of 1810 patients (1.6%). The incidence of adverse events was higher during painful procedures than during painless procedures: 313AEs/1810 patients (17.3%) versus 1,951AEs/14439 patients (13.5%).

The most frequent use of chloral hydrate as a treatment was to reduce agitation during mechanical ventilation, followed by treatment of neonatal diseases and treatment of neurological disorders. The reported success rate was high throughout all treatment procedures (86%–100%). The incidence of hypoxia was found to be the

highest, when it was used for the treatment of agitation 71 cases/438 patients (16.2%).

Due to the heterogeneity between the studies it was not possible to perform meaningful statistical analysis.

The effectiveness and safety of triclofos (a chloral hydrate derivative) was evaluated for procedural sedation in children, in a systematic review of the literature. The success rate was variable (ranging from 50 to 100%), shorter procedures such as CT scanning were more likely to be successful. Vomiting and hypoxia were the most frequently reported adverse events, 10% (62/613) and 7.8% (48/613) respectively.

A systematic literature review of the safety and effectiveness of paraldehyde as a sedative agent for children was performed, as it was named as a second line agent in the sedation policy of the Derbyshire Children's Hospital. The literature is scant; only five studies were located and involved 157 patients. The reported effectiveness of paraldehyde ranged from 75- 93%. Vomiting was the most commonly reported adverse event (2 cases/8 patients, 25%). Due to the small numbers of patients and poor methodology of studies, its clinical use cannot be supported.

A further systematic literature review of 29 studies involving 6342 children on the safety and effectiveness of midazolam for imaging procedures was conducted. The procedural success rate was variable (0%–100%, median 82%). Hypoxia was the most commonly reported adverse event (74 cases/2046 patients, 3.6%) with (32 cases/2046 patients) 1.6% of cases being reported as moderate hypoxia.

Palatability of the two most commonly used sedative agents, chloral hydrate and midazolam, was evaluated by conducting a literature review and a prospective study at the Derbyshire Children's Hospital. Only 9 studies were identified during the literature review. Of these, 8 studies evaluated the palatability of midazolam, while only 2 evaluated the palatability of chloral hydrate. Midazolam was reported as more

acceptable to patients than chloral hydrate. The prospective study supported this, and showed that patient acceptance of midazolam was good, while it was poor for chloral hydrate. The success rate of procedures was lower with midazolam, then chloral hydrate.

A further literature review evaluated the use of sedation in Middle Eastern countries. Limited numbers of reports were found. Of the 37 studies, the majority (43%) were conducted in Turkey, within single centres and only examined a single procedure. Very limited evidence on the use of sedation guidelines was reported.

Further exploration of the current sedation practice in the Kingdom of Saudi Arabia was done using a national survey. The questionnaires were completed by 81 health care professionals. Only 61% documented the use of sedation guidelines, although 91% reported monitoring of patients during procedural sedation. The most commonly reported agents for both painless and painful procedures were chloral hydrate and midazolam.

This research aimed to add to the evidence base for paediatric sedation. The results suggest a need for future research to cover further areas, including the safety and effectiveness of other drugs, worldwide practice and patient monitoring.

PUBLICATIONS, PRESENTATIONS AND AWARDS RELATED TO THIS THESIS

Publications and presentations related to this thesis

Paper:

1. Alotaibi B, Choonara I, Sammons H. Safety of Chloral Hydrate for Dental Procedural Sedation in Children: A Systematic Review of the Literature (Paper submitted to International Journal of Paediatric Dentistry).

Conference abstracts:

1. Alotaibi B, Choonara I, Sammons H. Safety and Clinical Effectiveness of Chloral Hydrate for Painless Procedural Sedation in Children. Arch Dis Child 2014, 99:1, a169.

2. Alotaibi B, Choonara I, Sammons H. Midazolam for Imaging Procedural Sedation in Children: A Systematic Review. Arch Dis Child 2015, 100:e1.

3. Alotaibi B, Choonara I, Sammons H. Safety and clinical effectiveness of triclofos for procedural sedation in children: a systematic review. Arch Dis Child 2015, 100:e1.

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To all of those I dedicate this modest effort.

LIST OF ABBREVIATIONS

ACE	Acetaminophen
ADRs	Adverse Drug Reactions
AE(s)	Adverse event(s)
BAEP	Brainstem auditory evoked potential
BMT	Behavioral management technique
CH	Chloral hydrate
CT	Computed Tomography
DCF	Data collection form
DI	Diphenhydramine
EEG	Electroencephalography
F	Flunitrazepam
HBR	Hearing breuer inflation
HY	Hyoscine
HYD	Hydroxyzine
IM	Intramuscular
IN	Intranasal
IPA	International Pharmaceutical Abstracts
IQR	Interquartile range
IV	Intravenous
K	Ketamine
Kg	Kilogram
M	Midazolam
MCUG	Micturating cystourethrogram
MEP	Meperidine
MRI	Magnetic Resonance Imaging
N_2o	Nitrous oxide

NA	Not available
NICE	National Institute for Clinical Excellence
P	Placebo
PEN	Pentobarbital
PO	Orally
PR	Per-rectal
PR	Paraldehyde
PRO	Promethazine
PS	Procedural sedation
P-value	Probability
RCTs	Randomise controlled trials
RR	Relative risk
SPSS	Statistical Package for Social Science
STROBE	Strengthening the Reporting of Observational Studies
TR	Tramadol
VCUG	Voiding cystourethrogram

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CHAPTER ONE

General introduction

1.1 Introduction

The use of sedatives in the paediatric population has been increasing. This is due to advances in the treatment of childhood diseases and the consequent use of newer diagnostic procedures, such as computerised tomography (CT) scan and Magnetic resonance imaging (MRI) [1]. Dental procedures for instance cause pain, stress and even frighten children, hence most medical practitioners have found the need for sedatives before such procedures [2]. Despite the benefits of sedatives, inappropriate use of this group of drugs can lead to unwanted effects.

The use of sedatives in children has become a controversial subject among paediatricians. While some believe that some diagnostic procedures such as radiological imaging can be done without sedating the children, others claim that the success of such procedures depends greatly on sedation. For instance, some physicians believe that procedural sedation (PS) prior to neuroimaging in paediatric patients is less convenient and poorly tolerated compared to general anaesthesia [3, 4]. Procedural sedation (PS) has an unpredictable onset level and duration of action [5]. Besides, sedatives need extensive monitoring due to their long half-life; and levels beyond the therapeutic limit may depress the respiratory reflexes and cause deep sedation leading to respiratory insufficiency [5].

With the growing prescription rates of sedatives by clinical professionals for therapeutic and diagnostic procedures in paediatrics, there are increasing concerns about the safety of these drugs. Therefore, this thesis will focus on the use of sedatives in children, particularly with respect to their safety and efficacy.

1.2 Background to sedation in children

Although the use of sedative drugs began as early as the 19th century, data regarding their safety and efficacy in children was rather poor. Prior to the 1980s, the availability of data about the use of sedatives in children was limited. There were no specific paediatric guidelines for appropriate dosage and route of administration [6].

In 1985, Dr Charles Cote and Dr Theodore Striker wrote the first guideline for sedation in children [7]. This was written with the assistance of the American Academy of Pediatrics (AAP). The aim of the guideline was to improve the safety of sedatives for children undergoing painless procedures. This guideline classifies the depth of sedation into; conscious sedation, deep sedation, and general anaesthesia. It also focused on the need for monitoring these children. Measurement of vital signs, availability of basic life support, and well trained practitioners were recommended.

In 1992, the 1985 guideline was revised by the committee on drugs of the AAP (American academy of Paediatrics Committee on Drugs 1992) [8]. This guideline stated that patients could be given an extra dose of sedation in order to progress from one level of sedation to another. It also recommended adequate supervision when giving extra doses of sedatives (American Academy of Pediatrics Committee on drugs 1992) [8]. Furthermore, out of hospital administration of any sedative in children was discouraged.

In 2002, the previous guideline was amended by the AAP Committee and the term "conscious sedation" was eliminated. The guideline's applicability was further extended to out of hospital sedative use (Committee on drugs American Academy of Pediatrics 2002)[9]. In addition, expressions such as minimal sedation, moderate sedation, deep sedation, and anaesthesia which are in fact used in the current guidelines were adopted (Committee on drugs American Academy of Pediatrics 2002) Currently, there are several guidelines by different organisations such as: the

American Academy of Pediatrics in the USA (ASA) [8], the Scottish Intercollegiate Guidelines Network (SIGN 2014)[10] and the British National Institute for Health and Clinical Excellence (NICE 2010) in the UK [11] which were established according to the recommendations of literature reviews and health economics data. Although these guidelines have some inconsistencies on various points, they all emphasize the importance of safety precautions and the need for training and continuous education for sedative drug providers. Other key components of most of the guidelines are the need for patient assessment before sedation as well as monitoring during and after sedation [12]. They are all based on the levels of sedation needed instead of the type of sedative drugs.

1.3 Aims of sedation

Sedation provides an environment conducive to good patient care, for both treatment and diagnostic procedures. There is increasing demand for it from both parents and medical practitioners [12]. Parents want their children free from the anxiety that they may experience during procedures; while medical practitioners also want cooperative and immobile children. This has often led to the misuse of some of the sedative drugs during the course of patient care [13]. Depending on the planned diagnostic and/ or therapeutic procedure, sedation may be necessary for, immobilisation, induction of sleep, reduction of anxiety and reduction of distress [14].

Anxiety during diagnostic and therapeutic procedures can seriously put children at risk. Krauss and Green (2006) suggested that anxiety and pain during diagnostic procedures often stimulate a stress response. Such stimuli can incite the sympathetic pathway which can lead to increased heart rate, blood pressure, and blood glucose levels [2]. Reduction of anxiety and distress will lead to better acceptance of diagnostic or treatment procedures [15]. In addition, the anxiolytic properties of sedatives are useful during mechanical ventilation, especially when using newer ventilating machines with less physiological mechanisms, such as high frequency

oscillatory ventilation with tracheal insufflation. Another major objective of sedation in children is immobilisation, in order to ensure cooperation during procedures. Although some painful procedures such as wound treatments can be done under local anaesthesia in adult patients, it is often impossible to achieve a similar level of cooperation in children without some sedation. As Sury (2004) points out, children are less able to tolerate pain and discomfort than adults and the thought of a procedure may be sufficient to make a child agitated [16].

Sedatives have also been used successfully for inducing sleep. This benefit makes them a fundamental part of treatment intervention especially for critically ill children. Furthermore, the use of sedation can optimise analgesic drugs' appropriate effects while minimising their harmful effects [17] . For example, to reach an optimal level of analgesia with an opiate, sedation with drugs such as benzodiazepine should be increased to the level of prompting unconsciousness. This combination is commonly used in critically ill children [17] . Conversely, concomitant use of analgesics with sedatives could increase the incidence of serious adverse events [18]. Sury et al. (2011) however affirms that the use of sedatives and analgesia is safe and effective in children particularly after evaluation by well-trained practitioners [19]. It is important to note that concomitant administration of sedatives with analgesia should be guided by well-planned sedative and analgesic procedures (PSA) in order to avoid adverse harmful effects of either the sedative and analgesic agent [20].

The benefits of sedation should be adequately weighed against the risk of unwanted adverse effects. These two effects must be put in perspective when formulating sedation guidelines.

1.4 Definitions

In order to be able to differentiate between anaesthesia and sedation, it is important to ascertain the meaning of these terms. The American Society of Anaesthesiologists (2002) defines anaesthesia as the use of specific medication or medical intervention to induce partial or complete loss of consciousness [21]. However, sedation is defined as the decrease of irritability or agitation by the administration of sedative drugs to facilitate a medical or diagnostic procedure [22]. Sedation can also be defined as a decrease in the level of consciousness [23]. In fact, the decreased level of consciousness is usually associated with a reduction of muscle tone of the oropharynx and the tongue, including the airways. Indeed airway obstruction could be associated with deep sedation, which made the Royal College of Radiologists and Anaesthetists define safe sedation or conscious sedation as "a technique.... during which verbal contact with the patient is maintained" [24]

In the USA, the term "deep sedation" was defined as and refers to a state deeper than conscious sedation other than anaesthesia [25]. Deep sedation is defined as: *"...a state of depressed consciousness from which the patient is not easily aroused…*" [25]. Any sedation deeper than conscious sedation may progress to 'too deep' and should be supervised by anaesthetists [26]. Table (1.1) shows definitions of sedation and anaesthesia.

Table 1. 1: Sedation and anaesthesia definitions

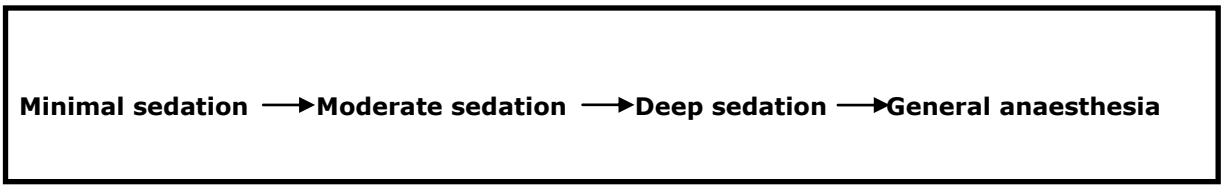
Term	Definition
Sleep	"A quiet and immobile state, induced without drugs or occurring spontaneously, from which the individual can be roused".
Sedation	"A "sleep-like" state induced by drugs, from which the individual may be aroused" • "Conscious sedation: can be aroused by gentle stimulation" • "Unconscious sedation: difficult to arouse even with vigorous stimulation. Appreciable depression of vital reflexes must be expected".
Anaesthesia	"An unrousable "sleep-like" state induced by drugs. Appreciable depression of vital reflexes is commonplace". • "Conventional anaesthesia: intervention is often necessary to support the airway, breathing and circulation". • "Minimal anaesthesia: "Anaesthetic" doses are used to induce an unrousable sleep lasting a few minutes".

This table adapted from [26].

1.5 Levels of sedation

Sedation often happens in a continuous pattern [27]. The continuum of sedation is dynamic and it depends on individual variables such as: age, weight, surface area of the body, general health condition, and use of other drugs as combination. This continuum starts from minimal sedation and ends with general anaesthesia[28]. Figure (1.1) illustrates the continuum of sedation levels.

Figure 1. 1: The continuum of sedation levels



This figure adapted from American Society of Anaesthesiologist (2009).

The change from one level to another, such as, from minimal to moderate sedation is usually unpredictable. Consequently, any medical practitioner who provides sedative medication should understand the possibility of the occurrence of an unexpected level of sedation [29]. According to the Joint Commission on Accreditation of Healthcare Organizations (JCAHO), medical practitioners responsible for providing sedation should have the ability to resuscitate a patient at any level of sedation [30] . Since the level of sedation is associated with both pulmonary and cardiovascular functions, the current guidelines by the American Academy of Paediatrics (AAP) and the American Society of Anaesthesiologists (ASA) have considered these while providing definitions for the different levels of sedation [29]. According to AAP and ASA, there are four levels of sedation. These are described in the next sections.

1.5.1. Minimal sedation (anxiolysis)

Minimal sedation or anxiolysis, is a state of sedation in which the patient obeys verbal commands while cognitive and motor functions may be affected. At this level of sedation, pulmonary and cardiovascular functions remain normal.

1.5.2. Moderate sedation (conscious sedation)

Conscious sedation can be defined as a medication induced reduction of consciousness that still permits purposeful reaction to verbal orders and or tactile stimulation. Generally, pulmonary and cardiovascular functions are maintained. There is usually no need to protect airway patency because the patient's automatic ventilation is sufficient.

1.5.3. Deep Sedation/Analgesia

This level of sedation can be defined as a medication induced reduction of consciousness from which patients cannot be easily awakened. Patients however react purposefully after recurrent or painful stimulation. Often, cardiovascular function remains normal, but support of airway patency is often required and the patient's own ventilation may not be enough.

1.5.4. General Anaesthesia

This is a medication induced loss of consciousness from which patients are not awakened by verbal instruction or painful stimuli. Cardiovascular function may be affected. In addition, it is necessary to maintain airway patency by positive pressure ventilation because of the loss of airway patency. Cravero and Blike (2004) stated that qualified anaesthesiologists are the only medical practitioners who should provide and/or organise the general anaesthesia intervention plan [6]. Table (1.2) shows the ASA definitions of levels of sedation.

Table 1. 2: Definitions of levels of sedation from the American Society of Anaesthesiologists (ASA)

	Minimal sedation/ Anxiolysis	**Moderate sedation/ Conscious sedation**	**Deep sedation**	**General anaesthesia**
Responsiveness	Responds normally to verbal commands	Purposeful response to verbal commands, either alone or with light tactile stimulation	Not easily aroused, however purposeful response after repeated or painful stimulation	Unarousable, even upon painful stimulation
Airway	Unaffected	No intervention needed	Intervention may be needed	Intervention often needed
Spontaneous ventilation	Unaffected	Adequate	May be insufficient (intervention may be needed)	Ventilation often required
Cardiovascular function	Unaffected	Usually maintained	Usually maintained	May be impaired

This table adapted from American Society of Anaesthesiologists (2009)[28]

1.6 Impact of sedation on airway control and respiratory drive

1.6.1 The Paediatric Airway

- **Anatomical Considerations**

The capacity to evaluate and manage the paediatric airway is considered as the most significant aspect of carrying out safe paediatric sedation [31]. Regarding the upper airway, it consists of three parts; namely the supraglottic, laryngeal and intrathoracic [31, 32].

1. Supraglottic: Included in the supraglottic area are pharyngeal structures, which refers to the most inadequately maintained and collapsible element of the upper airway. This area is the most likely to be affected by sedation [31].
2. Glottic (laryngeal): regarding the glottic structures, they comprise the vocal cords, subglottic part, and cervical trachea. Laryngospasm represents the most prevalent factor causing airway block in this area [31].
3. Intrathoracic: This part is composed of both the thoracic trachea and bronchi [31].

Differentiating the paediatric airway from the adult airway are a number of developmental features, including: the size of the paediatric airway, which is smaller in diameter and shorter in length; the young child's tongue, which is comparatively bigger in the oropharynx; the larynx in infants and young children, which is positioned more to the anterior; and the relative length, floppiness, and narrowness of the epiglottis in infants and young children [33]. In children aged below 10 years, the narrowest part of the airway is underneath the glottis at the point of the cricoid cartilage [31].

Other characteristics predisposing young children to airway obstruction during sedation include the small calibre of the paediatric upper airway, the relatively large tongue, and the "floppy" and relatively long epiglottis [33]. Similarly, the infant's large occiput puts the head and neck in the flexed position if the patient is positioned recumbent, which further aggravates airway blockage [33].

Whilst in normal respiration, a pressure gradient from the mouth to the airways is created through a negative intrapleural pressure produced in the thorax, leading to airflow into the lungs [31]. There is a decrease in the extrathoracic airway calibre during inhalation, as opposed to the increase in the intrathoracic airway diameter [31]. In typical circumstances, there are clinically insignificant changes in the airway calibres during respiration [32]. Tightening of the paediatric upper airway may considerably increase airway resistance given that resistance is inversely proportionate to the fourth power of the radius [32]. A higher-pressure gradient

across the airway is needed for elevated airway resistance and the associated improved airflow velocity (Bernoulli effect) in order to maintain tidal volume and minute ventilation [33]. The normal inspiratory and expiratory impacts are heightened on the airway through a larger pressure gradient produced across the airway [33]. As a consequence, there appears to be a further collapse of the upper airway resulting from the greater negative pressure produced in the pharynx during respiration [32].

- **Airway Control**

Pharyngeal Obstruction: A collapsible part positioned between two fairly well-maintained structures; namely, the nasal passage and the trachea refers to the supraglottic area [34]. During the process of sedation or anaesthesia, diaphragmatic activity (phrenic nerve) is inhibited to a lesser degree than neuromuscular control of the upper airway [35]. As a result, the negative pressures emanating with diaphragmatic contraction and the decreased overall tone of the upper airway aggravate the reduction in diameter of the pharynx during inspiration, as shown in the [34, 35].

In the process of sedation, reduced pharyngeal tone leads to a narrower anterior-posterior distance between the posterior pharynx and the soft palate, epiglottis, and, to a lesser extent, the base of the tongue [35]. In so doing, the pharyngeal segment is used as a "Starling resistor", a collapsible tube with a calibre which is affected by compressions within the lumen of the airway and soft tissue [34, 35]. There appears to be an airway obstruction during moderate or deep sedation in the supraglottic structures, essentially as a result of the soft palate and epiglottis "leaning back" to the posterior pharynx [34, 35]. Despite the fact that it was formerly believed that the base of the tongue could be the principal reason of upper airway blockage during unconsciousness, it has been shown in MRI studies of the upper airway in sedated children that the most likely structures causing pharyngeal obstruction are the soft palate and epiglottis [36]. The single most prevalent, serious and negative action

taking place during sedation refers to pharyngeal obstruction. There are some basic airway exercises, such as a chin lift which usually suffice to release the airway obstruction referring to pharyngeal collapse [36].

Laryngospasm: Another major reason for the obstruction of the upper airway during sedation is laryngospasm, which takes place at the level of the glottis [37]. Defining laryngospasm, it refers to a glottic musculature spasm and may cause limited or complete airway obstruction [35]. There are a number of risk factors associated with laryngospasm, including being passively exposed to tobacco smoke, utilisation of an airway instrument, being young, higher ASA classification, upper airway secretions, airway manipulation, recent upper respiratory infection, and gastroesophageal reflux disease [37]. As opposed to pharyngeal obstruction, laryngospasm is not reversed by simple airway manoeuvers [35]. There is a stepwise method required for the treatment of laryngospasm, which may necessitate positive pressure ventilation, enlarging the depth of sedation and in acute cases neuromuscular blockade [37].

- **Respiratory Drive**

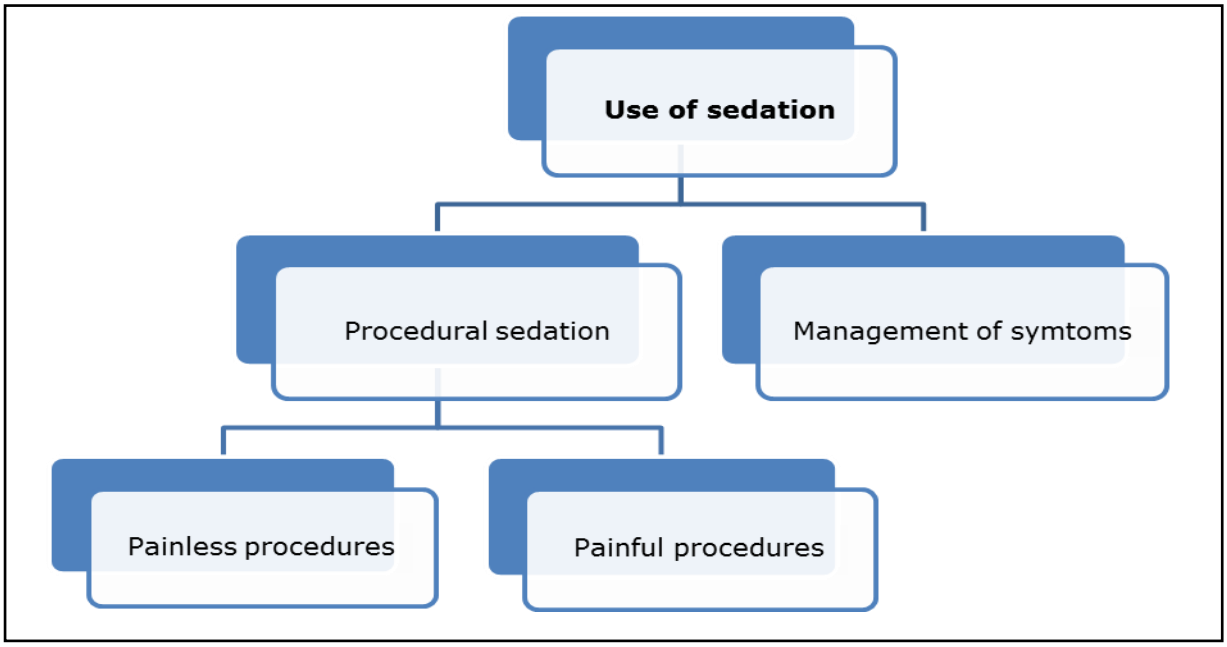
The breathing process as a basic need comes from within the central respiratory centre positioned in the brainstem [38]. The modulation of output from the respiratory centre occurs through the interaction of several chemicals, including CO2 and O2 and mechanical controllers like lung mechanics [39]. Regarding the most significant factors of the respiratory drive from the medullary respiratory centre include changes in carbon dioxide concentration [38]. There is a free diffusion of carbon dioxide across the blood-brain barrier, which leads to a rise in H+ and a decline in pH in the cerebral spinal fluid [39]. In addition, while there is a decline in pH, there is an increase in neural output from the respiratory centre and ensuing surge in minute ventilation (V_E), which characteristically rises linearly with increases in PCO2 in experimental situations [40].

Overall, sedative drugs suppress the central respiratory centre and decrease the ventilatory response to a particular carbon dioxide level [38, 39]. Sedative drug doses that do not result in complete loss of consciousness (e.g., low-dose midazolam) frequently shift just the CO2 ventilation response curve to the right while keeping the slope of the response [39]. With deeper levels of sedation, as well as the response changing to the right, the slope of the CO2 ventilation response curve is also reduced [40]. This reaction may take place upon the combination of sedative drugs or utilising any sedative that causes unconsciousness [39]. A decreased slope signifies less of a rise in ventilator response for any given increase in carbon dioxide [40]. This is an instance that may result in acute hypercapnia, hypoxemia, or apnoea [40].

1.7 Sedation for procedures

Procedural sedation can be defined as a medical technique that involves administration of one or more sedative drugs, with or without supplemental analgesia, while cardiopulmonary function is conserved [16]. Generally, the purpose of sedation can be for diagnostic procedures, for treatment procedures or both. Procedures can be subdivided into painless or painful procedures according to the degree of pain which they induce [16]. Figure (1.2) illustrates the different types of procedural sedation.

Figure 1. 2: Types of procedural sedation



1.6.1. Painless (non-invasive) procedures

These can be defined as diagnostic or treatment techniques which do not need insertion of a medical device via a body cavity or cause disruption of body organs function. This type of procedure, for instance, CT scan and MRI can often require a high level of child immobilisation [16].

1.6.2. Painful (Invasive) procedures

These can be defined as diagnostic or treatment techniques which need insertion of a medical device via a body cavity or cause disruption of body organ function. Painful procedures such as liver biopsies and wound care are also often associated with anxiety, which reduce the effects of analgesic drugs [41].

1.8 Sedation outcome

1.8.1. Safety issues

Assessment of the safety of children's sedation practice has proven difficult due to the available prospective studies. Many descriptive studies were conducted to evaluate the safety of specific sedative(s) in a variety of settings. The definitions of adverse events reported by most of these studies are vague. It is difficult to assess the accurate incidence rate of adverse events from the available literature due to the difficulty in combining the results from studies which have used different terminology to define the same adverse events.

A retrospective study conducted in the United States to evaluate outcomes of the adverse events of sedation in children reported to the American Food and Drug Administration from 1969 to 1996, revealed that of the 95 cases of sedation related adverse drug events, 51 resulted in death, 9 neurological injuries, 21 increase in hospital stay and 14 had no injury [42]. Predisposing factors were (1) outside hospital settings, (2) physiologic parameters were monitored inappropriately, (3) resuscitation skills were lacking or inadequate, (4) inadequate monitoring before sedation and (5) inadequate monitoring after procedural sedation. Increased safety and efficacy of sedative drugs can be achieved when children are supervised by knowledgeable anaesthesiologists [6]. There are specific standards that should be adhered to these specialists. Firstly, these individuals should know how to manage any airway problems like airway obstruction. They should also document any disease that may interfere with the sedative procedure, for instance, history of cardiovascular diseases. Thirdly, it is important for them to be familiar with details of sedatives such as: doses and side effects. Hospitals should be well equipped and should also have a well-organized monitoring system [43].

Side effects of sedation in the paediatric population may occur as a result of medication overdose, other medication errors, inexperienced prescribers, and early

discharge [44]. Most harmful effects of sedatives are preventable; they are mostly caused by provider errors and improper management of adverse events [45].

The most serious complication of sedation in children is death, usually resulting from the untreated pulmonary depressant effect of the sedative drugs. A prospective study evaluating 1140 paediatric patients administered sedatives for diagnostic procedures, according to AAP guidelines, showed that about 5.3% developed respiratory side effects and one percent had air way obstruction [46]. These complications can occur at any level of sedation and with any sedative dose, although high doses are believed to be the leading cause for most serious adverse effects [47].

Adverse events can occur even when clinicians follow current practice guidelines for procedural sedation in children [6]. Nevertheless, in order to be able to avoid or even to reduce the incidence of sedation adverse events, it is important to ascertain the definitions of adverse events. Subsequently, it has been found that there are various definitions for medication adverse events such as definitions by the World Health Organization (WHO) guideline and the Federal Drug evaluation Agency (FDA)[48, 49].

The definitions by the European Medicines Agency (EMA) and the ICH Harmonised Tripartite Guideline are the strongest definitions for drug adverse events. It is important to note that the definitions by the EMA will be used later as a base line for analysing sedative drugs safety.

According to the EMA guidelines adverse events have been categorised into serious or mild adverse events according to their severity[50]:

- A serious adverse event is defined as "*any untoward medical occurrence that at any dose: results in death, is life-threatening, requires inpatient hospitalisation or prolongation of existing hospitalisation, results in persistent or significant disability/incapacity, or is a congenital anomaly/birth defect*".

- A mild adverse event is defined as "*any adverse event that occurred that did not need any intervention*".

The most common adverse events of sedation are airway obstruction, aspiration, vomiting and cardiovascular complications [51].

- **Airway obstruction**

One of the most common side effects during moderate or deep sedation is airway obstruction which may cause hypoxia. This is characterised by low oxygen levels in the blood and tissues. Hypoxia occurs when the oxygen pressure in arterial blood (PaO2) is decreased. Hypoxia due to sedation can be classified as mild (SpO2 90-95%), moderate (SpO2 75-89%), severe (SpO2 40-75%) and extreme hypoxia (SpO2 <40%) [52]. Severe and extreme hypoxia are capable of causing permanent injury to the brain and cardiopulmonary system [53].

Airway obstruction may occur due to laryngospasm or pharyngeal obstruction [54], and represents approximately 80% of sedative related complications during procedural sedation in paediatric patients [42].

Although sedatives such as chloral hydrate, ketamine, midazolam and pentobarbital can cause airway obstruction, the most serious respiratory airway obstructions are often attributable to propofol. Propofol related obstruction accounts for 5 to 15% of airway obstruction in children undergoing diagnostic or treatment procedures [55]. It can cause unpredictable, irreversible respiratory collapse as well as reduction in airway tone and reflexes which may lead to death [56]. A study by Carvero et al (2009) showed that one out of every 65 sedations with propofol was associated with laryngospasm and airway obstruction [57].

Several factors can worsen airway obstruction in patients administered sedatives, among which is the co-administration with other sedatives, especially benzodiazepines

(for example administration of chloral hydrate with midazolam). Paediatric patients under two years are more prone to airway obstruction than older children [58]. Children with a medical history of bronchiolitis and/ or obstructive sleep apnea also have a higher risk. A study by Green and colleagues (2009) showed that 3.9% of 8,282 paediatric patients receiving ketamine for procedural sedation developed airway obstruction. 0.3% developed apnoea and 0.8%, laryngospasm. They reported that for those aged less than two years, overdosing and co-administration with other sedative drugs were predictors of more serious respiratory adverse events [58]

The management of airway obstruction can be accomplished by proper assessment of patients for respiratory risk factors such as bronchiolitis before procedures [59]. Additionally, during sedation, airway obstruction can be avoided by using simple techniques such as suctioning of oral secretions, keeping the head in the right position and administering oxygen by a mask valve ventilation bag [60].

- **Aspiration**

Aspiration is another complication of sedation in children and can lead to death [61]. Although, the risk is high, the incidence rate is low, especially with conscientious patient monitoring [62]. In a study by Warner and colleagues (1999), the risk of pulmonary aspiration in paediatric patients with preoperative procedural sedation was 1 in 8000 patients [63]. Aspiration occurs as a result of muscle tone relaxation in both the gastrointestinal tract and oesophagus. This in turn leads to passage of stomach contents as well as oesophageal secretions into the distal respiratory airway [64]. A variety of risk factors can contribute to the incidence of aspiration during sedation, including reflux and obesity [47].

In order to avoid the risk of aspiration following sedation, it is important to rule out oesophageal reflux during the pre-anaesthetic assessment of the child. Similarly,

fasting guidelines should be adhered to; drugs that reduce stomach content or to raise pH especially are also important for obese children [65]. Antibiotics are also useful to forestall bacterial infection [66]. In patients with risk of aspiration, tracheal intubation should be used to protect the airway. A study by Borland et al. reported that of 3300 cases of paediatric patients receiving preoperative sedation, 52 developed pulmonary aspiration; 29 of whom needed tracheal intubation or prolonged hospitalization [67].

- **Vomiting**

Another common adverse effect of sedation is vomiting. Sedatives increase vagal tone, thus stimulating the neuromuscular reflex leading to vomiting [6]. Occurrence of vomiting during sedation can be fatal, because of its association with aspiration pneumonia, and is a major contributor to mortality in sedated paediatric patients [43]. Chloral hydrate is associated with a high incidence of vomiting. According to Greenberg et al. (1991), of 295 children receiving oral chloral hydrate, 7% developed adverse effects with vomiting accounting for most of these effects (4.3%)[68].The risk of complications of vomiting worsens in hypovolemic and obese children [69]. Some procedures such as dental procedures can themselves cause vomiting independent of sedatives. In order to mitigate the effect of these procedures, administration of anti-emetic medication for instance, ondansetron and continuous suctioning can be effective.

- **Cardiovascular complications**

Some sedatives have deleterious cardiovascular effects such as: bradycardia, arrhythmias, hypotension, hypertension, and tachycardia [70]. Even cardiovascular friendly sedative medications such as etomidate, fentanyl and ketamine can cause hypotension, bradycardia and tachycardia [71]. Cardiovascular complications are dose and sedation level dependent [46]. Generally, medications in standard normal doses are believed to have only minor effects on cardiovascular function, however

cardiovascular adverse effects can also happen with normal doses. Arrhythmias have been reported in children following administration of chloral hydrate at recommended dose [72]. Chloral hydrate induces arrhythmias through direct alteration of the pacemaker cells or catecholamine sensitization. Side effects can also occur from the direct effect of drugs on the cardiovascular system leading to myocardial depression. Barbiturates, ketamine and propofol are examples of drugs that act this way. Concurrent illness and co-administration with other drugs such as furosemide can worsen myocardial depression [73].

Respiratory changes, mainly hypoxia and hemodynamic complications like hypervolemia have been shown to be major causes of cardiovascular complications [74, 75]. Propofol and dexmedetomidine are the main sedatives associated with these effects. In a study of 56 children administered propofol and dexmedetomidine as preoperative sedative drugs, Anger and colleagues found that the incidence of hypotension was high in both groups (61% versus 32%) [76].

Ultimately, the presence of qualified personnel to assess patients before, during and after procedural sedation is important in order to avoid complications. According to Cravero and Blike (2004) increased safety and efficacy of sedative drugs can be achieved when children are supervised by knowledgeable anaesthesiologists. This is said to improve the safety of any sedative procedure by 10-fold [6]. There are specific standards that should be adhered to these specialists. Firstly, these individuals should know how to manage any airway problems like airway obstruction. They should also document any disease that may interfere with the sedative procedure, for instance, history of cardiovascular diseases. Thirdly, it is important for them to be familiar with details of the sedatives such as doses and side effects. Hospitals should be well equipped and should also have a well-organised monitoring system [6].

1.8.2. Effectiveness of sedation

When sedation is tried for procedures in children, the reported effectiveness of different sedatives differs substantially. Assessment of sedation effectiveness is evaluated by many clinical studies by measuring two outcomes. The most measured outcome is completion of the procedure and the less measured outcome is child, parent or anesthesiologist satisfaction [77]. In this context Cravero et al. in his review explained that the patient who is administered an oral dose of midazolam for a lumbar puncture procedure and cries or screams is often regarded an equal success as a child who given brief propofol sedation lies perfectly without crying, although objective observers would clearly count one strategy a success and the other a failure [6].

Generally for evaluating the value of sedation, two measures must be taken into consideration. First, maximise patient's comfort by providing optimal health care. This means that when distraction techniques or minimal sedation become insufficient to keep the patient comfortable, additional effective sedation should be applied [78, 79]. Secondly, cost-effectiveness of sedation has to be taken into account. The cost of procedural sedation includes the time cost of medical staffs required for the providing and monitoring of sedative agent or general anesthesia, in addition to the time cost of the medical staffs throughout the procedure [80]. The cost strategy also consists of the unit cost of medication for sedation and general anesthesia, and other medical consumables which are used for administering them. Some strategies include the cost effectiveness of sedation resulting complications and the treatment of these complications [80].

1.9 Assessment of sedation level

It is believed that the best method of sedative assessment is by directly asking patients about their comfort. This could however be difficult in young children and ill

paediatric patients due to their inability to express their emotions. The large number of available sedative drugs, different routes of administration and lack of proven information about the best way for sedation evaluation have made the assessment of level of sedation very difficult [81].

There are various methods of assessing level of sedation in paediatrics. Scoring systems and neurophysiological method are the two widely used methods.

1.9.1. Scoring systems

Since the introduction of the first scoring scale in 1974, a number of other scales for sedation level assessment have been introduced [82]. A systematic review by De Jonghe et al (2000) on the use of sedation scoring systems showed that 25 tools for sedation assessment were published between 1996 and 1999 [83]. Only three of these have been tested and assessed for their validity and consistency. These tools are: the sedation agitation scale (SAS), the motor activity assessment scale (MAAS) and the Ramsay sedation scale [84]. Scoring systems often evaluate consciousness, level of agitation and pain level [85].

An ideal sedation scoring instrument should be easy to use, precise, safe, and should not increase staff workload. The Glasgow Coma Scale (GCS), Ramsay Scoring System (RSS), The Observer's Assessment of Alertness/Sedation (OOA/S), Sedation visual analogue scale (VAS) and COMFORT scale are the most commonly used tools for sedation level assessment in paediatric patients [84].

1.9.2. Neurophysiological methods

This sedation assessment method is often based on measurement of sedation depth. It relies on the hypothesis that ascribes the best indicator of brain function to its electrical activity [86]. Examples of neurophysiological assessment tools include: electromyography (EMG), electroencephalography (EEG) and evoked potentials.

1.10 Palatability of oral sedative agents

1.10.1. Definitions

Taste can be defined as 'the sensation of flavour perceived in the mouth on contact with a substance' [87]. Palatable food or drug is considered 'pleasant to taste' [87]. Specific epithelial cells with unique receptors in the tongue have the ability to detect four different modalities of basic taste, namely bitter, sour, salty and sweet [88]. Recently, a fifth taste modality called umami – that is, 'substantial' or 'delicious' – has been described [88].

Children and adults are known to respond to certain tastes differently [89]. Children prefer sweet-tasting materials [90]. This preference decreases during late adolescence to resemble that of adults [91]. In contrast, dislike of bitterness starts from a very young age; thus, bitter tastes are expected to reduce palatability [90]. In addition, there are inherited variances in sensitivity to certain tastes [92]. Cultural differences may also influence the taste sensation associated with various substances [89].

1.10.2. Taste and medication adherence

While adults may think that the worse a drug tastes, the better it is likely to work, children do not seem to have the same view [90]. Palatability has been found to be an important feature, after safety and clinical effectiveness, to both children and their parents [93]. Many researchers have argued that palatability is an important factor in enhancing drug treatment adherence through ensuring successful drug administration during the therapeutic course in children. A study by Craig et al. (2009) assessed the outcome related to children's treatment and drug administration; these researchers emphasised taste and palatability as the most important barrier to treatment of children [94].

1.10.3. Assessment of the palatability of drugs in children

Assessment of palatability of various medications is mainly based on the assessment of their taste [90]. Studies of palatability assessment have often been conducted in adult patients. However, these results may not be applicable to paediatric patients [90]. A prospective study conducted by Matsui et al. (1997) to assess the palatability of antibiotic drugs in children and adults showed significant differences between children and adults regarding the choice of drug that they considered had the worst taste [95]. This emphasises the importance of further well-designed palatability assessment studies in children.

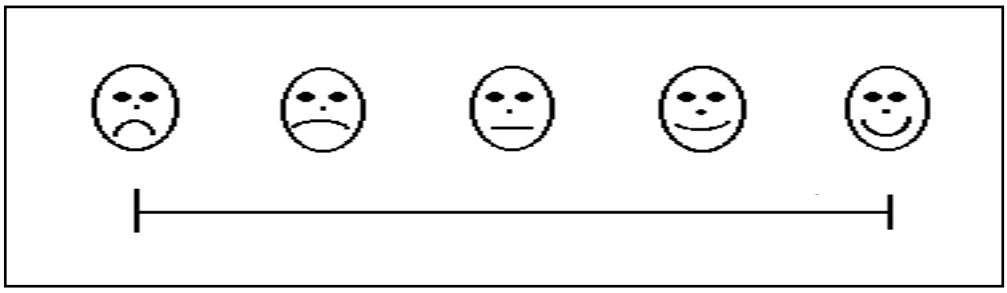
Currently, there are several methods for the assessment of taste perception in paediatric patients to measure drug palatability [96]. These range from the simple, such as verbal judgments, to the advanced, such as taste sensor systems [97]. Assessment of palatability of specific medication by evaluating the time needed for a drug to be given and observing the verbal judgments after administration of oral medications have been considered the most effective ways to compare various flavours [96]. In contrast, it has been found that the assessment of medication tastes in children younger than 5 years of age is difficult [98].

Throughout the literature, standardised visual analogue scales (VASs) such as the facial hedonic method are widely used to assess children's perception to the tastes of drugs [99, 100].

In a systematic literature review of palatability testing of medications in children, Davies and Tuleu (2008) reviewed 30 articles published between 1984 and 2008. They showed that approximately half of the included articles used a facial hedonic scale ranging from 2 to 10 points, with a 5-point scale being the most common [101]. In addition, it has been found that facial scales can be applied to assess drug palatability in paediatric patients as young as 3 years of age, while VASs are widely

used for children aged 6 years and older (Figure 1.3) [100-102]. Parents' opinions regarding the taste and acceptability of oral sedatives have been used to assess the palatability of oral medicines in children with developmental disabilities and children 2 years old and younger using the parents' reaction to the facial reaction of the child based on a modified 10-cm VAS incorporating a 5-point facial scale (1 = really good, 2 = good, 3 = not sure, 4 = bad, 5 = really bad [101]. Furthermore, it has been found that the time a nurse needs to give the drug to a child has been preferred as an effective method for measuring the effect of various flavours on the acceptance of medications in children younger than 5 years [103]. Open questionnaires can only be used for older paediatric patients who are able to clearly articulate their responses. In fact, a validated assessment scale is preferred because it provides a standardised assessment form to determine the palatability of various medications. Such a measurement scale avoids biases that may occur via the use of ranking alone [101].

Figure 1. 3: A 10-cm visual analogue with a facial hedonic scale



This figure retrieved from Matsui (2007) [90].

1.11 Common drugs used for sedation in children

Some of the most commonly used drugs for sedation in children include sedative-hypnotics, such as benzodiazepines (e.g. midazolam), barbiturates (e.g. pentobarbital) and other drugs such as chloral hydrate and propofol. Since analgesic properties are lacking in most sedative-hypnotics they are often used in conjunction with opioids, such as fentanyl and morphine for acute cases. Dissociative sedation (ketamine) and inhalational sedation (nitrous oxide) account for the other two prevalent methods for PS.

1.11.1. Mechanisms of action

The different pharmacological effects of the sedative drugs are the outcomes of interactions at particular receptor locations in the central and peripheral nervous systems. One can refer to the receptor kinds and anatomical sites as possibly identical in nature or markedly dissimilar; however, the general effects are complementary to one another in the sedative-analgesia system [104].

The major inhibitory neurotransmitter in the nervous system is Gamma aminobutyric acid (GABA) [105]. The discharge of this neurotransmitter comes from the terminals of presynaptic neuron cells into the synapse and carries out its activities by being attached to its own GABA receptor [105]. This in turn hinders the process of transmitting neuronal cells and eventually prevents the distribution of action potentials via the Central Nervous System (CNS), producing sedative effects[105]. An influx of chloride (Cl) ions is triggered when GABA opens Cl channels. Hyperpolarisation of the neuron results from the Cl ions influx, which ultimately prevents neuronal release [106]. The entry of calcium into the cell reverses the hyperpolarisation action [106].

There are three kinds of GABA receptors; namely GABA-A, GABA-B and GABA-C receptors [105]. GABA-A receptors are acted on by a number of sedative agents, while the binding of these receptors can lead to a decrease in neuronal firing percentage [105]. Consisting of numerous forms, such as alpha, beta, and gamma, the GABA-A receptor subunit is thought to be the functional unit on which benzodiazepines and barbiturates function [105].

- **Inhalation agents**

- **Nitrous oxide (N2O)**

Mild analgesia and anxiolytic effects are produced through inhaling nitrous oxide. It is usually used at concentrations that range between 30% and 70% with oxygen making up the rest of the combination [107]. There is a rapid onset of action within 30 to 60 seconds; an optimal impact after about five minutes, and swift recovery upon stoppage [107].

- Mechanism of N2O-induced anxiolysis.

N2O is likely to act through the benzodiazepine binding site given that its effects are stopped by flumazenil. Aminobutyric acid (GABA) activation of its binding site is thus facilitated through this action, causing a chloride ion influx [108]. In addition, activation of calmodulin (CaM) is caused by the added chloride ion concentration in the neuron, which then leads to the enzyme nitric oxide synthase (NOS) being triggered [108]. The amino acid L-arginine (L-Arg) is then transformed by NOS into L-citrulline (L-Cit) and nitric oxide (NO), thus stimulating the enzyme soluble guanylyl cyclase and producing the second messenger cyclic guanosine monophosphate (cyclic GMP) [108]. The cyclic GMP stimulates a cyclic GMP-dependent protein kinase (PKG), which results in the anxiolytic drug effect.

- Mechanism of N2O-induced analgesia.

The neuronal release of endogenous opioid peptide or dynorphins (DYNs) is thought to be stimulated by N2O; however, nothing is known with regards to the molecular features through which this process is instigated [108]. L-arginine (L-Arg) is taken up by the presynaptic nerve terminal, with L-Arg being transformed by the enzyme nitric oxide synthase (NOS) into L-citrulline (L-Cit) and nitric oxide (N2O) [108]. It seems that NO is included in the stimulated DYNs discharge [108]. While passing the synaptic cleft, DYNs activate postsynaptic opioid receptors, which are part of the 7-transmembrane–spanning, G protein–coupled superfamily of receptors [108].

It can also be shown that N2O can affect the descending inhibitory pathways. N2O can also trigger the discharge of endogenous opioid peptides (EOP), thus initiating opioid receptors on -aminobutyric acid (GABA)-ergic pontine nuclei [108]. In the meantime, this pathway triggers the descending noradrenergic system in the dorsal horn of the spinal cord [108]. This process leads to the direct or indirect inhibition by means of a GABA interneuron of the nociceptive processing at the point of the principal afferent and second-order neurons that convey sensory signals up the ascending nociceptive pathway [108].

Nitrous oxide should be administered with oxygen in order to avoid hypoxia [109]. During mild or moderately painful invasive procedures, N2O can be given alone or in combination with one of the other sedative drugs with a mild sedative effect, such as midazolam [110]. It is often used in a 50% concentration (50% N2O and 50% O2) as a premixed drug [111]. It can also be given in a 70% concentration and it has been found to be effective and safe in children. According to a study by Babl et al (2008), the use of high concentrations of nitrous oxide (70%) as a single sedative agent in 762 children for procedural sedation was found to be effective and safe [112]. Moreover, this drug has mild cardiopulmonary adverse effects even when it is combined with a strong sedative such as pentobarbital [113]. A study done by Griffin

et al. (1981) failed to indicate any substantial risk of cardiopulmonary depression after administering nitrous oxide during 3,000 paediatric invasive procedures [113].

- **Dissociative agent**

- **Ketamine**

Ketamine is a dissociative sedative agent derived from phencyclidine compound. It has both amnesic and analgesic effects [114]. These effects are often dose dependent. For example, its analgesic effect occurs at a low dose; in contrast, its sedative effect (dissociative sedation) occurs at a high dose [114]. Ketamine selectively depresses the basic operation of the associative cortex and thalamus, while improving the activity in the limbic systemic, causing an operational separation between the thalamus and the limbic cortex [104]. This process leads to a cataleptic-like state of unconsciousness, known as dissociative anaesthesia [104]. Involving non-competitive inhibition of the N-methyl- D-aspartate (NMDA) receptor, a glutamate-gated cationic channel selective for calcium appears to be Ketamine's principle action [104, 115]. In terms of this NMDA glutamate receptor subtype, it is part in the extended potentiation of synaptic responses linked to the wind-up, central sensitisation phenomena [104, 115]. It is also possible that Ketamine would be involved with subcategories of endogenous opioid receptors, monoaminergic and muscarinic, cholinergic receptors [114].

Ketamine produces rapid sedation because it has a short half-life of approximately 5 minutes. It can be administered through various routes; however the intravenous route has been clinically proven as the most effective and safest route in a study of 11,000 paediatric patients [116]. Emergence reactions are one of the major drawbacks of ketamine. Emergence phenomena include hallucinations, vivid dreams and delirium. Benzodiazepines were found to be effective in prevention of these

symptoms [117]. Increased blood pressure, heart rate, and intracranial pressure are some of the commonly associated adverse effects. Laryngospasm has been reported in a few patients [118].

- **Sedatives with hypnotic effect**
- **Chloral hydrate/ triclofos**

Chloral hydrate is a central nervous depressant that has been widely used as sedatives in paediatrics for many years [119, 120]. It is a pure sedative-hypnotic drug without analgesic properties. In the body, chloral hydrate and triclofos are rapidly metabolised and converted to trichlorethanol, which the active metabolite [121]. It enhances the action of GABA at GABA (A) receptors, through binding to specific receptor locations thereby increasing its inhibitory actions on neurons of central nervous system to produce it's sedation effect [105, 122].

Chloral hydrate was introduced for medical use in 1869 by German physician called Lieberch [123] and its use in children was begun in 1894. Its effectiveness as a sedative drug for non-invasive diagnostic procedures especially CT and MRI has been well established with more than 85% success rate recorded [120, 124]. It is thought to be very effective in paediatric patients younger than two years old undergoing non-invasive procedures [123].

In the UK chloral hydrate is recommended by National Institute of Health and Care Excellence (NICE) guidelines for painless diagnostic imaging procedures in children under 15 kg [80]. It produces a relatively mild to moderate sedation effect when given orally in doses from 50 to 75 mg/kg [125]. Major drawbacks are the unpredictability of its onset of action, prolonged duration of its sedative effect and

poor taste [42, 46, 126]. Common AEs are respiratory complication and vomiting [127].

Triclofos is a phosphoric ester of trichlorethanol (chloral hydrate active metabolite). It was indroduced in UK by Glaxo in 1962 [128]. Its onset of action is about 30 to 45 minutes [129]. Both chloral hydrate and its active metabolite are effective and safe as sedatives and hypnotics [130]. However, triclofos is thought to have a more pleasant test and is less of a gastric mucosa irritant than chloral hydrate [129].

- **Barbiturates**

A class of sedative recognised for deep sedation, hypnosis, loss of memory, and anticonvulsant characteristics but no inherent analgesia is Barbiturate [121]. The interaction of barbiturates with the inhibitory neurotransmitter gamma-aminobutyric acid (GABA) occurs through attachment to, and instigation of, the GABA-A receptor subunit. Increased chloride current conductance can be caused by GABA-A receptor initiation, leading to the postsynaptic membrane being hyperpolarised and postsynaptic neurons being inhibited [104, 105].

It is possible that barbiturates will also imitate the action of GABA resulting in the chloride ion channels being directly activated [104, 105]. Excitatory alpha-amino-3-hydroxy- 5-methyl-4-isoxazole propionic acid (AMPA) subtypes of glutamate receptors are also inhibited by Barbiturates [104]. The CNS sedative impacts of barbiturates, are therefore dependent on the initiation of inhibitory GABA-A receptors and the inhibition of excitatory AMPA receptors [104]. Barbiturates selectively depress neurotransmission within the peripheral nervous system by inhibiting the excitatory autonomic ganglia and nicotinic cholinergic, acetylcholine receptors [104]. Similarly, barbiturates are able to reversibly impair the action of the majority of excitable neural tissues, especially suppressing polysynaptic neuron responses [104]. They are also

responsible for suppressing the reactions of the reticular activating system in the brainstem which ensures the regulation of the level of consciousness, in addition to key respirational and cardiac roles [104].

- **Secobarbital**

Secobarbital is a barbiturate derivative agent which was previously known as quinalbarbitone. It is an intermediate acting agent which is well absorbed from the GI tract and its doses for sedation in children range from 7.5 to 10 mg/kg (maximum of 200 mg) [131]. A study conducted in the UK to evaluate secobarbital safety and effectiveness in 40 children with mean age of 32 months showed that adequate sedation was achieved in 34 (85%) children [131]. The success rate was better with children younger than 5 years (91%), with sedation onset time ranging from 10 to 50 minutes. The most common reported adverse event was Paradoxical excitement [131].

- **Pentobarbital**

This is occasionally used in paediatric patients and can be effective for non-invasive procedures needing complete immobility [124, 132]. With intravenous titration, sedation is evident in 3–5 min with a duration of roughly 30–40 min [68]. Pentobarbital is often associated with respiratory depression; however, this unwanted effect can be tolerated by healthy paediatric patients [70]. Hemodynamic adverse effects are the most common effects of this drug, particularly in hypovolemic paediatric patients and those with history of hemodynamic instability [133].

- **Benzodiazepines**

There are a group of highly lipophilic agents with anxiolytic, amnesic, anti-depressant and hypnotic features. As in the case of barbiturates, benzodiazepines enhance the action of the inhibitory neurotransmitter GABA by attaching to the GABA-A receptor subtype at a particular location different from that of the GABA binding position on the receptor [134]. This increases chloride ion channel conductance resulting in a hyperpolarised postsynaptic membrane and decreased neuronal excitability. Benzodiazepine- receptor binding largely takes place on the postsynaptic nerve membranes mostly within the cerebral cortex [104]. As opposed to barbiturates, GABA-A receptors are not directly activated by benzodiazepines, which instead modulate GABA binding [104]. The attachment of benzodiazepines to distinctly different specific GABA-A subunits is considered as to be the mechanism of the particularly different pharmacologic properties of the benzodiazepines [104].

It could be that benzodiazepine-sensitive GABA receptors with alpha-1 subunits are the most significant in terms of regulating sleep and are the assumed targets of depressant-hypnotic agents and anterograde amnesia [135]. Similarly, benzodiazepine-sensitive GABA-A receptors with alpha-2 subunits could be as equally essential for the regulation of anxiety and are targets of anxiolytic agents [135]. The benzodiazepine antagonist flumazenil attaches to GABA-A receptors and is used clinically to quickly antagonise the impact of benzodiazepine overdoses [105].

- **Midazolam**

Midazolam is the most common benzodiazepine used for procedural sedation. It produces anterograde amnesia which is considered as a positive feature of this drug [92]. In a randomised double blind study evaluating the effectiveness of midazolam and fentanyl as sedative drugs for invasive oncology procedures in paediatric patients; 72% of children preferred midazolam, while fentanyl was preferred by only 28% (P =

0.0278). This was reported to be due to the midazolam amnesic effect [136]. Predictable induction time and short duration of action are the most important advantages that make it one of the most popular sedative drugs [92].

It can be administered orally, buccally, intranasally, and rectally. When it is given orally, the onset of action starts after 10-30 minutes and lasts for approximately 60 minutes. The bioavailability of this drug is less than 50% due to the first pass effect of the liver [137]. It rapidly crosses the blood brain barrier because of its lipophilicity [138]. The volume of distribution of midazolam is large and the elimination half-life, of approximately 1.2 hours, is short [139]. The action of intravenous injection is more rapid than oral; the effect starts within 30 to 60 seconds and lasts for approximately from 15 to 80 minutes [140]. The most common adverse effects reported are gastro intestinal upset. In addition, it can lead to paradoxical reactions, hiccups, and dyspnoea [141].

- **Paraldehyde**

Paraldehyde is one of the oldest sedative drugs; it also possesses hypnotic and anticonvulsant properties. It was synthesized by Wildenbusch in 1829 and first used in various industrial and medical preparations [142]. Paraldehyde was introduced into clinical practice by an Italian physician named Vincenzo Cervello in 1882 [142]. The mechanism by which paraldehyde produces its effect is still unclear, however it may produce imbalances between facilitatory and inhibitory mechanisms by depressing various levels of the central nervous system including the ascending reticular activating system [142].

Paraldehyde is rapidly absorbed after administration via oral, intramuscular (IM) or rectal routes. It can be given rectally after mixing with olive oil [143]. Caution is needed in the administration of paraldehyde as it can melt plastic [143]. However, a

plastic syringe will not be affected if the enema solution is drawn up and administered within 10 minutes [143]. It produces its action within 10 to 15 minutes after oral administration and within 2 to 3 minutes after IM injection. It is widely distributed and has a half-life ranging from 8 to 27 hours (7.5 hours). Approximately 80 to 90% of the drug is metabolised in the liver to acetaldehyde and approximately 30% is excreted in expired air unchanged by the lungs. This gives an unpleasant odour to the breath of paraldehyde treated patients. Only trace amounts are excreted in the urine.

- **Propofol**

Propofol is an extremely lipid-soluble, ultrashort-acting alkyl phenol agent with clear depressant features. In spite of offering no analgesia, propofol has the potential to induce a condition of deep sedation, enabling painful procedures to be tolerated [114]. It is believed that propofol works through the enhancement of inhibitory GABA neurotransmission by reducing the GABA receptor dissociation percentage, hence enhancing the conductance of chloride ion channels, hyperpolarisation of the postsynaptic cell membrane, and inhibition of neuron initiation. Propofol's action is fairly selective in the modulation of the GABAA receptor [144].

Following a single intravenous dose, there is a rapid effect within 30 to 45 seconds, and quick effect- site equilibration time [104]. As for the effect length, it is short (five to 10 minutes), mainly as a result of redistributing into peripheral tissues [104]. Because of the wide-ranging inconsistency in the therapeutic window for dosing propofol, should be titrated to effect [145].

The most frequent adverse effect of propofol is profound respiratory depression which can be associated with airway obstruction. Cravero and colleagues evaluated the incidence of adverse events during children sedated with propofol from 2004 to 2007 and they found that hypoxia and airway obstruction occurred 154 and 575 times

respectively per 10,000 propofol administrations [57]. Another serious adverse event of propofol is "propofol infusion syndrome" which can occur due to long term infusion of propofol for sedation of critical ill children in intensive care units [146]. This syndrome is characterized by the incidence of severe metabolic acidosis and rhabdomyolysis i.e the rapid breakdown of muscle tissues accompanied by liver enlargement, lipaemia, heart failure and hyperkalemia [146, 147].

- **Alpha-2 Adrenergic Agonists**

These include clonidine and dexmedetomidine and have depressant as well as dose-dependent analgesic features [148]. It is thought that this analgesia results from an agonist interaction with presynaptic alpha-2 Adrenergic receptors positioned on small primary afferents, which reduces the transmitter discharge [148]. Furthermore, these agonists are believed to interact with postsynaptic alpha2-adrenergic receptors on projection neurons[148]. This process results in the hyperpolarisation of the cell by enhancing the potassium conductance by Gi coupled potassium (K) channels[148]. Apart from their subarachnoid analgesic properties, alpha-2 agonists generate dose-dependent sedation at supraspinal position [148]. It is thought that the mechanism of sedation is the same as the analgesic activity via postsynaptic alpha-adrenoreceptors and inhibitory G proteins [149].

- **Clonidine**

Clonidine is an alpha-2 agonist with sedative, anxiolytic and analgesic properties [150]. It inhibits the release of peripheral norepinephrine by stimulation of the inhibitory alpha-2 adrenoceptors [151].

Clonidine is absorbed rapidly after oral administration [150] with a bioavailability of 75 to 95% [150]. Approximately 20-40% of clonidine is bound to plasma proteins [151].

50% of the active drug is metabolised in the liver and excreted in the urine as inactive metabolites [150]. The half-life of the drug ranges from 12-33 hours [151].

Clonidine clearance in neonates is around one-third of that in adults due to immature elimination pathways; by one year of age it reaches approximately 82% of adult rate [152]. Administration of 2.5 microgram/kg of clonidine by the rectal route in children, about 20 minutes prior to induction of anaesthesia has been shown to achieve drug plasma concentrations known to be effective in adults [153].

Intravenous administration of 1 microgram/kg/hour of clonidine with 50 microgram/kg/hour of midazolam was not associated with substantial changes in blood pressure and heart rate and was associated with satisfactory sedation scores [154]. Therefore clonidine use as a sedative was found to be cardio-stable when used with midazolam in critically ill ventilated infants [155].

- **Dexmedetomidine**

Dexmedetomidine is a highly selective α-2 receptor agent with analgesic and hypnotic, effects [114]. It has advantages such as: natural sleep stimulation, absence of respiratory depression, and cooperative sedation – patients are often able to follow simple orders during the procedure [156]. However, intravenous administration of dexmedetomidine may lead to cardiovascular complications like bradycardia and hypotension [157]. Dexmedetomidene can be administered via the oral, intranasal, submucosal and intravenous routes. This drug has been shown to be effective in paediatrics patients with autism [158]. According to a recent study by Mason and colleagues (2009), dexmedetomidine did not interfere with or impair EEG results [159]. Thus it is often useful for sedation prior to EEG in paediatric patients.

- **Sedatives with analgesic effects**

In terms of this category of medicines, they are largely utilised for invasive processes, including dental activities and wound management procedures. In addition, their analgesic effects may be improved by combination with other hypnotic or anxiolytic agents [160]. The drugs most widely used in children are fentanyl and ketamine.

- **Fentanyl**

This opioid agonist is widely utilised in children in painful procedures. It is a potent opioid that has no intrinsic anxiolytic or amnesic characteristics [107]. The opioid receptors interact with inhibitory G-proteins, closing N-type voltage-operated calcium channels and opening potassium channels leading to hyperpolarisation. In addition, they reduce intracellular cyclic adenosine monophosphate (cAMP) by reducing adenylate cyclase [161].

It has a rapid onset of action and high protein binding properties. It reaches peak blood concentrations within 4-5 minutes thus it should be administered 4-5 minutes before an invasive procedure [131]. Administration of fentanyl in combination with other sedative agents provides a synergistic effect resulting in an increased sedative effect [160]. Pruritus, vomiting and respiratory depression are the most common adverse effects of fentanyl, accounting for 44%, 15-20% and 5% of all adverse effects respectively [162].

1.12 The aims of this thesis

Because of the increasing use of sedation in paediatric practice, research is needed to evaluate its safety and effectiveness in current practice

The first aim of this thesis was to evaluate, as accurately as possible, the safety and clinical effectiveness of some of the most commonly used sedative agents in children.

The local hospital's sedation policy (Derbyshire Children's Hospital) and the national UK NICE guidance were used as a guide [80]. Therefore, systematic reviews of the literature on safety and clinical effectiveness of chloral hydrate and midazolam were conducted **(Chapter 2, 3, and 4)**. The aims were as follows:

- To evaluate the effectiveness and the incidence of adverse events reported for sedative agent (chloral hydrate and triclofos) during each type of procedural sedation including: painless, painful, and treatment procedures **(Chapter 2** and **Chapter 3)**
- To evaluate the effectiveness and the incidence of adverse events of midazolam during diagnostic imaging procedures **(Chapter 4)**

The second aim was to evaluate paraldehyde effectiveness and safety for procedural sedation in children. Paraldehyde is part of the local hospital sedation policy, as a second line agent. There is very little research available about its use for procedural sedation in children, as it is mainly used for treatment of convulsive episodes in patients with tetanus and status epilepticus [163]. It was therefore decided to conduct a systematic review to evaluate paraldehyde as a sedative agent during procedural sedation in paediatric patients **(Chapter 5)**.

Based on the results from the previous chapters, it was noticed that the palatability of oral sedative agents plays a major role in drug acceptance and therefore treatment adherence. The subject of palatability was explored further by conducting a literature review to assess the palatability of the two most commonly used oral sedative agents (chloral hydrate and midazolam) **(Chapter 6)** and a prospective pilot study was performed to assess the palatability of these medicines in a Children's Hospital setting **(Chapter 7)**.

- The literature review aimed primarily to evaluate the current published clinical evidence concerning the palatability of chloral hydrate and midazolam in children. The secondary aim was to review the methodology used in previous studies of sedative agents to inform the protocol for the prospective study **(Chapter 6)**.
- The primary aim of the study was to examine children's opinions on the taste and acceptability of oral chloral hydrate and midazolam **(Chapter 7)**.
- The secondary aims were as follows:
    - To examine nurses' and parents' opinions on the taste and acceptability of the given sedative agents.
    - To assess if there could be a relationship between the drug acceptability and the success rate of procedural sedation.
    - To assess the requirement of supplemental sedation during procedures.

Due to the fact that I am from the kingdom of Saudi Arabia and will return to work there as a pharmacist, the final part of my thesis evaluated the use of sedation in children (outside the operating theatre) in the Middle East countries. This was achieved through conducting a systematic review of the literature and also assessed the use of practical sedation guidelines in these countries **(Chapter 8)**.

Finally as little information was found in the previous literature review, a survey was conducted to evaluate the current practice of sedation in Saudi Arabia. This survey aimed to evaluate the views of practitioners on; use of sedation, availability of guidelines, the drugs currently being used and the level of practice being undertaken **(Chapter 9)**.

Chapter 10 contains the conclusions of the thesis.

CHAPTER TWO

Systematic Review of Chloral Hydrate for Procedural Sedation in Children; An analysis of its safety and effectiveness

Part 2.1.Chloral Hydrate for Painless Procedural Sedation

2.1.1. Introduction

Paediatric patients undergoing painless diagnostic procedures such as computer tomography (CT) scanning are frequently sedated with the aim of reducing anxiety and enabling a successful procedure by helping the child to remain still [2, 164]. The ideal sedative drug for procedural sedation (PS) would be an agent that has a rapid onset of action and a short half-life, allowing easy titration of response and a quick recovery time [165]. In addition, it would have few adverse events (AEs). Unfortunately it is difficult to find a single sedative agent that possesses all these properties [123].

Several sedative drugs, such as chloral hydrate, nitrous oxide and the benzodiazepines, are available for procedural sedation in children. Chloral hydrate is a central nervous depressant that has been widely used as a paediatric sedatives [119, 120]. Assessment of clinical studies evaluating its safety and effectiveness, particularly for painless diagnostic procedures in children is important.

A systematic literature review was designed to evaluate the clinical effectiveness and toxicity of chloral hydrate for painless PS in children (≤18 years).

2.1.2. Methods

A systematic literature search for articles, evaluating chloral hydrate safety and clinical effectiveness in children up to the age of 18 years was electronically conducted using four medical databases including: MEDLINE (1948 to January 2012) and EMBASE (1980 to January 2012) , COCHRANE (1974 to January 2012) and CINAHL (1974 to January 2012). EMBASE, MEDLINE, and COCHRANE library were searched separately and then combined to remove duplications. The CINAHL database was searched and reviewed manually to remove duplication and relevant articles identified.

The keywords involved in this systematic review were selected based on their sensitivity and specificity according to the validated age specific search strategy by Hedges Team [166]. Therefore, the most sensitive and specific keywords were as following: chloral hydrate AND children OR infant OR pe*diatric* OR neonate OR adolescence OR adolescences or adolescent AND sedation.

All retrieved abstracts were reviewed according to the study inclusion criteria; original studies assessing or reporting the safety (AEs) and/or effectiveness of chloral hydrate as a sedative agent in children and adolescents from birth up to 18 years, undergoing painless procedure(s). All languages were included in this systematic review. The exclusion criteria were: studies that evaluated or reported the use of chloral hydrate for other uses rather than painless procedural sedation as well as letters, comments, editorials or review articles. The full articles of all related abstracts were read carefully according to the study inclusion and exclusion criteria.

Articles were classified according to the type of painless PS, according to Sury (2004)[16] and all related data including: sample size, study region, study period, study design, dose of chloral hydrate, AEs of chloral hydrate, other used sedative drug

(s), supplementary dose of sedative drug(s), induction time of sedation, duration of sedation, failure rate, success rate were extracted onto a data collection sheet. paediatric patients were grouped into the following age groups: preterm neonates (<36 weeks gestation, 0–27 days); full-term neonates (0–27 days, >37 weeks gestation); infants and toddlers (28 days to 23 months); children (2–11 years); and adolescents (12–17 years)[167].

The primary endpoint was to evaluate the toxicity of chloral hydrate, while the secondary endpoint was to evaluate chloral hydrate clinical effectiveness. According to the European Medicines Agency (EMA) [50], AEs were categorised according to their severity into serious or mild AEs. A serious AE is defined as "any untoward medical occurrence that at any dose: results in death, is life-threatening, requires inpatient hospitalisation or prolongation of existing hospitalisation, results in persistent or significant disability/incapacity, or is a congenital anomaly/birth defect". A mild AE is defined as "any AE that occurred that did not need any intervention" ([50]). Successful procedural sedation was defined as the ability to sedate the child to the targeted sedation level and the completion of designated painless diagnostic procedures.

The quality of all included studies was assessed in order to assess bias risk. The studies' quality was assessed by two reviewers (BS and HS) independently. Jadad scoring checklists for harm reporting were used to evaluate randomised clinical trials (RCTs) [168]. For all RCTs to be considered as good quality, rating should be ≥ 3 out of five criteria according to the Jadad scoring checklists. The qualities of prospective observational and retrospective studies were assessed using the STROBE checklist [169]. Any study with a minimum score of 70% was considered a good quality study.

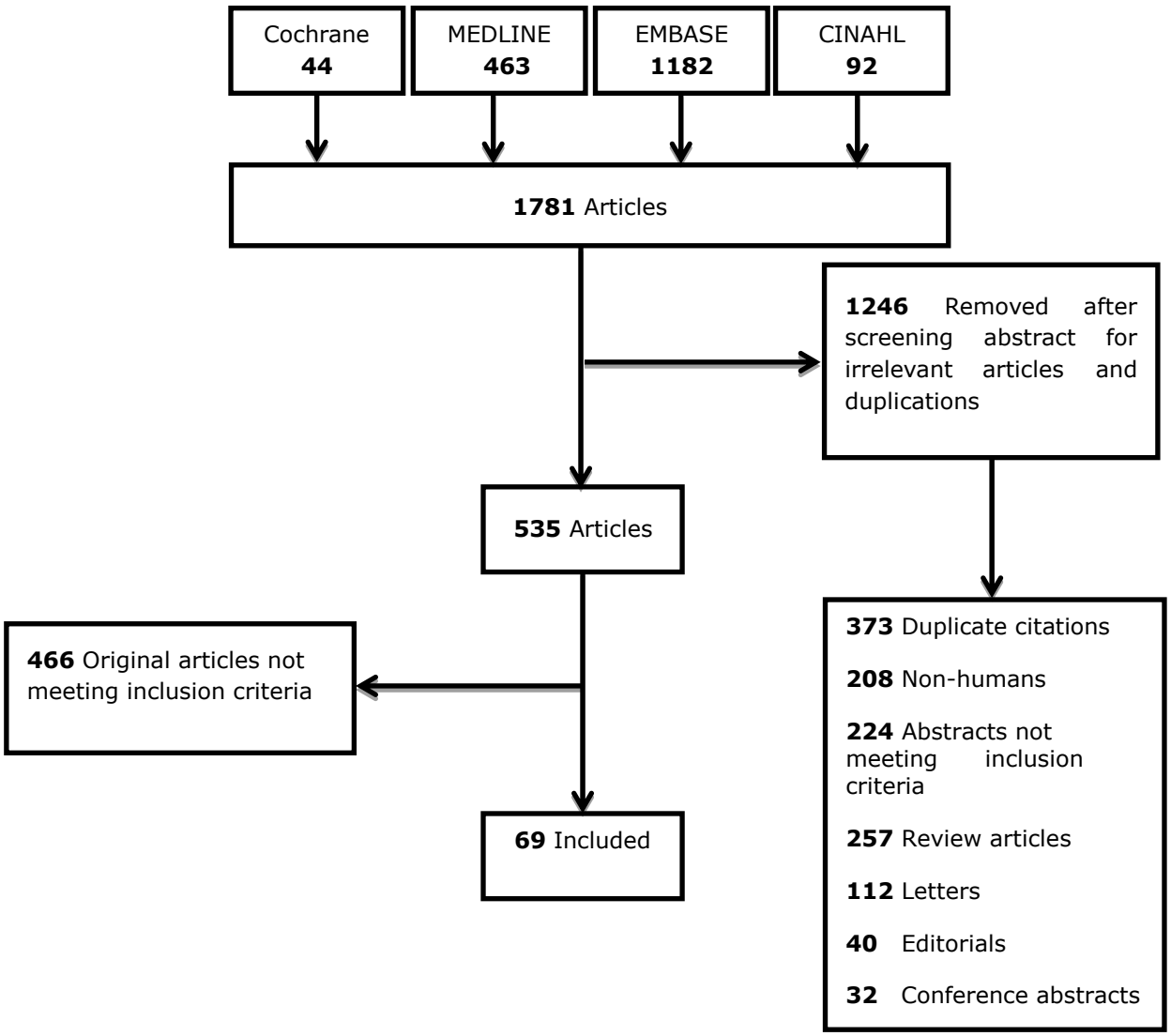
Data from included clinical studies were analysed statistically using SPSS version 22. The chi-squared test was used to determine the association between success rates of each type of diagnostic procedure. At $p<0.05$, differences were considered statistically significant. Incidences were calculated for AEs, excluding case reports. Incidences were calculated by dividing the total number of AEs by the total number of children exposed to chloral hydrate. Meta-analysis was not performed due to the heterogeneity of the studies.

2.1.3. Results

2.1.3.1. Overview

Our search strategy identified a total of 1781 articles. After reviewing the abstracts of these articles, 1246 articles were excluded because they did not fulfill the inclusion criteria (figure 2.1.1). The full texts of the remaining articles (535 articles) were read carefully and 69 articles met the study inclusion criteria.

Figure 2.1. 1: Flow diagram of search and review process



The studies were published between 1972 and 2011. The total number of children who received chloral hydrate was 15238, the age ranged between birth and 18 years. These studies were conducted in 11 different countries, most (40) took place in the Americas (38 in United States of America (USA), one in each of Canada and Chile); 19 in Europe (five in Italy, four in Spain, two in Germany, two in United Kingdom, two in Belgium, one in each Greece, one in France, one Norway and one in Turkey); eight in Asia (two in Israel, one in each China, Iran, Japan, Jordan, Kingdom of Saudi Arabian and in Thailand) and two in Australia. Chloral hydrate was administered orally in the majority of the studies (65 studies). The most common study methodology was the prospective observational studies (9055 patients), followed by retrospective studies (5472 patients). Twenty (29%) of the studies involved infants younger than two years (Table 2.1.1).

The chloral hydrate dose ranged from 25 to 100 mg/kg (median 100 mg/kg maximum 2g). Procedural sedation indications were CT and/or MRI, EEG, ECG, BAEP and pulmonary function test. Oral route (94%) was the most common route of administration (Table 2.1.1).

Table 2.1. 1: Summary of 69 studies that reported on clinical effectiveness and safety of chloral hydrate in children

Studies' characteristics	No. of studies	No. of children
Type of study	**N=69**	**N=15238**
• Prospective observational	33	9055
• Retrospective	15	5472
• Case report	11	16
• Randomised controlled trial	10	695
Type of procedure		
• CT and/or MRI	51	10863
• ECG	6	2272
• EEG	6	430
• BAEP	3	1646
• Pulmonary function test	3	27
Route of Administration		
• Oral/ dose range (median mg/kg)	65/25 to 100 mg/kg (100)	15184
• Rectal/dose range (median mg/kg)	4/55 to 77mg/kg (75)	54
Age groups		
• Preterm neonates	0	0
• Term neonates	0	0
• Infants	20	2705
• Children	7	1933
• Other patient age groups*	42	10600

* Studies involving multiple age groups (the number of patients within each age group was not documented)

BAEP = Brainstem auditory evoked potential, (CT) =Computerised Tomography scan, (ECG) = Electrocardiogram test, (EEG) = Electroencephalogram test, (MRI) = Magnetic Resonance Imaging

2.1.3.2. Trial quality

Ten RCTs compared the effectiveness of chloral hydrate versus other sedatives (Table 2.1.1). Two studies fulfilled all 5 Jadad scoring criteria. Six studies met >3 criteria or more whereas 2 studies met ≤ 2 criteria (Figure 2.1.2, Table 2.1.2). The scores for the STROBE checklist for observational studies are illustrated in table (2.1.3). 30 of the 48 pooled observational studies were rated with above 70%. Despite this all studies were included in the systematic review to avoid missing any data from these articles due to the small number of articles related to each painless procedure. The quality scores and selection of paper and abstract were checked by two independent reviewers (BS and HS).

Figure 2.1. 2: Quality assessment criteria of included RCTs

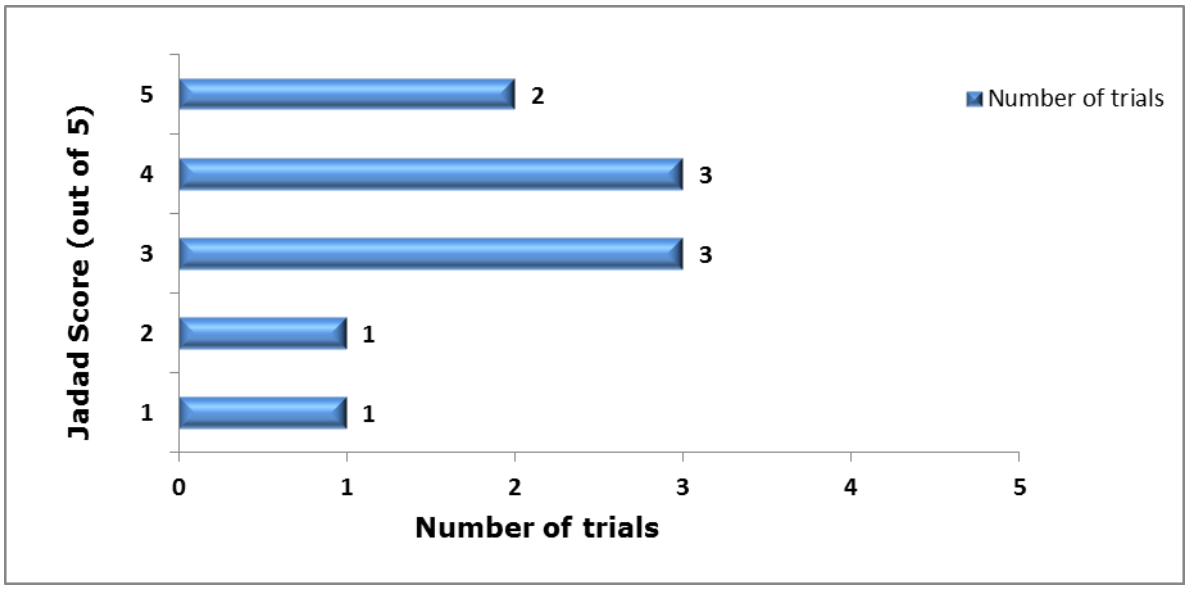


Table 2.1. 2: Quality assessment criteria of included RCTs

References	Jadad score (out of 5)
Marti-Bonmati et al. 1995[170]	5
D'AGOSTINO and TERNDRUP 2000[171]	5
Malviya et al. 2004[172]	4
Sury and Fairweather 2006[23]	4
Layangool et al. 2008[173]	4
Millichap 1972[174]	3
Wheeler et al. 2001[175]	3
Ashrafi et al. 2010[176]	3
McCarver-May et al. 1996[177]	2
Thompson et al. 1982[178]	1

Table 2.1. 3 Quality assessment criteria of included observational studies

References	STROBE scoring (out of 22)	%
Kannikeswaran et al. 2011[179]	21	95
Lipshitz et al. 1992[180]	20	91
Loewy et al. 2005[181]	20	91
Heistein et al. 2006[182]	20	91
Manuli and Davies 1993[183]	19	86
Chung et al. 2000[184]	19	86
Litman et al. 2010[125]	19	86
Roach et al. 2010[185]	19	86
Malviya et al. 1997[46]	18	82
Thoresen et al.1997[186]	18	82
Kao et al. 1999[187]	18	82
Mason et al. 2004[127]	18	82
Allegaert et al. 2005[188]	18	82
Avlonitou et al. 2011[189]	18	82
Strain et al. 1986[132]	17	77
Pereira et al. 1993[190]	17	77
Woolard and Terndrup, 1994[191]	17	77
Casillas et al. 1995[192]	17	77
Vade et al. 1995[120]	17	77
Napoli et al. 1996[193]	17	77
Rooks et al. 2003[194]	17	77
Treluyer et al. 2004[195]	17	77
Hijazi et al. 2005[196]	17	77
Wang et al. 2005[197]	17	77
Cortellazzi et al. 2007[198]	17	77
Abdul-Baqi 1991[199]	16	73
Greenberg et al. 1991[68]	16	73
Ronchera et al. 1992[200]	16	73
Greenberg et al. 1993[201]	16	73
Slovis et al. 1993[202]	16	73
Mallol and Sly 1988[203]	15	68
Turner et al 1990[204]	15	68
Ronchera-Oms et al. 1994[205]	15	68
Malis, Burton 1997[206]	15	68
Malviya et al. 2000[207]	15	68
Szmuk et al. 2003[208]	15	68
Schmalfuss, 2005[209]	15	68
Hubbard et al. 1992[210]	14	64
Merola et al. 1995[211]	14	64
Beebe et al. 2000[212]	14	64
Dalal et al. 2006[213]	14	64
Rumm et al. 1990[119]	13	59
Temme et al. 1990[214]	10	45
Filippi et al. 2001[215]	10	45
Noske and Papadopoulos, 1993[216]	9	41
Marchi et al. 2004[217]	9	41
Woodthorpe et al. 2007[218]	9	41
Eelkema et al. 1977[219]	8	36

2.1.3.3. Chloral hydrate effectiveness

50 studies documented chloral hydrate effectiveness in six painless procedures. Eighteen studies described the effectiveness for CT/MRI, 13 studies for MRI, 6 each for CT and ECG, 5 for EEG, and one for each BEAP and Pulmonary test. The results will now be further explored according to the procedures.

2.1.3.3.1. CT and/or MRI scans

Eighteen studies were found. A total of 3854 children aged between 0 and 18 years received a median dose of 64 mg/kg, while 19 children with age range from 6 months to 6 years received 75 mg/kg rectally. Only 972 children were younger than five years old.

Therapeutic success was achieved in a median of 98% (94% to 100%) of patients. Children younger than five years old had a higher success rate, median 99% (98% to 100%).

232 (6%) children given chloral hydrate required sedation supplementation such as chloral hydrate 25 mg/kg and 2 mg/kg meperidine intramuscularly [46, 214] respectively (Table 2.1.4).

Table 2.1. 4: RCTs and observational studies for CT/MRI scan

Reference, country	Study design	Age	No. of patients	Drug	Dose mg/kg	Success rate (%)	Supplementary (No.)	Sedation (min)	
								Onset	Duration
D'AGOSTINO and TERNDRUP 2000, USA [171]	Double-blind RCT	2 months-8 years	11 22	CH M	75 PO 0.5 PO	100 50	Y (1) Y (12)	NA NA	mean 95 mean 76
RUMM, TAKAO et al. 1990, USA[119]	Prospective study	2 months- 14 years	50	CH	25- 81 PO	87	Y (3)	30	NA
Temme, Anderson et al. 1990, USA[214]	Prospective study	1 months- 18 years	350	CH	50 PO	98	Y (5)	30-60	NA
Vade, Sukhani et al. 1995, USA[120]	Prospective	1- 4 years	191	CH	50-100 PO	99	Y (10)	30	NA
Malis and Burton 1997, USA[206]	Prospective study	0- 5 years	31	CH	61 PO	94	NA	NA	NA
Malviya, Voepel-Lewis et al. 1997, USA[46]	Prospective study	0- 18 years	336	CH	Mean 13 PO	77	Y (34)	NA	NA
Kao, Adamson et al. 1999, USA[187]	Prospective study	2 months– 11 years	80	CH	47-100 PO	89	Y (14)	24	NA

CH: Chloral hydrate, M: Midazolam, PO: Orally, Y: Yes, NA: Not available.

Table 2.1.4: RCTs and observational studies for CT/MRI scan

Reference, country	Study design	Age	No. of patients	Drug	Dose mg/kg	Success rate (%)	Supplementary (No.)	Sedation (min)	
								Onset	Duration
Chung, Hoffer et al. 2000, USA[184]	Prospective study	2- 13 months	16	CH	50-100 PO	100	N	19	83
Malviya, Voepel-Lewis et al. 2000, USA[207]	Prospective study	0- 18 years	854	CH	62 PO	98	NA	30	NA
Rooks, Chung et al. 2003, USA[194]	Prospective study	3- 9 months	358	CH	50 PO	99	NA	16	86
Szmuk, Kee et al. 2003, USA[208]	Prospective study	Mean 5.7 years	26	CH	50-100 PO	99	NA	NA	NA
Treluyer, Andre et al. 2004, France[195]	Prospective study	6months- 6years	19	CH	75 PR	83.3	NA	18.6	NA
Hijazi et al., 2005, KSA[196]	Prospective study	0-12 years	148	CH	100 PO	79	Y (31)	30	NA
Schmalfuss 2005, USA[209]	Prospective study	Mean 28.2 months	310	CH	65.2 PO	94	NA	30-60	NA

CH: Chloral hydrate, PO: Orally, N: No, NA: Not available.

Table 2.1.4: RCTs and observational studies for CT/MRI scan

Reference, country	Study design	Age	No. of patients	Drug	Dose mg/kg	Success rate (%)	Supplementary (No.)	Sedation (min)	
								Onset	Duration
Hubbard, Markowitz et al. 1992, USA[210]	Retrospective study	1 day- 18 years	524	CH	60-75 PO	98	Y (131)	20-30	NA
Manuli, Davies 1993, USA[183]	Retrospective study	1 months-14 years	88	CH	50-100 PO	80	NA	28	66
MEROLA et al. 1995, USA [211]	Retrospective study	1 months-17 years	131	CH	75 PO	NA	Y (3)	NA	NA
Mason, Sanborn et al. 2004, USA[127]	Retrospective study	6-365 days	331	CH	50 PO	98	N	NA	NA

CH: Chloral hydrate

2.1.3.3.2. MRI procedures

A total of 5484 children aged between birth and 15 years were treated within 13 studies. These children received a median dose of 75mg/kg of oral chloral hydrate. There were 1930 patients younger than five years, including 1475 (76%) infants younger than two years. 448 (8%) children required supplementary sedative drugs, only 18 (4%) were children less than two years. Sedation time of chloral hydrate was varied (5 to 240 minutes) while the duration of action ranged from 0 to 165 minutes. A higher total failure rate of 36% was recorded in patients >5 years old; it did not exceed 5% in children aged <5 years old (Table 2.1.5).

Table 2.1. 5: RCTs and observational studies for MRI

Reference, country	Study design	Age	No. of patients	Drug	Dose mg/kg	Success rate (%)	Supplementary (No.)	Sedation (min)	
								Onset	Duration
Marti-Bonmati, Ronchera-Oms et al. 1995, Spain[170]	Double-blind RCT	1.5 months-14 years	97 97	CH CH	70 PO 100 PO	64 87	Y (14) Y (6)	28 21	NA NA
Malviya, Voepel-Lewis et al. 2004, USA[172]	Single-blind RCT	2-12 years	35 35	CH PEN	75 PO 2 IV	97 81	Y (13) Y (3)	14-42	22-68
Sury and Fairweather 2006, UK[23]	Double-blind RCT	1- 6 years	50 48	CH TEM+ DRO	50-100 PO 1+0.25 PO	100 80	Y (14) Y (22)	29 35	NA NA
Greenberg, Faerber et al. 1993, USA[201]	Prospective study	1-11 years	300	CH	100 PO	91	Y (2)	NA	NA
Slovis, Parks et al. 1993, USA[202]	Prospective study	0- 8 years	794	CH	50-75 PO	96	Y (35)	NA	NA
Ronchera-Oms, Casillas et al. 1994, Spain[205]	Prospective study	1 month– 15 years	596	CH	64 PO	94	Y (129)	5-240	0-120
Marchi, Orru et al. 2004, Italy[217]	Prospective study	3 months-12 years	77	CH	60-80 PO	99	Y (1)	60	NA
Woodthorpe et al., 2007, UK [218]	Prospective study	0- 4years	455	CH	50- 100 PO	97	NA	20-40	45- 60

CH: Chloral hydrate, PEN= Pentobarbital, TEM+ DRO= Temazepam+ Droperidol

Table 2.1.5: RCTs and observational studies for MRI

Reference, country	Study design	Age	No. of patients	Drug	Dose mg/kg	Success rate (%)	Supplementary (No.)	Sedation (min)	
								Onset	Duration
Ronchera, Martí-Bonmatí et al. 1992, Spain[200]	Retrospective study	Mean 42 months	172	CH	55 PO	93	NA	30	NA
Beebe, Tran et al. 2000, USA[212]	Retrospective study	2 months-14 years	448	CH	80- 100 PO	97	NA	69	NA
Dalal, Murray et al. 2006, USA[213]	Retrospective study	16-341 days	102	CH	50-100 PO	96	Y (18)	NA	NA
Cortellazzi, Lamperti et al. 2007, Italy[198]	Retrospective study	Mean 30 months	888	CH	50-100 PO	NA	Y (216)	39.1	165
Litman et al., 2010, USA[125]	Retrospective study	0-1 years	1373	CH	50-75 PO	95	NA	NA	NA

CH: Chloral hydrate

2.1.3.3.3. CT scan

Six studies involving 766 children examined the effectiveness of chloral hydrate. 120 (16%) of those were under the age of five years. Chloral hydrate was given orally in most identified studies (median dose, 80 mg/kg).

Median success rate was 100% in children younger than five years old, while it was 97% in the studies that evaluated children aged from birth to 17 years. 64 (8%) patients needed median supplementary dose of either chloral hydrate or midazolam (50 mg/kg orally or 0.1 mg/kg intravenously) respectively in order to achieve therapeutic success.

Onset of action was variable between studies, ranging from 3 to 135 minutes. Duration of action was also highly variable, lasting from zero to 180 minutes (Table 2.1.6).

Table 2.1. 6: RCTs and observational studies for CT scan

Reference, country	Study design	Age	No. of patients	Drug	Dose mg/kg	Success rate (%)	Supplementary (No.)	Sedation (min)	
								Onset	Duration
Thompson et al. 1982, USA[178]	Single-blind RCT	0- 9 years	241 101	CH AMPS	80 PO 0.08 IM	85 88	Y (25) Y (10)	55 53	NA NA
McCarver-May et al. 1996, USA[177]	Single-blind randomised cross-over	Median 14 days*	7 7	CH M	75 PO 0.2 IV	100 43	N N	9- 40 3-15	15- 55 15- 55
Greenberg et al. 1991, USA[68]	Prospective study	Mean 2.18 years	295	CH	80-100 PO	99	Y (5)	NA	NA
Pereira et al. 1993, Canada[190]	Prospective study	0-17 years	110	CH	50-80 PO	97	Y (6)	5-135	0-150
Strain et al. 1986, USA[132]	Retrospective study	0-5 years	93	CH	35-75 PO	87	Y (16)	30-105	60- 120
Noske and Papadopoulos 1993, Germany[216]	Retrospective study	4 months- 4 years	20	CH	50-100 PR	100	Y (12)	30	60-180

AMPS Cocktail=Atropine 0.016 mg, Meperidine 1.0 mg, Promethazine 1.0 mg , Secobarbital 4.0 mg, CH= chloral hydrate, IM=intramuscular, M=midazolam, PO: Orally, PR: Per-rectal

* All children were term new-born infants

2.1.3.3.4. ECG

Six studies; five studies were performed in the USA and one in Thailand. 2272 children received a median dose of 75 mg/kg orally. There were 1867 children under five years. The onset of action ranged from 5 to 110 minutes and the duration of action ranged from 15 and 240 minutes. The success rate ranged from 89 to 97 % in children less than five years and it was 98% in children aged from three weeks to 14 years old. Supplementary dose(s) of chloral hydrate (25-50 mg/kg) were given to 25 children (Table 2.1.7).

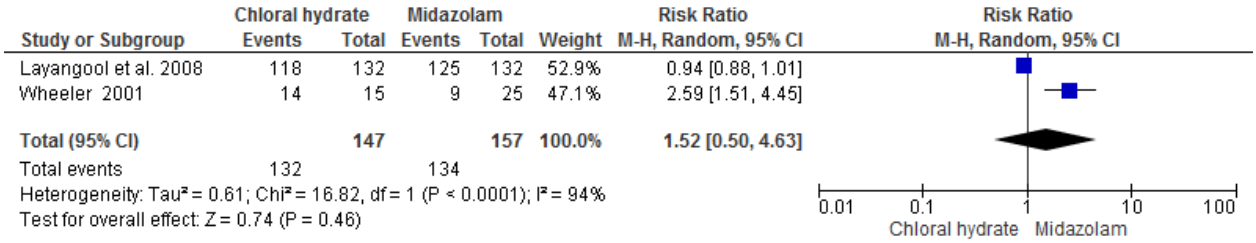
Table 2.1. 7: RCTs and observational studies for ECG

Reference, country	Study design	Age	No. of patients	Drug	Dose mg/kg	Success rate (%)	Supplementary dose/med (No.)	Sedation (min)	
								Onset	Onset
Wheeler et al. 2001, USA[175]	Single-blind RCT	1- 5 years	15 25	CH M	75 PO 0.5 PO	93 36	Y (5) Y (13)	mean 25 mean 27.3	mean 25.6 mean 21.69
Layangool et al. 2008, Thailand[173]	Double-blind RCT	6 months-5 years	132 132	CH M	50 PO 0.5 PO	89 95	Y (14) Y (7)	25.1 11.13	78.9 40.10
Lipshitz et al. 1992, USA[180]	Prospective study	0-36 months	140	CH	51-145 PO	94	Y (6)	5-105	NA
Napoli et al. 1996, USA[193]	Prospective study	3 weeks-14 years	405	CH	25-125 PO	98	NA	30-60	NA
Heistein et al. 2006, USA[182]	Prospective study	1 month-3 years	1095	CH	80 PO	NA	NA	30-50	NA
Roach et al. 2010, USA[185]	Retrospective study	2- 4 years	485	CH	75 PO	97	N	5-110	15-204

CH= chloral hydrate, M=midazolam, PO: Orally

Two RCTs compared chloral hydrate success rate with midazolam in children aged from 6 months to 5 years [173, 175] (figure 2.1.3). The relative risk of procedural success rate in the chloral hydrate group was not statistically different from those sedated with midazolam (RR 1.52, 95 % CI: 0.5 – 4.63, P=0.46).

Figure 2.1. 3: The success rate of chloral hydrate versus midazolam



2.1.3.3.5. EEG

Five studies involving 428 children were identified. The dose of chloral hydrate ranged between 50 and 100 mg/kg (median 68.5 mg/kg). The sedation success rate ranged from 50% to 100%. In the studies with the highest success rate, chloral hydrate was given at a higher median dose of 100 mg/kg versus 69 mg /kg in all others. The average induction time for sedation using chloral hydrate was from 10 to 150 minutes, while the average duration of sedation was between 15 and 240 minutes. 18 children required sedative supplementary dose(s). In the two randomised controlled trials chloral hydrate was compared with either triclofos or melatonin. The procedural success rate of chloral hydrate was compared with triclofos and it was higher, 88% and 84%. 100% success was seen with both chloral hydrate and melatonin but, a higher amount of supplementary sedation was seen with melatonin[174, 176] (Table 2.1.8).

Table 2.1. 8: RCTs and observational studies for EEG

Reference, country	Study design	Age	No. of patients	Drug	Dose mg/kg	Success rate (%)	Supplementary (No.)	Sedation (min)	
								Onset	Duration
Ashrafi et al. 2010, Iran[176]	Single-blind RCT	1-64 months	174 174	CH ME	50 PO 2-6 mg PO	100 100	Y (6) Y (20)	10-150 5-210	15-240 15-240
Milichap 1972, USA[174]	Double-blind RCT	4-14 years	34 37	CH TRI	100 PO 15/Ib PO	88 84	NA NA	mean 37.3	mean 37.3
Loewy et al. 2005, USA[181]	Prospective study	1month-5years	24	CH	60 PO	50	Y (12)	mean 32	mean 226
Thoresen et al.1997, Norway[186]	Prospective study	1.5-13.5 years	13	CH	55-77 PR	NA	NA	20-30min	mean 164.5
Wang et al. 2005, China[197]	Prospective study	1 months-12 years	183	CH	100 PO	100	NA	NA	NA

ME=Melatonin, TRI=Triclofos, CH: Chloral hydrate, PO: Orally, PR: Per-rectal

2.1.3.3.6. BAEP procedure

There was one prospective study conducted in Greece to evaluate the effectiveness of chloral hydrate in 1586 children aged from birth to 14 years[189]. The dose was 40 mg/kg. The success rate in infants aged six months or younger was 100% compared to 72% in children older than six months. The onset of sedation time ranged from 15 to 30 minutes and the duration required between 34 and 49 minutes.

2.1.3.3.7. Pulmonary function test

One prospective observational study was conducted in Australia to evaluate chloral hydrate effectiveness in ten infants aged from 7 to 33 weeks, mean, 17.4 weeks[203]. Chloral hydrate was given orally in a dose range of 70 to 100 mg/kg. The mean onset of action was 28 minutes; however the duration of action was ranged between 15 and 240 minutes. All diagnostic procedures were completed successfully.

- **In Summary**

Summing up the results of chloral hydrate effectiveness, Table (2.1.9) compares effectiveness in all painless diagnostic procedures.

Table 2.1. 9: Sedation success rates for all painless procedures

Type of painless procedures	Chloral hydrate dose (median dose mg/kg)	Success rate (median success %)
Pulmonary function test	70 to 100 mg/kg (85 mg/kg)	100%
CT	35 to 100 mg/kg (77.5 mg/kg)	84 to 100% (98%)
CT/MRI	25 to 100 mg/kg (64 mg/kg)	77 to 100% (98%)
MRI	50 to 100 mg/kg (75 mg/kg)	64 to 100% (96%)
Electrocardiogram (ECG)	25 to 100 mg/kg (75 mg/kg)	89 to 98 % (94%)
Electroencephalograph (EEG)	55 to 100 mg/kg (68.5 mg/kg)	50 to 100% (94%)
Brainstem auditory evoked potential (BAEP)	40 mg/kg	72 to 100% (86%)

2.1.3.4. Chloral hydrate safety

Fifty four studies explored the safety of chloral hydrate. The total number of children exposed to chloral hydrate was 14439, and there were 1,951 reported AEs. This gave an estimated risk of an AE as 13.5 in every 100 patients, or one AE in every seven children receiving chloral hydrate. The most frequently occurring AEs were hypoxia, vomiting, hyper activity, restlessness and motor imbalance (Table 2.1.10).

Table 2.1. 10: Reported AEs from 54 studies

Body system	AEs	Frequency	Incidence (%)(AEs cases/14439)
Respiratory system	Hypoxia	774	5.3
	Airway obstruction	39	0.3
	Respiratory depression	28	0.2
	Wheezing	1	0.01
	Respiratory arrest	1	0.01
	Apnoea	4	0.03
Central nervous system	Vomiting	430	2.9
	Hyperactivity	210	1.45
	Motor imbalance	93	0.64
	Emesis	52	0.36
	Restlessness	52	0.36
	Prolonged sedation	43	0.3
	Paradoxical reaction	38	0.26
	Ataxia	34	0.24
	Drowsiness	23	0.16
	Excessive sedation	23	0.16
	Nervousness	8	0.06
	Dizziness	8	0.06
	Mental confusion	8	0.06
	Seizure	3	0.02
Cardiovascular system	Bradycardia	16	0.11
	Agitation	10	0.07
	Hypotension	5	0.03
	Tachycardia	1	0.01
Others	Skin rash	14	0.1
	Cough	3	0.02
	Salivation	3	0.02
	Hiccup	2	0.01
	Abdominal pain	1	0.01
	Urticaria	1	0.01
	Not specified	23	0.16
Total		1,951	13.5

There were 847 reported respiratory complications which represent greater than 40% of all reported AEs. Hypoxia was the most common and accounted for more than 90% of all respiratory AEs. Four hundred and ninety three cases/14439 patients (3.4%) of hypoxia were mild (SpO2 90-95%), whereas 281 cases/14439 patients (1.9%) were moderate (SpO2 <90%) and one case/14439 patients (0.007%) was severe. There were no discontinuation of any painless procedures as a result of hypoxia, and all cases improved after administration of oxygen supplement. Other respiratory complications were: airway obstruction and respiratory depression, which were reported for 39/14439 patients (0.3%) and 28/14439 patients (0.2%) cases respectively. These complications were resolved by using simple manoeuvres, such as giving oxygen supplementation and airway opening. There were no medication related deaths reported, however, 16 children needed medical interventions due to chloral hydrate toxicity (Tables 2.1.12, 2.1.16,2.1.18, 2.1.19).

In this review, all studies that identified chloral hydrate AEs have been subdivided according to the type of diagnostic procedures. Eighteen studies evaluated the safety of chloral hydrate as a sedative drug for CT and/or MRI, 15 studies for MRI, 5 studies for CT, 6 ECG, 5 EEG, 3 BAEP, and 2 Pulmonary function test .

2.1.3.4.1. CT/MRI

18 studies involving patients who were administered chloral hydrate for CT and/or MRI were identified [46, 119, 120, 127, 171, 183, 184, 187, 191, 194, 196, 202, 206-209, 211, 214]. Data was not separated for each procedure, a total of 4249 children, aged from birth to 18 years. The dose of chloral hydrate was from 25 to 100 mg/kg, median 64 mg/kg. 405 AEs were documented. The overall estimated risk of AEs is 9.5 in 100 paediatric patients. There were no deaths due to chloral hydrate AEs, however, one infant with pulmonary stenosis and tricuspid atresia developed severe hypoxia

(SpO2< 85%) and required medical intervention, oxygen supplement and airway support[120].

There were no studies that specially evaluated chloral hydrate safety in children with developmental disabilities. Table (2.1.11) shows the frequency and incidence risk of AEs (%) children population of the most common AEs of chloral hydrate according to the age groups.

Table 2.1. 11: Most common reported AEs

AEs		Frequency number of AEs cases/total number of children exposed to chloral hydrate (incidence %)/Age groups-(number of children)			
		<2 years (354)	**<5 years (558)**	**Mixed (3337)**	**Total of AEs**
Hypoxia	**Mild**	10 (2.8)	30 (5.4)	18 (0.5)	58 (1.4%)
	Moderate	-	-	-	-
	Severe	-	1 (0.2)	-	1 (0.02%)
Vomiting		-	9 (1.6)	41 (1.2)	50 (1.2%)
Hypotension		4 (1.1)	4 (0.7)	-	8 (0.19%)
Hyperactivity		2 (0.6)	-	29 (0.9)	31 (0.73%)
Emesis		1 (0.3)	9 (1.6)	-	10 (0.24%)
Motor imbalance		-	-	84 (2.5)	84 (1.98%)
Paradoxical reaction		-	-	13 (0.4)	13 (0.31%)

4 patients developed severe AEs. One prospective study reported one case of severe hypoxia that developed following administration of 50mg/kg chloral hydrate and resolved by oxygen therapy and changing head position[120].

One case series reported one case of overdose and two cases of accidental intravenous administration[220]. Ingestion of 219 mg/kg of chloral hydrate resulted in lethargy and transient bigeminy in a child aged 3 years old whereas, IV administration

of chloral hydrate in two children aged 15 months and 3 years old resulted in CNS AEs and local effects in the site of injection (Table 2.1.12).

Table 2.1. 12: Chloral hydrate serious AEs for CT/MRI

Reference, country	Patient age	Dose of CH	AEs	Treatment	Hospital stay/ days
Vade, Sukhani et al. 1995[120]	<1 year	50 mg/kg	Severe hypoxia	Oxygen therapy, Head repositioning manipulation	NA
Sing et al. 1996, USA[220]	3 years	219 mg/kg PO	Lethargy, Transient bigeminy	Intubation, O2 therapy	Y (2 days)
	15 months	88 mg/kg IV*	Cyanosis, Skin sloughing at the site of injection	O2 therapy	Y (2 days)
	3 years	39 mg/kg IV*	Lethargy, Skin sloughing at the site of injection	O2 therapy	Y (>2 days)

*Medication errors

2.1.3.4.2. MRI

15 studies involving 5034 children reported AEs of chloral hydrate for MRI, patients range from birth to 15 years (mean 34 months) [23, 125, 170, 172, 179, 192, 198, 200, 201, 205, 212, 213, 215, 217, 218]. A median oral chloral hydrate dose of 100 mg/kg was administered and 810 AEs were reported. The estimated risk of AEs is 16.1 in 100 children.

In one case report study by Rowert et al. (1997) a 9 days old infant developed apnoea immediately after receiving oral doses of chloral hydrate (70 mg/kg) [221]. This led to the stopping of the MRI. Table (2.1.13) illustrates the frequency and incidence risk of AEs per 100 children population of the most common AEs of chloral hydrate according to the age groups.

Table 2.1. 13: Most common reported AEs

AEs		Frequency number of AEs cases/total number of children exposed to chloral hydrate (incidence %)/Age groups-(number of children)			
		<2 years (1475)	<5 years (1490)	Mixed* (2069)	Total of AEs
Hypoxia	**Mild**	35 (2.4)	29 (1.9)	270 (13)	334 (6.6%)
	Moderate	273 (18.5)	-	-	273 (5.4%)
	Severe	-	-	-	-
Bradycardia		3 (0.2)	-	-	3 (0.06%)
Airway obstruction		2 (0.1)	19 (1.3)	21 (1.0)	42 (0.8%)
Vomiting		2 (0.1)	24 (1.6)	68 (3.3)	94 (1.9%)
Hypotension		1 (0.07)	-	-	1 (0.02%)
Tachycardia		1 (0.07)	-	-	1 (0.02%)
Drowsiness		-	15 (1.0)	-	15 (0.3%)
Hyperactivity		-	-	15 (0.7)	15 (0.3%)
Motor imbalance		-	-	9 (0.4)	9 (0.18)
Ataxia		-	-	8 (0.4)	8 (0.16%)
Dizziness		-	-	3 (0.1)	3 (0.06%)

There were 892 children (1 to 10 years old) with developmental disabilities and they experienced 74 AEs/892 patients (8.3% children). These included; hypoxia 33/892 patients (3.7%), airway obstruction 21/892 patients (2.4%), ataxia 8/892 patients (0.9%), hyperactivity 7/892 patients (0.8%), dizziness 3/892 patients (0.3%) and vomiting 2/892 patients (0.2%) children.

Two studies reported 273 children experiencing moderate hypoxia, oxygen saturation (SpO2) level of <90% [125, 198]. Chloral hydrate was given orally during these studies in doses ranging from 50-100 mg/kg (median 63 mg/kg). The median age of the children with moderate hypoxia was 18 months or less (it was not possible to calculate the median exactly as individual ages were not given). There was no discontinuation of any MRI procedures as a result of moderate hypoxia. 269 of the 273 cases of moderate hypoxia responded to supplemental oxygen therapy. For the remaining 4 children the authors did not mention the medical interventions which were given (Table 2.1.14).

Table 2.1. 14: Summary of the 273 children who developed moderate hypoxia

References	**Study design**	**No. of pt. receiving chloral hydrate**	**No. of pt. with moderate hypoxia**	**Age***	**Drug** (doses)	**Monitoring device(s) and intervention(s)**
Cortellazzi, Lamperti et al. 2007, Italy[198]	Retrospective study	888	4	Mean 30 months	50-100 PO	▪ Continuously monitored of SpO2 and P_ECO2 ▪ Not mentioned
Litman et al, USA [125]	Retrospective study	1373	269	0-1 years, mean 5 months	50-75 PO	▪ Pulse Oximetry ▪ Supplemental oxygen therapy

* Individual data about the age of each patient was not given

2.1.3.4.3. CT scan

Five studies looked at the safety of chloral hydrate during CT [68, 177, 190, 216, 219]. These involved 785 children from birth to 17 years old, mean age 18 months. 27 AEs with an overall estimated risk of 3.4 in 100 patients were reported. Vomiting accounted for the majority of the total events (14 cases/785 patients representing incidence of 1.8%). Other common AEs were moderate hypoxia (8 cases/785 patients, 1%) and hyper activity (5 cases/785 patients, 0.6%) children. There were 20 children under the age of two years, 12 of them experienced AEs with hypoxia the most common AEs in this age group, with 5 cases/20 patients (25%) reported. Other AEs include; vomiting 4 cases/20 patients (20%) and hyper activity 3 cases/20 patients (15%) children. The median dose was 80 mg/kg. All doses were given orally except in one instance when it was administered rectally. The effect of chloral hydrate in children with developmental disabilities was not assessed in any studies.

Two studies reported 8 children experiencing moderate hypoxia [177, 190]. Chloral hydrate was given orally in doses ranging from 50-100 mg/kg (median 80 mg/kg). The mean age of the children with moderate hypoxia was 13 months. This is similar to the mean age of children in all the studies, which was 18 months or less (Table 2.1.15).

Table 2.1. 15: Summary of the 8 children who developed moderate hypoxia

References	**Study design**	**No. of pt. receiving chloral hydrate**	**No. of pt. with moderate hypoxia**	**Age**	**Drug** (doses)	**Monitoring device(s) and intervention(s)**
Pereira et al. 1993[190]	Prospective study	110	4	0.1-6 years, mean 1.1 years*	50-80 mg/kg PO	▪ Pulse Oximetry ▪ Supplemental oxygen therapy ▪ Changing in the position of the neck ▪ Suctioning of the oral secretion
McCarver-May et al., 1996[177]	Double blind Cross-over design	7	4	Median 14 days *	75 mg/kg PO	▪ Continuously monitored of hemoglobin oxygen saturation ▪ Supplemental oxygen therapy ▪ Administration of albuterol nebulization (in one patient)

* Individual data about the age of each patient was not given

Seven children developed serious AEs. These children had an age range from 28 days to 66 months (median, 13 months). The dose of chloral hydrate given ranged between 10 and 667mg/kg. In 2 cases, toxicities were due to medication errors (Table 2.1.16).

Table 2.1. 16: Chloral hydrate serious AEs for CT scan

Reference, country	Patient age	Dose of CH	AEs	Treatment	Hospital stay/ days
Farber 1985, Israel[222]	18 months	100mg/kg	Severe dyspnea, Tachycardia, Tachypnea severe, Severe laryngeal Oedema, Respiratory acidosis	Hydrocortisone (IV), Racemic adrenalin (INH)	N
Abel 1987, Germany[223]	40 weeks	10 mg/kg	Respiratory arrest	Immediate resuscitation, O2 therapy	NA
Greengerg and Faerber 1990, USA[224]	13 months	100mg/kg	Respiratory failure, severe hypoxia, respiratory acidosis, hypercapnia	Intubation, O2 therapy	NA
	66 months	100 mg/kg	Respiratory failure	Intubation, O2 therapy	Y (>2 days)
Kirimi et al. 2002, Turkey[225]	28 days	250 mg/kg*	Respiratory distress, Excessive salivation, Respiratory depression, Severe hypoxia	IV fluid O2 therapy	Y (>1 day)
Andereola et al.2006, Italy [226]	16 months	75 mg/kg	Cyanosis, Excessive salivation Generalized clonic seizures, Respiratory depression, Severe hypoxia	Intubation, O2 therapy, Lorazepam 0.05 mg/kg IV, Thiopental 3.5 mg/kg	Y (5 days)
Dogan-Duyar et al. 2009, Belgium[227]	3 months	667 mg/kg*	Tachycardia, Dyspnea,	Intubation, O2 therapy, IV fluid	Y (>7days)

*Medication errors, Inh=Inhalation, IV= Intravenous

A summary of the most common AEs associated with chloral hydrate PS for CT, MRI and CT and/or MRI is shown in the following table.

Table 2.1. 17: Summary of CT/MRI AEs

Body system	AEs	Frequency number of AEs cases/total number of children exposed to chloral hydrate (incidence %) / painless procedure		
		CT	MRI	CT/MRI
Respiratory system	Hypoxia	8 (1.0%)	607 (12.1%)	59 (1.39%)
	Airway obstruction		42 (0.8%)	
Central nervous system	Vomiting	14 (1.8%)	94 (1.9%)	50 (1.2%)
	Hyperactivity	5 (0.6%)	15 (0.3%)	31 (0.73%)
	Drowsiness		15 (0.3%)	
	Motor imbalance		9 (0.18)	84 (1.98%)
	Paradoxical reaction			13 (0.31%)
	Emesis			10 (0.24%)
	Ataxia		8 (0.16%)	
	Dizziness		3 (0.06%)	
Cardiovascular system	Bradycardia		3 (0.06%)	
	Hypotension		1 (0.02%)	8 (0.19%)
	Tachycardia		1 (0.02%)	

2.1.3.4.4. ECG

Six studies were found [173, 175, 180, 182, 185, 193]. The total number of children was 2272, aged from birth to 14 years old. All studies stated that chloral hydrate was given orally, with median dose of 75 mg/kg.

There were 302 documented AEs/2272 patients (13.3% of patients). The most frequent was hypoxia in 98 cases/2272 patients (4.3%), followed by vomiting 55 cases/2272 patients (2.4%), emesis 41 cases/2272 patients (1.8%), prolonged sedation 36 cases/2272 patients (1.6%), paradoxical reaction 25 cases/2272 patients (1.1%), and ataxia 24 cases/2272 patients (1.1%).

2.1.3.4.5. EEG

Five studies were published from 1972 to 2010 [174, 176, 181, 186, 197]. These studies reported on 428 patients aged from one month to 14 years. The studies were conducted in China, Iran, Israel, Norway and the USA. Chloral hydrate dose ranged from 55 to 100 mg/kg, median 80 mg/kg. All doses were given orally except in one administered rectally. Only two patients (out of a total of 428 children) experienced six (1.4%) mild to moderate AEs. They were both less than 5 years old. Ataxia and dizziness was seen in both patients (2 cases/428 patients, 0.4%) and cough and urticarial rash in one each. There were no discontinuations of EEG due to AEs. The Chloral hydrate median dose was 80 mg/kg.

One case report detailed two children who developed a cough and urticaria of the whole body 30 minutes after receiving 500mg of chloral hydrate rectally [228] (Table 2.1.18).

Table 2.1. 18: Chloral hydrate serious AEs for EEG

Reference, country	Patient age	Dose of CH	AEs	Treatment	Hospital stay/ days
Yamada et al. 2002, Japan[228]	2 years	500 mg PR	Cough, Urticaria	Hydroxyzine, Hydrocortisone	NA
	4 years	500 mg PR	Cough, Urticaria	β2 stimulant Inh.	NA

2.1.3.4.6. BAEP

Chloral hydrate safety was evaluated by three prospective observational studies including 1646 children [188, 189, 199]. The dose of chloral hydrate ranged from 30 to 40 mg/kg, median 40 mg/kg. There were 396 AEs/1646 patients (24% children) Vomiting was the most common 217 cases/1646 patients (13.2%). The second was hyper activity 152 cases/1646 patients (9.2%), followed by bradycardia 13 cases/1646 patients (0.8%), skin rash 10 cases/1646 patients (0.6%) and apnoea 4 cases/1646 patients (0.2%) children. All AEs were mild and self-resolved.

There was only one prospective study which identified chloral hydrate safety in 26 children with age younger than two years (mean 33.1 weeks)[188]. The only AE reported was bradycardia in which occurred in 13 of the 26 children (50%).

2.1.3.4.7. Pulmonary function test

Two studies evaluated chloral hydrate toxicity in 25 infants (< 2 years)[203, 204]. Chloral hydrate dose was ranged from 50 to 100 mg/kg, median 70 mg/kg. There were two AEs which developed in two infants, both of which were mild hypoxia, 2 cases/25 patients (8.0%).

A Case report described two male infants aged 20 months and 24 months who were given oral chloral hydrate for lung function test in doses of 80 mg/kg[229]. Subsequently, one infant developed severe obstructive apnoea, while the other developed severe hypoxia. Both of them required medical interventions and hospitalisation (Table 2.1.19).

Table 2.1. 19: Chloral hydrate serious AEs for pulmonary function test

Reference, country	Patient age	Dose of CH	AEs	Treatment	Hospital stay/ days
Biban et al. 1993, Italy[229]	20 months	80mg/kg PO	Severe obstructive apnoea, Severe hypoxia	Intubation , O2 therapy	Y (>3 days)
	24 months	80mg/kg PO	Severe obstructive apnea, Severe hypoxia	O2 therapy	Y (NA)

Summary of chloral hydrate AES has been shown in table (2.1.20).

Table 2.1. 20: Summary of all Reported AEs

Type of painless procedures	Chloral hydrate dose (median dose mg/kg)	Frequency (incidence %)
Brainstem auditory evoked potential (BAEP)	30 to 40 mg/kg (40 mg/kg)	396 AEs/1646 patients (24)
MRI	50 to 100 mg/kg (100 mg/kg)	810 AEs/5034 patients (16.1)
Electrocardiogram (ECG)	25 to 100 mg/kg (75 mg/kg)	302 AEs/2272 patients (13.3)
CT/MRI	50 to 100 mg/kg (64 mg/kg)	405 AEs/4249 patients (9.5)
Pulmonary function test	50 to 100 mg/kg (70 mg/kg)	2 AEs/25 patients (8)
CT	50 to 100 mg/kg (80 mg/kg)	27 AEs/785 patients (3.4)
Electroencephalograph (EEG)	55 to 100 mg/kg (80 mg/kg)	6 AEs/428 patients (1.4)

2.1.4. Discussion

The systematic literature review in this study focused on the safety and effectiveness of chloral hydrate for painless PS in paediatric patients.

This review showed a variable rate of success across various procedures, ranging between 50% and 100%. The success rate for CT scanning and pulmonary function test was higher than for MRI and ECG (Table 2.1.17). Some studies reported a 100% success rate for pulmonary function test and CT scanning (median 98%) The success rate for MRI was from 64 to 100% (median 96%). This finding was consistent with studies results of Vade et al. (1995) and Mallol et al. (1988) which reported higher sedation success for CT and pulmonary testing than MRI[120, 203]. In the current review, the median dose of chloral hydrate for MRI (75mg/kg) was higher than for (BAEP; 40 mg/kg). This may be because MRI procedures are usually longer, very noisy and need complete sedation for the child to remain still enough. This systematic review corroborated previous studies in which the patients required higher doses of chloral hydrate for MRI procedures than for CT [120, 201].

The success rate for sedation in painless diagnostic procedures can be increased by supplemental dose(s) of other sedatives, such as midazolam (0.05 mg/kg intravenous) or by an additional dose of chloral hydrate (25 mg/kg oral)[213, 217]. The current review showed that supplemental sedative drug(s) were required more during MRI (8%) than they were for a CT scan (4%). Similarly, Kao et al. (1999) reported that an additional dose of chloral hydrate increased the success rate of the procedure from 89% to 98%[187].

The induction time of sedation was highly variable between procedures and ranging between 3 and 240 minutes. The duration of procedural sedation was also highly variable; the shortest was 10 minutes, and the longest was 240 minutes. This may be

due to the longer half-life of chloral hydrate, which may lead to an unpredictably long recovery time[179, 201].

With regard to the safety of chloral hydrate, this review demonstrated a high rate of AEs during BAEP 396 AEs/1646 patients (24%) followed by, MRI 810 AEs/5034 patients (16.1%) and ECG 302 AEs/2272 patients (13.3%) (Table 2.1.20). This could be because these painless diagnostic procedures require a longer period and this may lead to administration of high chloral hydrate dose[170]. The higher median chloral hydrate dose of 100mg/kg for MRI compared with 80mg/kg for CT scan supports this reason. It may also be explained by the use of supplemental sedative dose (s) during the procedure. Treluyer et al. (2004) described a better safety profile of chloral hydrate for CT scanning when compared to MRI[195]. In addition, the variable rate of AEs may be explained by the use of supplemental sedatives during the procedure. Vade et al. (1995) recorded no failure of treatment in children aged 1 to 4 years who received chloral hydrate in combination with hydroxyzine, but reported a 3% failure rate in infants aged less than 1 year who were not given supplementary sedation [120].

This systematic review confirmed that the most common AEs attributed to chloral hydrate were vomiting and respiratory complications. The types of AEs were similar, irrespective of the type of painless diagnostic procedure. Hypoxia was the most commonly reported AE in paediatric patients undergoing sedation prior to painless diagnostic procedures (774 cases/14439 patients, 5.3%), but in most cases (493 cases / 774 cases, 64%), it was mild and self-limiting.

The current review noted 16 serious AEs that required medical intervention and hospitalisation; most of them were respiratory complications [120, 220, 226-228].

This review showed that the incidence of hypoxia was high in infants younger than two years (2 cases/ 25 patients, 8%). This result corresponds with those obtained in various other studies. Litman et al. (2010) reported that the risk of hypoxia was directly associated with younger age and tended to be higher in infants with mean age 58.7 days (3.1%) than infants with mean age 152 days (1.7%) ($p<0.0001$)[125]. In a study of paediatric patients undergoing CT and MRI imaging, Malviya et al. (1997) found that infants younger than 12 months of age had more respiratory AEs (mainly hypoxia) than children aged from 25 months to 12 years ($p<0.0001$)[46].

The literature review for this study found few studies that evaluated the safety of chloral hydrate sedation specifically for paediatric patients with developmental disabilities. The incidence of AEs in children with developmental disabilities (74 AEs/892 patients, 8.3%) in this systematic review was comparable with the 7.6% reported by Cortelazzi et al. (2007)[198]. This may have been due to the difficulty of sedating children who were hyperactive or displayed exaggerated reactions to unusual environments[230, 231]. Consequently, they may have required supplemental sedation or a higher dose than typically developing children[231].

This review indicated that children with developmental disabilities are more likely to develop hypoxia than others, 3.7% (33 cases/892 patients) versus 1.7% (70 cases/4142 patients) in children without developmental disabilities older than two years old. Kannikeswaran et al. (2009) found that children with developmental disabilities were 3.2 times more likely to develop hypoxia than children without developmental disabilities were ($P < 0.01$)[231]

Vomiting was the second most frequently reported AE in this review, with a risk of 2.9% (430 cases/14439 patients) across all painless procedures. Vomiting often leads

to complications such as aspiration pneumonia during PS [232]. The emetic effect of sedatives, especially opioids, is well-recognised[112].

Vomiting may occur due to the unpleasant taste of chloral hydrate. Children may refuse to swallow the drug, while some that swallow it do not retain[127, 170].

Fasting before PS reduces the incidence of vomiting[233]. Antiemetic drugs such as metoclopramide and ondansetron can mitigate the problem[232]. Most of the vomiting noted in this review was not severe and did not warrant medical intervention.

2.1.5. Limitations

Our systematic review was limited by the number of clinical studies. The relatively small number of studies of each procedure may limit the generalisability of the results. Similarly, the comparisons between patients with BAEP, CT and pulmonary test sedation and those with EEG, ECG and MRI sedation may be inadequate because of the relatively small number of studies and patients. Additionally, studies that were determined to have poor quality were not excluded from this systematic review, which may have introduced bias.

The difficulty of calculating the safety data was compounded by the heterogeneous reporting styles of the authors. Many did not use standard definitions of AEs and the effectiveness of chloral hydrate. Follow-up was generally poor; only a few studies included post-discharge data. Hence, it may be difficult to know how the patients reacted to the drugs after they left the hospital. Information on events after discharge would have enriched this systematic review.

2.1.6. Conclusions

Chloral hydrate has been used extensively as a sedative for painless diagnostic procedures. It is effective as a sedative agent for painless diagnostic procedures with success rates up to 100%, particularly in shorter procedures such as CT scanning. Hypoxia is a significant problem with chloral hydrate use. Monitoring children during sedation, especially infants, is important, and a practitioner who is confident in resuscitation should conduct the sedation.

Part 2.2. Chloral Hydrate for Painful Procedural Sedation

2.2.1. Introduction

Painful procedures, such as some forms of dental procedures, can make children anxious. For many children, procedures that are essential for diagnosis and treatment are worse than the disease itself [234]. Additionally, the memory of an unpleasant or painful event may cause negative behaviour towards future procedures [234]. Therefore, children undergoing painful procedures need sedation to reduce anxiety, control pain and decrease movement. The NICE guidelines recommend midazolam or nitrous oxide for painful procedures [80]. However, chloral hydrate is frequently used around the world as an oral sedative for painful procedures in paediatric patients [78]. Several studies have investigated the effectiveness and safety of chloral hydrate for these procedures [235]. In part 2.1 of this chapter, a systematic literature review showed chloral hydrate to be effective and relatively safe for children undergoing painless procedures. In this part, the effectiveness and safety are assessed for painful procedures.

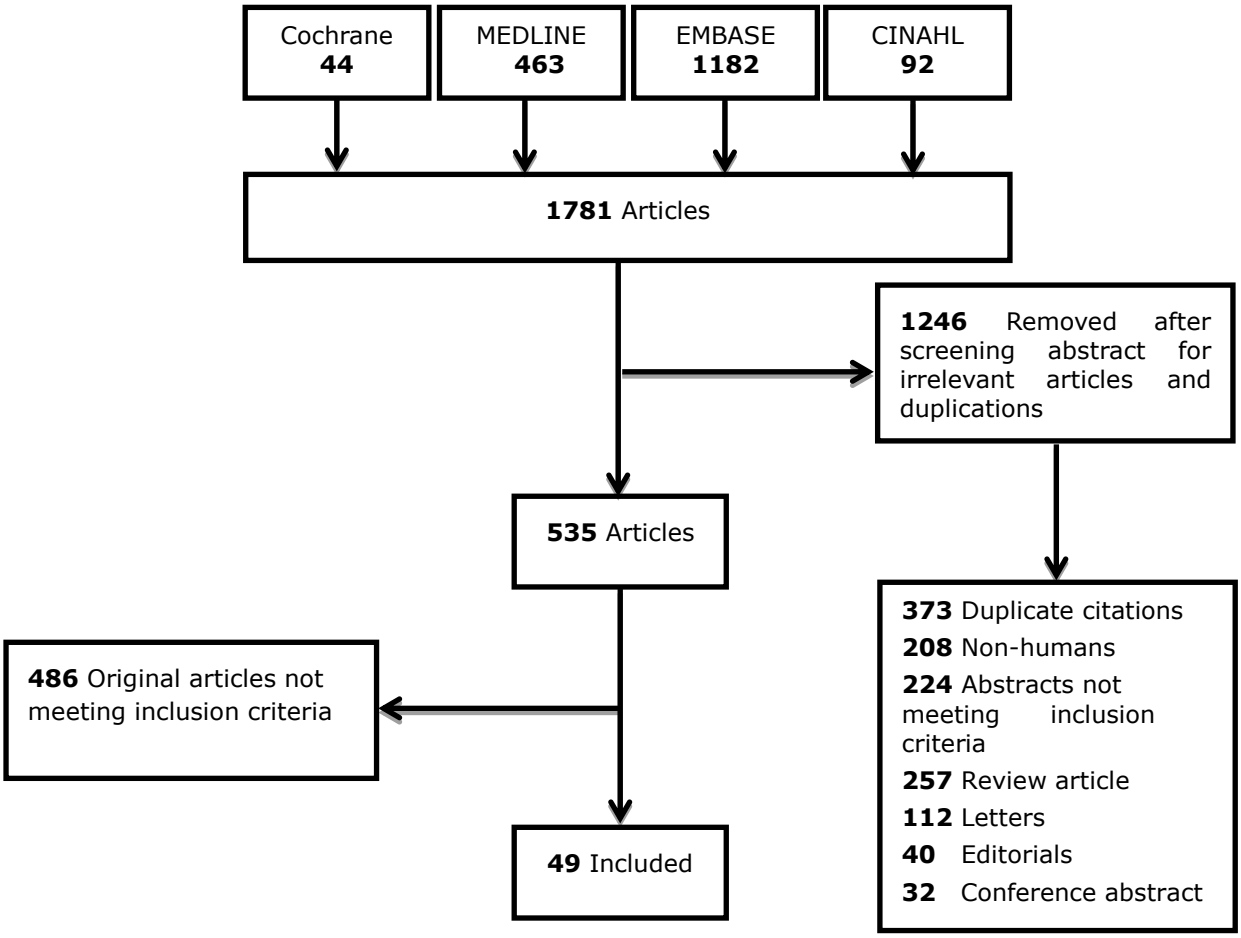
2.2.2. Methods

This was identical to the systematic literature review described in part 1 of this chapter.

2.2.3. Results

1781 related abstracts were found. After screening the abstract for irrelevant articles and duplications, 535 articles were identified. The full texts of these articles were read carefully and 49 studies that met the inclusion criteria were included (Figure 2.2.1). These studies were divided according to the type of painful procedures into six categories. Accordingly, the results will be explored based on type of procedure.

Figure 2.2. 1: Flow diagram of search and review process.



2.2.3.1. Characteristics of the studies

There were 26 RCTs and 17 prospective observational studies (Table 2.2.1). The largest number of children were involved in prospective studies (853 children), followed by 677 children in RCTs. Twenty nine (59%) of the studies involved children aged up to five years old (Table 2.2.1). Studies were conducted in twelve different countries; 33 in the USA, three in Brazil, two in each Mexico, the UK and Turkey, and one in each of Australia, Canada, Ceylon, Chile, Finland, Singapore, and Taiwan.

Chloral hydrate was only administered via the oral route. The dose ranged from 25 to 100 mg/kg

Table 2.2. 1: Summary of 49 studies that reported on clinical effectiveness and safety of chloral hydrate in paediatrics

Characteristics of studies	Number of studies	Number of children
Type of study	**N=49**	**N=1789**
• Randomised controlled trial	26	677
• Prospective observational study	17	853
• Retrospective	3	253
• Case report	3	6
Type of procedure		
• Dental procedures	34	957
• Minor surgery and sleep induction	8	323
• Ophthalmic examination	4	373
• MCUG	1	18
• Nasofibroscopy test	1	100
• SCE (Blood taking)	1	18
Route of Administration		
• Oral	49	1789
Age groups		
• Preterm neonates	0	0
• Term neonates	0	0
• Infants	5	32
• Children	29	1267
Other patient age groups*	15	490

* Studies involving multiple age groups (the number of patients within each age group was not documented). MCUG=Micturating cystourethrogram imaging procedure, SCE= Sister chromatid assay

2.2.3.2. Trial quality

The scores for the Jadad scoring checklist for quality assessment of the RCTs are shown in figure 2.2.2. Fifteen of the 26 RCTS scored ≥3 and so were considered to be of high methodical quality. Level of agreement was calculated and there was a substantial agreement between the two blinded assessors (0.93) [236]. The scores for the STROBE checklist for observational studies are illustrated in Table (2.2.2). Fifteen of the eleven pooled observational studies were rated with above 70%. All studies were included in the systematic review to avoid missing any data from these articles due to the small number of articles related to each painless procedure. The quality scoring and selection of papers and abstracts was checked by two independent reviewers (BS and HS).

Figure 2.2. 2: Quality assessment criteria of included RCTs

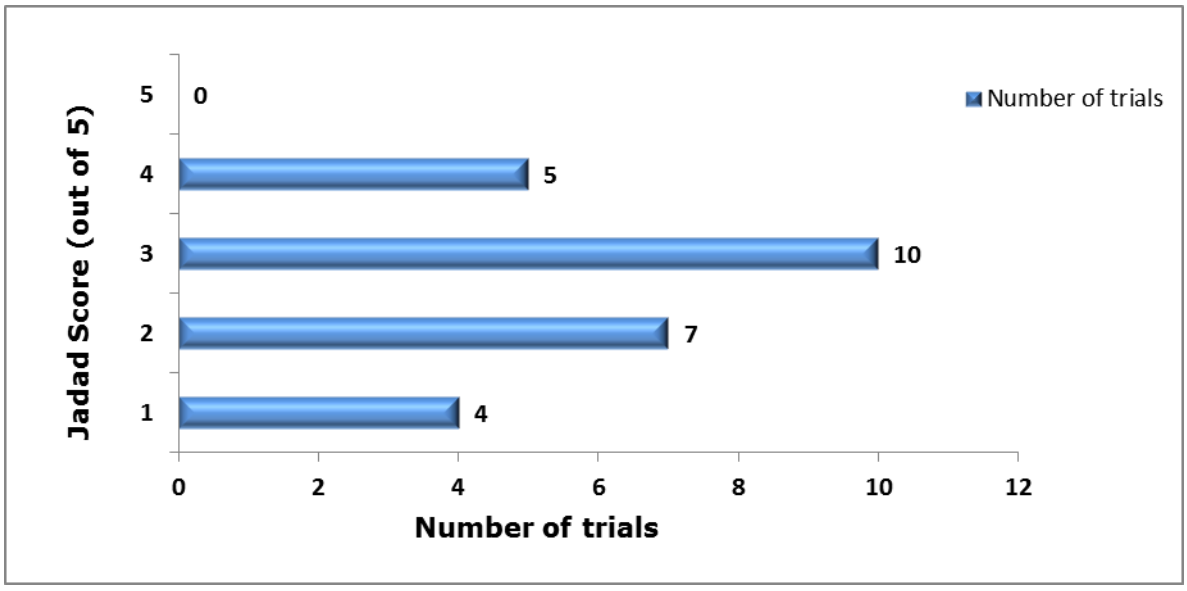


Table 2.2. 2: Quality assessment criteria of included observational studies

References	STROBE scoring (out of 34)	%
Needleman et al. 1995[237]	20	91%
Costa et al. 2012[238]	20	91%
Castro et al. 1994[239]	18	82%
Fishbaugh et al. 1997[240]	18	82%
Patrocínio et al. 2001[241]	18	82%
Ikbal et al. 2004[242]	18	82%
Nathan and West 1987[243]	17	77%
Fox et al. 1989[244]	17	77%
Lopez et al. 1995[245]	17	77%
Ong et al. 1996[246]	17	77%
Litman et al. 1998[247]	17	77%
Chowdhury and Vargas et al. 2005[235]	17	77%
Iwasaki et al. 1989[248]	16	73%
Binder and Leake 1991[249]	16	73%
Sams et al. 1991[250]	16	73%
Wright et al. 1986[251]	15	68%
Jaafar and Kazi 1992[252]	15	68%
Duncan et al. 1994[253]	15	68%
Campbell et al. 1998[254]	13	59%
Mueller et al. 1985[255]	13	59%

2.2.3.3. Chloral hydrate Effectiveness

34 articles evaluated the clinical effectiveness of chloral hydrate (22 for dental procedures, 6 for Minor surgery and sleep induction, 3 for ophthalmic examination, and 1 for each MCUG, Nasofibroscopy test, and SCE). The study results will be further described according to these categories.

2.2.3.3.1. Dental procedure

22 studies (14 RCTs, 5 prospective studies, and 3 retrospective studies) evaluated chloral hydrate effectiveness during dental procedures (Table 2.2.3). These studies included 704 children with ages that ranged from 1 to 17 years. Chloral hydrate was given in most studies in combination with other sedative and analgesic agents including: hydroxyzine, meperidine, nitrous oxide and promethazine and acetaminophen. Chloral hydrate was given via the oral route in all studies. Total doses of chloral hydrate ranged between 20 mg/kg and 75 mg/kg, median 75 mg/kg max. 2gm.

The induction time was varied and it was ranged from 30 to 60 minutes. The success rate of dental procedures was highly varied between studies. It was 100% in some studies [126, 240, 254, 256-260], while it ranged from 40% to 53% in others[258, 261]. There were 29 (4%) patients that required supplemental dose(s) of sedation.

There were 521 children younger than five years who received chloral hydrate in an oral dose ranging between 25 to 75 mg/kg. The success rate, in this group of children, varied between 53% and 100%.

Table 2.2. 3: RCTs and observational studies for dental procedures

Reference, country	Study design	Age	No. of patients	Drug	Dose mg/kg	Success rate (%)	Supplementary dose/med (No.)	Sedation (min)	
								Onset	Duration
Barr et al. 1977, USA[259]	Double-blind RCT	1- 17 years	21 21	CH P	40 PO	100 100	NA NA	30 NA	NA NA
Moore et al. 1984, USA[260]	Double-blind RCT	2- 5 years	45 15	CH P	20,40,60 PO	100 100	N N	NA NA	NA NA
Houpt et al. 1989, USA[262]	Double-blind RCT	19- 41 months	19 19	CH P	50 PO	84 63	NA	45 NA	NA NA
Houpt et al. 1984, USA[258]	Single-blind RCT	21- 46 months	17 17	CH CH	50 PO 75 PO	53 84	Y (17) N	45 45	NA NA
Houpt et al. 1985, USA[263]	Double-blind RCT	15- 45 months	21 21	CH CH+PRO	50 PO 50 PO+ 25 PO	72 89	NA NA	45 45	NA NA
Moody et al. 1985, USA[261]	Single-blind RCT	27-74 months	10 10 10	CH CH CH+HYD	50 PO 50 PR 30 PO+ 25 PO	40 70 70	NA	NA	NA
Badalaty et al. 1990, USA[264]	Double-blind RCT	20- 48 months	30 30	CH D	50 PO 0.3, 0.6 PO	60 73, 93	N N	45 >45	NA NA

CH=Chloral hydrate, D=Diazepam, HYD=Hydroxyzine, P=Placebo, PRO=Promethazine.

Table 2.2.3: RCTs and observational studies for dental procedures

Reference, country	Study design	Age	No. of patients	Drug	Dose mg/kg	Success rate (%)	Supplementary dose/med (No.)	Sedation (min)	
								Onset	Duration
Meyer et al. 1990, USA[126]	Single-blind RCT	21- 74 months	20 20	CH TR	40 PO 0.02 PO	100 100	NA NA	30 NA	NA NA
Tsinidou et al. 1992, UK[265]	Double-blind RCT	20- 60 months	20 20	CH+HYD TEM	50+25 PO 0.3 PO	70 65	N N	NA NA	NA NA
Sams et al. 1993, USA[266]	Double-blind RCT	18- 48 months	13 11	CH+PRO MEP+PRO	50+1 PO 1+1 PO	100 100	NA NA	NA NA	NA NA
Haas et al. 1996, Canada[257]	Double-blind RCT	3.6- 10.8 years	23 23	CH M	50 PO 0.6 PO	100 100	NA NA	NA NA	NA NA
Reeves et al. 1996, USA[267]	Double-blind RCT	27- 73 months	20 20	CH+HYD M+ACE	50+25 PO 0.5+10 PO	100 95	N N	NA NA	NA NA
Avalos-Arenas et al. 1998, Mexico[256]	Double-blind RCT	Mean age Gp1 27.7 months Gp2 29.2 months	20 20	CH+P CH+HYD	70 PO 70+2 PO	100 100	NA NA	60 45	Mean 78 Mean 70
Dallman et al. 2001, USA[268]	Double-blind RCT	26- 58 months	31 31	CH+PRO M	62.5+12.5 PO 0.2 PO	71 68	NA NA	NA NA	NA NA

ACE=Acetaminophen, MEP=Meperidine, P=Placebo, TR= Triazolam, PRO=Promethazine, HYD=Hydroxyzine, TEM:Temazepam, M:Midazolam

Table 2.2.3: RCTs observational studies for dental procedures

Reference, country	Study design	Age	No. of patients	Drug	Dose mg/kg	Success rate (%)	Supplementary dose/med (No.)	Sedation (min)	
								Onset	Duration
Litman et al. 1998, USA[247]	Prospective study	1-9 years	32 32 32	CH CH+N2O CH+ N2O	70 PO 70+30% 70+50%	82 98 98	Y (8) Y (2) Y (2)	NA NA	NA NA
Duncan et al. 1994, USA[253]	Prospective study	13-50 months	50	CH	75 PO	85	N	30-45	NA
Fishbaugh et al. 1997, USA[240]	Prospective study	22- 48 months	30	CH	50 PO	100	NA	NA NA	NA NA
Nathan, West 1987, USA[243]	Prospective study	18- 60 months	44 90	CH+HYD CH+HYD+MEP	50-70+25 PO 50-70+25+20-30 PO	31 76	NA NA	NA NA	NA NA
Campbell et al. 1998, USA[254]	Prospective study	3-5 years	5 5 5	CH K K	50 PO 2 IM 3 IM	100 100 100	NA Y (3) Y (5)	43.8 16.6 15.2	NA NA NA
Needleman et al. 1995, USA[237]	Retrospective study	mean 2.6 years	113 296	CH CH+HYD	55 PO 55+1 PO	72 75	NA NA	Mean 66.6 Mean 66.6	NA NA
Sams et al. 1991, USA[250]	Retrospective study	20- 20 months	71 41	CH+PRO MEP	53.3 +1 PO 1+1 PO	66 54	NA NA	NA NA	NA NA
Chowdhury and Vargas et al. 2005, USA[235]	Retrospective study	24- 60 months	69 47	CH+HYD+MEP CH+N2O	25+1+1 PO 50+50% PO	90 70	NA NA	45 25	NA NA

CH=Chloral hydrate, N2O=Nitrous oxide, K=Ketamine, MEP=Meperidine, HYD=Hydroxyzine, P=Placebo, PRO=Promethazine.

- **Randomised controlled trials**

14 RCTs compared the effectiveness of chloral hydrate versus other sedative agents in paediatric patients undergoing dental procedures (Table 2.2.3). These RCTs have been placed in three groups:

• Studies comparing chloral hydrate effectiveness with a placebo

• Studies comparing effectiveness of different doses of chloral hydrate

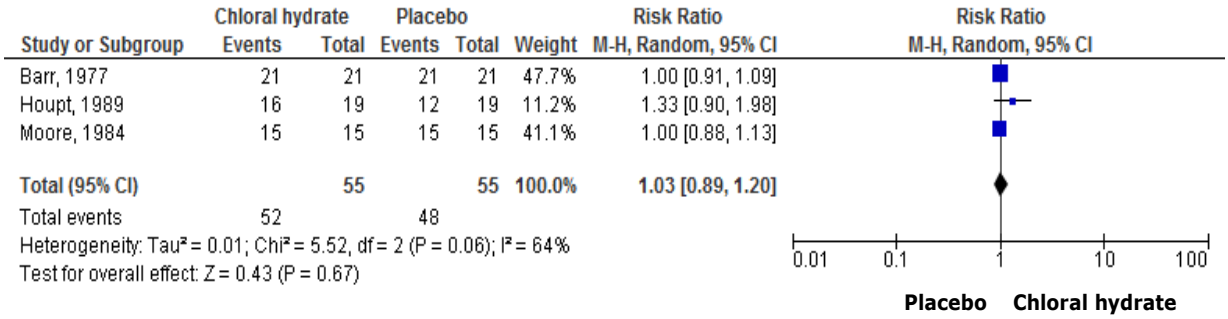
• Studies comparing chloral hydrate effectiveness with different sedative agents.

1. Studies comparing chloral hydrate effectiveness with a placebo

Three studies compared the effectiveness of oral chloral hydrate with placebo[259, 260, 262] (Table 2.2.3). Two studies found that there was no statistically significant difference in success rate between chloral hydrate and placebo groups, and all children completed dental procedures (Figure 2.2.3)[259, 260]. In contrast, the other study (Houpt et al. 1989) chloral hydrate was statistically more successful than than placebo($P < 0.05$), (84% in CH groups compared to 63% in placebo)[262].

Considering all 3 studies together, the relative risk of procedural success rate in the chloral hydrate group was not statistically different from those receiving placebo (RR 1.03, 95 % CI: 0.89 - 1.2, P=0.67)(Figure 2.2.3).

Figure 2.2. 3: Comparison of Chloral hydrate versus placebo



2. Studies comparing effectiveness of different doses of chloral hydrate

One study compared at the effect of low dose of CH (50 mg/kg) versus high dose (75 mg/kg)[258]. Children in higher dose of CH group had a statistically significantly high success rate compared to those in low dose CH groups ($P < 0.05$) (Table 2.2.3).

3. Studies comparing chloral hydrate effectiveness with different sedative agents

- **Chloral hydrate/hydroxyzine (CH/H)**

Five studies compared CH/H with other sedative agents [126, 256, 261, 265, 267] (Table 2.2.3). In Avalos-Arenas (1998) study children were given CH (70 mg/kg)/H (2 mg/kg) or CH (70 mg/kg) alone[256]. All children completed their dental treatment procedures.

Tsinidou (1992) looked at the effectiveness of oral CH (40 mg/kg)/H (25 mg) compared to oral hydroxyzine (0.3 mg/kg) in children aged between 20 and 60 months. The procedural success rate was slightly higher in the CH/H group but not statistically significant (70% vs 65%) respectively[265].

Meyer (1990) looked at the effectiveness of chloral hydrate (40 mg/kg, PO)/hydroxyzine (25mg, PO) compared to triazolam (0.02 mg/kg) in children aged between 21 and 74 months[126]. All children completed their dental treatment procedures[126].

Moody (1985) compared rectal CH (50 mg/kg) with either oral CH (30 mg/kg)/H (25 mg) or oral CH (50 mg/kg) alone, sedation was more effective with rectal CH and oral CH/H groups compared to oral CH alone (70%, 70% vs 40%) respectively[261].

Reeves et al. (1996) found that the success rate of procedures was higher in patients who received CH (50 mg/kg)/ H (25 mg) compared to patients who received

midazolam (0.5mg/kg)/acetaminophen (10mg/ kg), but this was not statistically significant[267].

- **Chloral hydrate/promethazine (CH/PRO)**

Three studies compared CH/P effectiveness to other agents [263, 266, 268] (Table 2.2.3).

Dallman et al. 2001 compared the effectiveness of CH (62.5 mg/kg)/PRO (12.5 mg/kg) to midazolam (0.2 mg/kg) and found it was relatively similar[268]. While Houpt et al. (1985) found that CH (50 mg /kg)/ PRO (25 mg) was more effective than CH (75 mg/kg) with procedural success rate 89%vs 72% respectively[263]. In a study carried out by Sams et al. (1993) children aged from 18 to 48 months were given CH (50 mg/kg)/PRO (1mg/kg) or meperidine (1mg/kg)/PRO (1mg/ kg)[266]. They found that the procedural success rate was similar between the two groups as all patients completed their procedures.

- **Chloral hydrate/diazepam (CH/D)**

One study conducted by Badalaty et al. (1990) compared the effectiveness of CH (50 mg/k) to diazepam (0.3 and 0.6 mg/kg) and they found that diazepam at 0.3 or 0.6 mg/kg was more effective than chloral hydrate (73%, 93% and 60%, respectively).

- **Chloral hydrate/midazolam (CH/M)**

Hass et al. (1996) compared the effectiveness of CH (50 mg/kg) to midazolam (0.6 mg/kg) and found the procedural success rate was similar between the two groups as all patients completed their procedures

2.2.3.3.2. Minor surgery and sleep induction

Six studies evaluated chloral hydrate effectiveness in 318 children aged from 6 months to 12 years. Chloral hydrate was given orally in a dose range from 25 to 75 mg/kg (median 50 mg/kg). Sedation time ranged between 20 and 70 minutes, while duration of sedation ranged from 20 to 60 minutes. The failure rate varied between studies. It was zero in some studies[239, 245] (Castro et al. 1994 and Lopez et al. 1995), but up to 30% in another [246]. There were two (0.6%) children who required supplemental doses of chloral hydrate.

There were 75 children younger than five years. Chloral hydrate dose ranged from 40 to 50 mg/kg (median 45 mg/kg) orally. All sedation was completed with 100% procedure success rate.

Table 2.2. 4: RCTs for Minor surgery

Reference, country	Study design	Age	No. of patients	Drug	Dose mg/kg	Success rate (%)	Supplementary dose/med (No.)	Sedation (min)	
								Onset	Duration
Saarnivaara et al. 1988, Finland[269]	Double-blind RCT	1-8 years	126 122	CH M	25, 50 or 75 PO 0.4, 0.5 or 0.6 PO	NA	NA NA	NA NA	21-35 21-35
Ong et al. 1996, Singapore[246]	Single-blind RCT	1-12 years	25 27 31 29	CH M TRI Pro P	40 PO 0.2 PO 3 PO 1 PO	70 42 55 39 32	NA	NA	NA
Anderson et al. 1990, Australia [270]	Double-blind RCT	6- 47 months	43 43	CH D	40 PO 0.25 PO	100 100	NA	70 84	30 27
Binder and Leake 1991, USA[249]	Prospective observational study	1-10 years	42	CH	25-50 PO	95	Y (2)	20-60	20-60
Castro et al. 1994, Brazil[239]	Prospective observational study	1- 12 years	50	CH	50 PO	100	N	NA NA	NA NA
Lopez et al. 1995, Chile[245]	Prospective observational study	1- 5 years	32 27	CH M	50 PO 1 PO	100 66	NA	Mean 21.8 Mean 117.5	NA NA

CH=Chloral hydrate, D= Diazepam, ALP= Alprazolam, Pro= Prometazine, P=Placebo, TRI=Trimeprazine, CH: Chloral hydrate, M: Midazolam

2.2.3.3.3. Ophthalmic examination

Chloral hydrate effectiveness was identified in three studies. The total number of children was 372 and their ages were ranged from birth to five years. The dose of chloral hydrate ranged from 80 to 100 mg/kg, median 100 mg/kg. Chloral hydrate induction time was between 20 and 45 minutes, with average duration from 30 minutes to two hours. The effectiveness of chloral hydrate was found to be high with success rates ranging from 88 to 100%. Supplementary dose(s) of sedation were not given during procedures in two studies[251, 252] while in the other study, data was not available[244].

Table 2.2. 5: RCTs for Ophthalmic examination

Reference, country	Study design	Age	No. of patients	Drug	Dose mg/kg	Success rate (%)	Supplementary dose/med (No.)	Sedation (min)	
								Onset	Duration
Jaafar, Kazi 1993, USA[252]	Prospective study	0- 5 years	60	CH	100 PO	100	N	20-45	30-150
Fox et al. 1990, USA[244]	Prospective study	1 month-5 years	302	CH	80- 100 PO	88	NA	NA	NA
Wright et al. 1986, USA[251]	Prospective study	4- 21 months	10	CH	80- 100 PO	100	N	NA	NA

CH= Chloral hydrate

2.2.3.3.4. MCUG procedure

One RCT evaluated chloral hydrate effectiveness[271]. This study was published in 2005 and it compared oral chloral hydrate 25 mg/kg with oral midazolam 0.6 mg/kg. The total number of children was 18, aged from 6 months to 15 years. Sedation time ranged between 10 and 20 minutes (median 16 minutes) and the duration time ranged from 20 to 35 minutes (median 28 minutes). The success rate was 100% in chloral hydrate group, while it was 94% in midazolam group.

2.2.3.3.5. Nasofibroscopy test

One study was published in 2001[241]. This prospective observational study was conducted in Brazil. The total number of children was 100 with the age ranging from one to four years. Chloral hydrate at a dose of 100 mg/kg was administered orally. The mean sedation time was 40 minutes. All patients completed their procedures successfully.

2.2.3.3.6. SCE assay (blood taking)

One prospective observational study was found from Turkey [242]. The total number of infants was 18, aged from 31 to 55 days. In this study chloral hydrate was administered via oral route in a dose of 50 mg/kg. The success rate was 100%.

- **Summary of chloral hydrate clinical effectiveness**

We found 34 articles evaluating the effectiveness of chloral hydrate for painful procedural sedation (PS). The following table illustrates the success rates per type of painful procedures (Table 2.2.6).

Table 2.2. 6: Success rate (%) of all types of painful procedures

Type of procedures	Chloral hydrate dose Range (median dose)	Success rate Range (median success)
Minor surgery, sleep induction	25 to 75 mg/kg (50 mg/kg)	70 to 100% (100%)
Ophthalmic examination	80 to 100 mg/kg (100 mg/kg)	88 to 100% (100%)
MCUG procedure	25 mg/kg	100%
Nasofibroscopy test	100 mg/kg	100%
SCE assay (blood taking)	50 mg/kg	100%
Dental procedure	20 to 75 mg/kg (50 mg/kg)	40 to 100% (84%)

2.2.3.4. Chloral hydrate safety

Forty six studies evaluated chloral hydrate safety for six different painful procedures including dental procedures, minor surgery and sleep induction, ophthalmic examination, MCUG, Nasofibroscopy test, and SCE. There were a total of 1810 children exposed to chloral hydrate with estimated risk of 17.3 in every 100 patients, or one AE in every six children receiving chloral hydrate. Hypoxia was the most frequently occurring AE followed by vomiting, and restlessness (Table 2.2.7).

All studies were subdivided according to the type of painful procedure. Thirty four studies evaluated chloral hydrate safety for dental procedures, six for minor surgery and sleep induction, three for ophthalmic examination, and one each for MCUG, Nasofibroscopy test, and SCE.

Table 2.2. 7: Reported AEs for all painful procedures

Body system	Adverse effects	Frequency	Incidence (%)(AEs cases/1810)
Respiratory system	Hypoxia	95	5.2
	Increased Respiratory rate	24	1.3
	Airway obstruction	12	0.7
	Decreased Respiratory rate	4	0.2
Central nervous system	Vomiting	59	3.3
	Restlessness	39	2.2
	Anxiety	15	0.8
	Irritability	15	0.8
	Drowsiness	11	0.6
	Dizziness	6	0.3
	Ataxia	1	0.1
Cardiovascular system	Increased heart rate	6	0.3
Others	Excessive sleep	19	1.0
	Fever	4	0.4
	Hiccup	1	0.1
	sickness	1	0.1
	Visual disturbance	1	0.1
Total		313	17.3

2.2.3.4.1. Dental procedures

28 studies reported AEs while 6 studies had none [257, 264, 267, 272-274]. 984 children received chloral hydrate (median dose 75 mg/kg) for dental procedures out of 1699 participants. The mean age of these children was 38 months (3 studies did not give the mean age [235, 255, 259]). There were 236 AEs (Table 2.2.8). The estimated risk of experiencing an AEs was 24%, or approximately one AE in every four children receiving chloral hydrate.

Table 2.2. 8: Reported AEs for dental procedures

Body system	Adverse effects	Frequency	Incidence (%)(AEs cases/984)
Respiratory system	Hypoxia	94	9.6
	Increased Respiratory rate	24	2.4
	Airway obstruction	12	1.2
	Decreased Respiratory rate	4	0.4
Central nervous system	Vomiting	42	4.3
	Irritability	15	1.5
	Anxiety	6	0.6
	Dizziness	6	0.6
	Ataxia	1	0.1
Cardiovascular system	Increased heart rate	6	0.6
Others	Excessive sleep	19	1.9
	Fever	4	0.4
	Hiccup	1	0.1
	sickness	1	0.1
	Visual disturbance	1	0.1
Total		236	24

Hypoxia was most common and accounted for almost 40% of all AEs. Sixty five cases/984 patients (6.6%) of hypoxia were mild (SpO2 90-95%), whereas 29 cases/984 patients (3%) were moderate (SpO2, 85-89%). There was no discontinuation of the dental procedure due to hypoxia. Other respiratory complications were: increased respiratory rate, airway obstruction and decreased respiratory rate which were reported for 24, 12 and 4 cases respectively (Table 2.2.8).

Seven studies reported children (29) experiencing moderate hypoxia, oxygen saturation (SpO2) level of <90% [248, 250, 255, 256, 265, 275, 276]. Chloral hydrate was given orally during these studies in doses ranging from 50- 100 mg/kg (median 50 mg/kg). 13 children received chloral hydrate only, whereas 16 also received other sedative agents [promethazine (10), hydroxyzine (4), and nitrous oxide (2)]. The median age of the children with moderate hypoxia was 36 months or less (it was not possible to calculate the median exactly as individual ages were not always given). This is similar to the mean age of children in all the studies, which was 38 months.

Most studies gave detailed information about monitoring and management of moderate hypoxia, six studies used a pulse oximetry to monitor oxygen saturation levels [248, 250, 255, 256, 265, 275]. 28 of the 29 cases of moderate hypoxia responded to changes in the position of the head and neck. One 25 month old female however failed to respond to changes in the head position, but the authors did not mention the further medical intervention which was given [248] (Table 2.2.9).

The second most common AE was vomiting, developed by 42 cases/984 patients (4.3%) children. All cases of vomiting were mild and resolved without requiring medical intervention.

Table 2.2. 9: Summary of the 29 children who developed moderate hypoxia

References	**Study design**	**NO. of children**	**Age** (months)	**Drug** (doses)	**Monitoring device(s)**
Mueller et al. 1985 [255]	Prospective study	2	24- 72 *	CH 100 mg/kg+ 50%N2O	▪ Pulse Oximetry
Iwasakiet al. 1989 [248]	Prospective study	5	< 36 (4 children)	CH 75 mg/mg	▪ Pulse Oximetry, Capnography
			25	CH 75 mg/mg	▪ Pulse Oximetry, Capnography
Sams et al. 1991[250]	Retrospective population based study	10	24	CH/P (mg) 800/12.5	▪ Pulse Oximetry
			24	CH/P (mg) 636/12.5	
			29	CH/P (mg) 700/15.0	
			29	CH/P (mg) 700/15.0	
			31	CH/P (mg) 600/12.5	
			31	CH/P (mg) 750/12.5	
			36	CH/P (mg) 750/12.5	
			39	CH/P (mg) 715/7.15	
			40	CH/P (mg) 570/12.5	
			59	CH/P (mg) 820/12.5	
Tsinidou et al. 1992 [265]	Double blind Cross-over design	3	20- 60 *	CH/H (mg/kg) 50/25 for each patient	▪ Pulse Oximetry
Avalos-Arenas et al. 1998 [256]	Double blind RCT	6	21- 36 *	CH (mg/kg) 70 for each patient	▪ Pulse Oximetry, precordial stethoscope, sphygmomanometer
Meyer et al. 2004 [275]	Double blind Cross-over design	2	32- 63 *	CH (mg/kg) 50 for each patient	▪ Capnography, Pulse Oximetry, precordial stethoscope
Torres-Pérez et al. 2007 [276]	Single blind RCT	1	12- 120 *	CH/H (mg/kg) 50/1.5	▪ NA

* Individual data about the age of each patient was not given, CH-chloral hydrate, P-promethazine, H- hydroxyzine.

2.2.3.4.2. Minor surgery

Six studies evaluated chloral hydrate toxicity in 318 children [239, 245, 246, 249, 269, 270]. A total of 61 adverse events with an incidence rate of 19.2 per 100 children were documented. The chloral hydrate dose ranged from 25 to 75 mg/kg (median dose 50 mg/kg). The most common AEs were restlessness 39 cases/318 patients (12.3%) followed by; drowsness 11 cases/318 patients (3.5%), anxiety 9 cases/318 patients (2.8%) and vomiting 2 cases/318 patients (0.6%) children.

A Case of corrosive burns of the upper respiratory airway was described in an 18 months infant male a few minutes after administration of oral chloral hydrate[277]. Immediate tracheal intubation and medical interventions was given. Hospitalisation for 24 hours was required.

2.2.3.4.3. Ophthalmic examination

AEs were evaluated in three prospective observational studies [244, 251, 252]. The total number of children was 372 and the total number of AEs was 16 events (4.3%). Vomiting occurred in 15 cases/372 patients (4%) patients, whereas mild hypoxia was seen in one cases/372 patients (0.3%) patient. There were no procedural sedation discontinuations due to AEs. This review also identified one case report for an 8 months infant male who developed severe oropharyngeal and oesophageal burn after a chloral hydrate overdose (8 gm instead of 0.4 gm) as a medication error [278]. Immediate intubation was carried out to support his airway and ventilation. Additionally 40 mg intravenous corticosteroid was given every six hours and the patient was followed up for approximately one year.

2.2.3.4.4. MCUG

One RCT by Akil et al. (2005) evaluated chloral hydrate safety in 18 children aged from 6 months to 15 years old[271]. This study compared oral chloral hydrate 25 mg/kg with oral midazolam 0.6 mg/kg. AEs were not observed in any of the children.

2.2.3.4.5. Nasofibroscopy

One prospective study was found [241]. The total number of children was 100 aged from 1 to 4 years old. Chloral hydrate was given orally at dose of 100 mg/kg. There were no AEs reported.

2.2.3.4.6. SCE assay

One prospective observational study evaluated chloral hydrate AEs[242]. Chloral hydrate was given orally to 18 infants aged from 31 to 55 days. AEs were not reported.

Summary of chloral hydrate AES has been shown in table (2.2.10).

Table 2.2. 10: Summary of all Reported AEs

Type of painless procedures	Chloral hydrate dose (median dose mg/kg)	Frequency (incidence %)
Dental procedures	50 to 100 mg/kg (75 mg/kg)	236 AEs/984 patients (24)
Minor surgery	25 to 75 mg/kg (50 mg/kg)	61 AEs/318 patients (19.2)
Ophthalmic examination	80 to 100 mg/kg (100 mg/kg)	16 AEs/372 patients (4.3)

2.2.4. Discussion:

Chloral hydrate effectiveness was highest in ophthalmic examinations (median 100%) and lowest in dental procedures (median 84%). It has been documented that the success rate depends on the dose administered [237]. Houpt et al. (1985) reported that 75 mg/kg of chloral hydrate was superior to 50 mg/kg for controlling the behaviour of paediatric patients in dental treatment [258]. In this review, the median dose of chloral hydrate was higher in ophthalmic examinations than in dental procedures (100 mg/kg versus 75 mg/kg respectively).

The current review indicated that the number of children who needed supplemental sedatives was higher during dental procedures compared to other procedures. This could have been due to the longer time for these procedures [258].

With regard to the safety of chloral hydrate, our systematic review revealed a high incidence of AEs (313 AEs/1810 patients, 17.3%) in painful procedures. Hypoxia and vomiting were the most common AEs across most studies that evaluated the safety of chloral hydrate. AEs were highest during dental procedures (236 AEs/984 patients, 24%) and minor surgery (61 AEs/318 patients, 19%).

Hypoxia was the most frequently reported AE in this systematic review. Almost 1 in 19 children experienced hypoxia. In 1/3 of these cases, the hypoxia was moderate, with saturation of peripheral oxygen (SpO2) reduced to <90%, requiring intervention.

Hypoxia was also the most frequent complication reported with other sedatives used for children undergoing painful procedures. For example, all 20 children who received alphaprodine in a clinical trial developed hypoxia [255]. Another study of midazolam reported hypoxia in 1 in eight children [235].

Vomiting was the second most common AE and was experienced by 3.3% of children (59 cases/1810 patients). All cases were self-limiting. Generally, chloral hydrate is known to cause gastric irritation and emetic stimulation [243, 258, 263]. The unpleasant taste of chloral hydrate may also cause vomiting or even prevent the child from swallowing the drug [70]. Additionally, some dental procedures may stimulate the gag reflex, which can lead to vomiting [279].

This systematic review found that the incidence of AEs following administration of chloral hydrate for painful procedures was higher than for painless procedures 313AEs/1810 patients (17.3%) versus 1,951AEs/14439 patients (13.5%).

In this systematic review, two serious AEs were found. The first case was an 18-month-old male who developed corrosive burns on his upper airway after receiving chloral hydrate. The other was a 9-year-old female who developed supraventricular tachycardia 7 hours after a dose of 600 mg of oral chloral hydrate. Both cases required medical intervention and hospitalisation [277, 280].

2.2.5. Limitations

This systematic review has several limitations. First, only a small number of studies evaluated chloral hydrate safety and effectiveness during painful procedures such as micturating cystourethrogram or nasofibroscopy. This may limit the generalisability of the results. Another important limitation is that the methods for measuring outcomes and the definitions of safety and effectiveness differed between studies. The statistical analysis methods also varied. Additionally, the majority of the studies focused on patients aged from 1 to six years. Consequently, it was difficult to locate robust data about chloral hydrate safety and effectiveness in the other age groups.

2.2.6. Conclusions

Chloral hydrate for painful procedures seems to have good effectiveness if it is used in relatively high doses (from 50 mg/kg to 75 mg/kg). Moderate hypoxia was the most serious reported AE. This underscores the importance of monitoring the respiratory system during sedation and that sedation should be conducted by a practitioner who is confident in resuscitation

Part 2.3. Chloral Hydrate for treatment uses

2.3.1. Introduction

Chloral hydrate has less frequently been used for medical treatment such as treatment of neonatal abstinence syndrome [213]. It is important to note that its uses depend on its ability to induce sedative and hypnotic effects through binding to $GABA_A$ receptors in the brain[123].

It is used for the treatment of several disorders, such as insomnia (short-term), agitation and cluster seizures in neonates[281]. Prolonged use may lead to a higher incidence of AES for example, hepatic toxicity. Martinbiancho et al. (2009) reported that 22.7% (78) of children who were given chloral hydrate for prolonged sedation experienced AEs. When given chloral hydrate for 6 days, 10.5% (24) of children developed AEs, and when given it for longer, 47% (54) of children developed AEs[282]. Hypoxia was the most common AEs (64.6%), followed by hypotension[282]. In fact, there is a lack of data on chloral hydrate safety and clinical effectiveness for prolonged sedation.

The aim of this systematic review is to evaluate the clinical effectiveness and safety of chloral hydrate for treatment uses in paediatric patients.

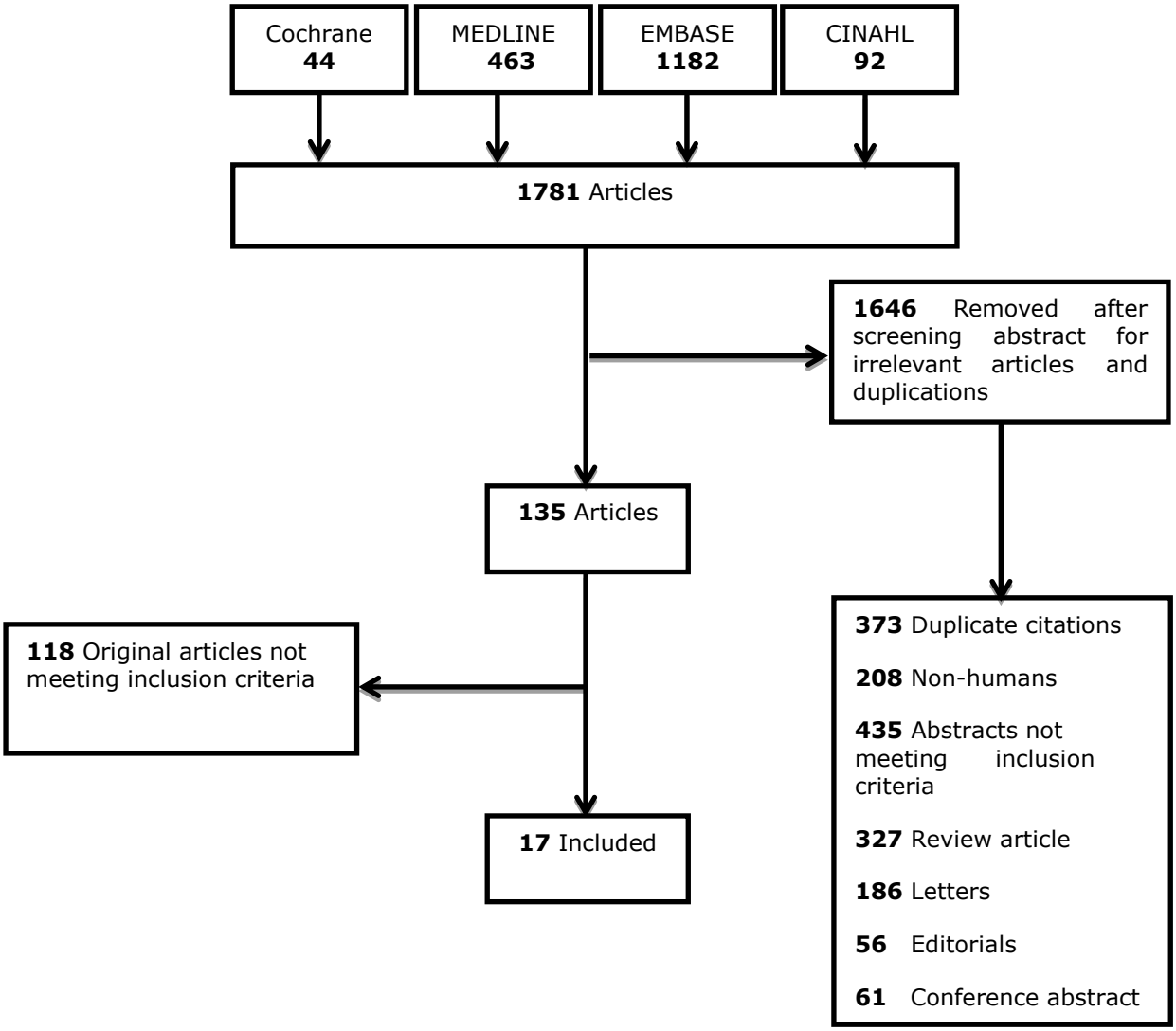
2.3.2. Methods

The search strategy and the key words are as discussed in the earlier part of chapter 2.

2.3.3. Results

1781 related abstracts were found. After screening the abstract for irrelevant articles and duplications, 135 articles were identified. The full texts of these articles were read carefully and 17 studies that met the inclusion criteria were included (Figure 2.3.1).

Figure 2.3. 1: Flow chart of study



Characteristics of the studies

17 studies were identified, 11 studies for treatment of agitation, 4 for neonatal diseases and 2 for neurological disorders (Table 2.3.1).

The largest group of studies was case reports (9), followed by prospective and retrospective studies (Table 2.3.1). Six were conducted in the USA, four in the UK, three in Canada, and one in each Czech Republic, Turkey, Germany, and Japan.

Chloral hydrate was given orally in 15 studies in doses that ranged from 20 mg to 100mg/kg, while it was given rectally in 2 studies in doses from 34 to 63 mg/kg.

Table 2.3. 1: Summary of 17 studies that reported on clinical effectiveness and safety of chloral hydrate for treatment use in children

Studies' characteristics	Number of studies	Number of children
Type of study	**N=17**	**N=517**
• Case report	9	11
• Prospective observational	3	368
• Retrospective	3	109
• Randomised controlled trial	2	29
Type of treatment procedure		
• Agitation	11	445
• Neonatal diseases*	4	48
• Treatment of neurological disorders**	2	24
Route of Administration		
• Oral	15	494
• Rectal	2	23
Age groups		
• Preterm neonates	1	1
• Term neonates	3	49
• Infants	7	13
• Children	3	24
• Other patient age groups***	4	430

* Neonatal diseases include: Hyaline membrane disease (HMD), neonatal abstinence syndrome, cluster seizures in benign convulsions and treatment of cryptogenic ohtahara syndrome

** Neurological disorders include: clustering seizure and treatment of refractory epilepsy

*** Studies involving multiple age groups (the number of patients within each age group was not documented)

2.3.3.1. Trial quality

After the application of the Jadad scoring checklists, no study fulfilled all 5 criteria. Two studies met ≤ 2 criteria (Table 2.3.2). The scores for the STROBE checklist for observational studies are illustrated in table (Table 2.3.3). 5 of the 6 identified studies were rated above 70%.

Table 2.3. 2: Quality assessment criteria of included RCTs

References	Jadad score (out of 5)
Reimche L. et al., 1989[283]	2
Kuaemko 1972[284]	3

Table 2.3. 3: Quality assessment criteria of included observational studies

References	STROBE scoring (out of 22)	%
Martinbiancho et al., 2009[282]	17	77
Esmaeili et al., 2010[285]	17	77
Lambert et al., 1990[286]	16	73
Hindmarsh et al., 1991[287]	16	73
Enoki et al., 2007[288]	16	73
Mayers et al., 1992[289]	15	68

2.3.3.2. Chloral hydrate Effectiveness

Six studies evaluated chloral hydrate effectiveness for treatment uses. Three reported use for seizures treatment. One retrospective study that evaluated the effectiveness of chloral hydrate for treatment of cluster seizures in 22 children, aged between 3 and 39 months was conducted in Japan[288]. The dose of chloral hydrate ranged from 33.8 to 62.5 mg/kg (mean 48.7 mg/kg) PR. The success rate was 86% (seizures completely ceased) after a single dose of chloral hydrate.

One case report identified the use of chloral hydrate for refractory epilepsy treatment[290]. There were two patients reported (4 days and 6 years old). The patients were given 30mg/kg of oral chloral hydrate every 3 and every 4 hours respectively. The seizures completely ceased after 48 and 24 hours respectively.

Another case study reported a 5 weeks old patient was treated with 58 mg/kg/day of oral chloral hydrate. 24 hours after treatment initiation all seizures ceased completely[291].

Two studies reported use for neonatal disease treatment. One retrospective study involved 29 neonate patients with abstinence syndrome (median gestational age was 38.5 weeks), conducted in Germany[285]. Chloral hydrate was administered orally in a dose from 30 to 50 mg/kg. All children were treated successfully and discharged after median 32 days (range, 14 to 56 days). Another RCT compared chloral hydrate effectiveness (80mg PO every 6 hrs for 24 hrs) to diazepam (1mg PO every 6hrs for 24 hrs) in 17 neonates (average gestational age was 40 weeks) treated for cerebral irritation[284]. All neonates in both groups were treated successfully within 4 days.

One study reported use for agitation treatment. This was a prospective observational study that evaluated chloral hydrate effectiveness in 19 neonatal patients with

agitation. All cases of agitation were controlled within 30 min following a chloral hydrate dose (50mg/kg oral)[289].

A summary of the data regarding chloral hydrate effectiveness of all treatment uses are compared in the following table.

Table 2.3. 4: Chloral hydrate sedation success rates of all treatment uses

Type of treatment uses	No. of patients	Chloral hydrate dose (mg/kg)	Success rate
Treatment of agitation	19	50 mg/kg	100%
Treatment of neonatal diseases	29	30 to 50 mg/kg	100%
Treatment of cerebral irritation	17	80 mg/kg	100%
Treatment of neurological diseases	22	33.8 to 62.5 mg/kg	86%

2.3.3.3. Chloral hydrate safety

15 studies evaluated chloral hydrate safety for treatment uses. One study reported use for seizure treatment. This was a retrospective study of 22 children aged from 3 to 39 months which reported no AEs [288].

Two studies evaluating the safety of chloral hydrate in 46 neonates for neonatal disease treatment reported 13 AEs in 17 neonates (Nine cases of vomiting and four of drowsiness) [284, 285].

Five studies reviewed the safety of chloral hydrate in 438 patients for the treatment of agitation [282, 283, 286, 287, 289]. There were 81 AEs with an incidence rate of 18.5%. Mild hypoxia occurred with the highest frequency in 71 children (71 cases/438 patients, 16.2%), while the other AEs was bradycardia 5 cases/438 patients (1.1%), diarrhoea 4 cases/438 patients (0.91%) and hypotension in 1 case/438 patients (0.2%). There were no severe AEs or death.

There were seven case reports of 8 children experiencing chloral hydrate toxicity [292-298]. All children required medical interventions and hospitalisation. Five children required intubation for respiratory failure/hypoxia (Table 2.3.3).

Table 2.3. 5: Chloral hydrate serious AEs for treatment of agitation from case reports/series

Reference, country	Patient age	Dose of CH	AEs	Treatment	Hospital stay/ days
Granoff et al. 1971, USA[292]	22 months	250 mg PO	Acute airway obstruction, cyanosis	Intubation, O2 therapy	Y (> 12 hours)
Watts et al. 1975, UK[298]	20 weeks	200-400 mg/24 hrs.	Hyperamino aciduria, Hypermethioninemia	Discontinuation of chloral hydrate	Y (NA)
Laptoo and Rosenfeld 1983, USA[293]	2 days	30 mg/kg PO After 4 hrs. an additional doses (40, 45 and 50 mg/kg) over 12 hours were given	Respiratory failure	Intubation, O2 therapy	Y (4 weeks)
Hartley et al. 1989, USA[294]	2.5 months	30 mg/kg PRN (2- 6 doses/day)	Severe bronchospasm developed after 2 weeks	Oxygen therapy, Discontinuation of chloral hydrate	Y (NA)
	3 months	20 mg/kg every 6 hrs.	Severe bronchospasm developed after 1 weeks	Oxygen therapy, Discontinuation of chloral hydrate	Y (NA)

Table 2.3.3: Chloral hydrate serious AEs for treatment of agitation from case reports/series

Reference, country	Patient age	Dose of CH	AEs	Treatment	Hospital stay/ days
Anyebuno, Rosenfeld 1990, USA[295]	14 days	44 mg/kg every 6 hrs. and after 17 days the dose increased to 50 mg/kg every 6 hrs.	Respiratory depression after 21 days	Discontinuation of chloral hydrate, Intubation, O2 therapy	Y (2 weeks)
Goldsmith 1993, USA[297]	35 weeks	20 mg/kg every 6 hrs.	After 4 days infant developed renal failure, respiratory depression, hypotension	Intubation, O2 therapy, Dopamine and dobutamine drip, Furosemide IV	Y (NA)
Cecen et al. 2009, Turkey[296]	4 months	50mg/kg chloral hydrate rectally, then after 5 min another dose of 50mg/kg was given orally	Tachycardia, Dyspnea, Respiratory insufficiency, cyanosis	Intubation, O2 therapy, Steroid and adrenaline inh.	Y (7days)

Inh=Inhalation, IV= Intravenous

2.3.4. Discussion

Over the last 100 years, chloral hydrate has been used to treat some diseases such as insomnia and agitation in both children and adults.

The most frequent use reported in this review was the treatment of agitation due to mechanical ventilation (445 (86.2%)). This might be because a sedation agent such as chloral hydrate is used to optimise ventilation [15, 299].

The incidence of AEs was higher in children who were given chloral hydrate for treatment of agitation than in neonates with 81 AEs in 438 paediatric patients compared to 13 AEs in 17 neonates. This might be because most children who were treated for agitation were under mechanical ventilation in the intensive care unit therefore they are very unwell and AEs are usually more frequent in this group, due to the use of high numbers of drugs and the possibility for drug interactions[300].

Hypoxia was reported as the most common AE. The higher incidence of hypoxia may be explained by the use of sedative drugs for long periods of time. Prolonged sedation was identified as a risk factor for AES [2], but it is not clear whether it resulted from the drug. Oxygen desaturation may have been related to insufficient mechanical ventilation and not directly to chloral hydrate AEs [282]. It is important to note that hypoxia was self-limiting in most of the evaluated cases.

The low incidence rate of other reported AEs may be due to inaccurate documentation of the safety data and the difficulty of knowing how the patients reacted to the drugs during prolonged sedation. Gastrointestinal AEs were the second most frequently reported AEs, including vomiting and diarrhoea, and most of these followed administration for treatment of agitation. Life-threatening hypoxia and respiratory

depression were reported in 8 children. No chloral hydrate-related deaths were reported.

The success rate of chloral hydrate was high across all treatment procedures, ranging from 86% to 100%. Interestingly, all cases of agitation were treated successfully. This might be attributed to the multiple doses used for agitation on mechanical ventilation[213]. Correspondingly, in a study by Koa et al. (1999), the success rate increased from 89% to 98% following an additional dose of chloral hydrate[187].

Some limitations of this systematic review must be taken into account when reporting the results. The small number of studies that evaluated chloral hydrate safety and effectiveness for treatment in children limited the generalisability of the result. AEs may have been under-reported due to the difficulty of identifying the clinical outcomes in children under prolonged sedation in some studies. Additionally, many studies did not use a standardised definition of AE and effectiveness.

2.3.5. Conclusions

This systematic review evaluated the clinical use and safety of chloral hydrate for treatment in paediatric patients. It has been found that chloral hydrate was effective in most cases in which the success rate ranged as high as 100%. However, hypoxia was a common AE, mainly in children who were treated for agitation due to mechanical ventilation. These results are limited by the small number of patients and the non-uniformity of systems for reporting outcomes. Further clinical studies with larger numbers of children and constant reporting of outcomes are needed to confirm our findings.

CHAPTER THREE

Systematic Review of Triclofos for Procedural Sedation in Children:

An analysis of its safety and effectiveness

3.1. Introduction

The safety and effectiveness of chloral hydrate in children was assessed in Chapter 2 and it was shown that chloral hydrate seems to be effective, but has a relatively high incidence of AEs. In this chapter, the safety and effectiveness of chloral hydrate active metabolite (triclofos) is assessed further. In the UK triclofos is no longer available as it was removed from the market in 2010 because tricofos has not been widely studied as a sedative agent for PS in children compared to chloral hydrate [301]. However, it still used in other countries such as India [301].

3.2. Aims

The aims of this systematic literature review are to evaluate the effectiveness and safety of triclofos for procedural sedation (PS) in children.

3.3. Methods

MEDLINE (1948–January 2012), EMBASE (1980–January 2012), COCHRANE (1974-January 2012) and CINAHL (1974- January 2012) were searched. EMBASE, MEDLINE, and COCHRANE library were searched separately and then combined together to remove duplications. CINAHL was searched manually to identify relevant articles and to remove duplication. All languages were included in this systematic review.

This search was conducted using combinations of the following search terms: "triclofos" and "children or infant or pe*diatric* or neonate or adolescence or adolescences or adolescent" and "sedation" [166].

The search was limited to the studies that assessed triclofos safety and/or effectiveness in children, up to 18 years, undergoing PS.

Exclusion Criteria were:

- Patients older than 18 years.
- Not used for sedation or treatment.
- Not used for diagnostic procedure.
- Any letter or review article; however, references were checked.

The population of the study was defined as children and adolescents 18 years and younger. Age was grouped as preterm neonates (<36 weeks gestation, 0–27 days),

full-term neonates (0–27 days, >37 weeks gestation), infants (28 days–23 months), children (2–11 years) and adolescents (12–17 years)[167].

3.3.1. Data extraction

The following data were extracted from each study:

- Sample size.
- Study region.
- Study design.
- Dose of triclofos.
- AEs of triclofos.
- Other used sedative drug (s).
- Supplementary dose of sedative drug(s).
- Induction time of sedation.
- Duration of sedation.
- Success rate.

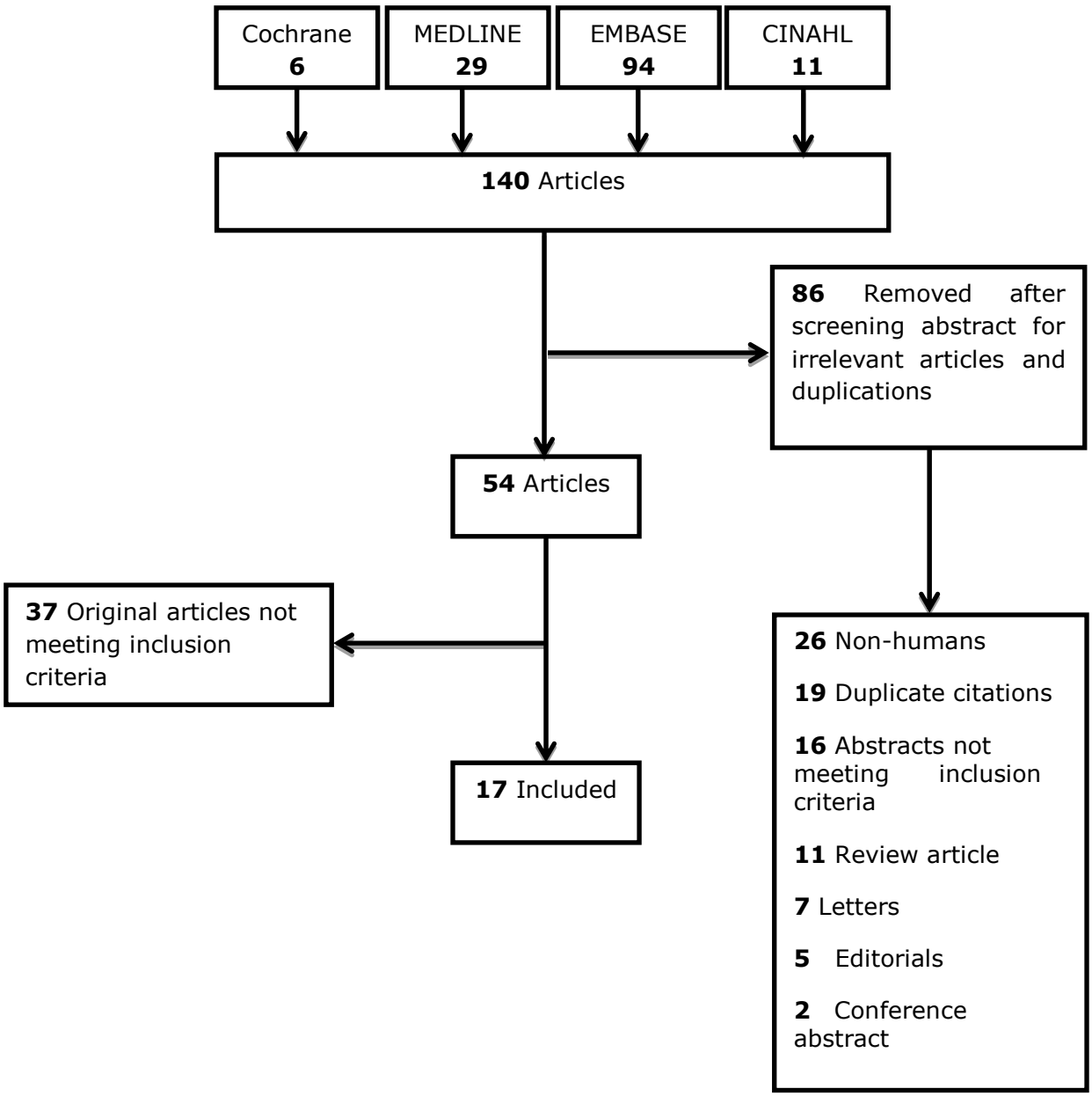
Data was extracted onto a data collection sheet. AEs were categorised according to their severity into mild or serious AEs. Subsequently, these AEs were analysed for each children group to detect their incidence. Data were analysed statistically using SPSS version 22. Incidences were calculated for AEs, excluding case reports. Due to the heterogeneity between the studies it was not possible to perform statistical meta-analysis.

Trial quality was assessed by two reviewers (BS and HS) independently. Jadad scoring checklists for harm reporting were used to evaluate RCTs [168]. Studies with a minimum score of ≥ 3 were considered as good quality. The STROBE checklist was used to evaluate the qualities of prospective observational and retrospective studies [169]. Any study with a minimum score of 70% was considered as good quality.

3.4. Results

140 clinical studies were identified after searching through EMBASE, MEDLINE, COCHRANE, and CINAHL data bases. After limitation to humans, the remaining articles were 114. Out of these articles, 19 articles were excluded because of duplication. The abstracts of the remaining articles were then reviewed according to the inclusion and exclusion criteria. After reviewing 95 abstracts, 54 articles were obtained as full text. Only 17 articles fulfilled our inclusion criteria (Figure 3.1). The included studies were then categorised according to the type of diagnostic or treatment procedure [16].

Figure 3. 1: Flow chart of triclofos



All 17 studies were published between 1972 and 2012. The majority (10) were RCTs. There were 4 prospective studies and 3 case reports. The studies were conducted in 6 different countries including: India (6), the UK (5), Japan (2), the USA (2), Finland (1), and Israel (1). The total number of children who were given triclofos was 688, aged from birth to 15 years. Five (29%) of the studies involved infants only. The largest group of children who received triclofos was in RCTs (543 children) (Table 3.1).

Triclofos was administered as a sedative for either painless or painful PS. It was given via the oral route in all studies, the dose ranged from 10 to 80 mg/kg.

Table 3. 1: Summary of 17 studies that reported on clinical effectiveness and safety of triclofos for painless and painful procedures in paediatrics

Studies' characteristics	Number of studies	Number of children
Type of study	**N=17**	**N=688**
• Randomised controlled trial	10	543
• Prospective observational	4	142
• Case report	3	3
Type of procedures		
• Painless procedures	5	170
• Painful procedures	12	518
Route of Administration		
• Oral	17	688
Age groups		
• Preterm neonates	0	0
• Term neonates	0	0
• Infants	5	86
• Children	4	185
• Other patient age groups*	8	417

*Including paediatric studies for which the age group was not stated or mixed ages.

A 96% agreement level between the two assessors was reached. No RCT study fulfilled all 5 Jadad criteria. Seven studies met ≥3 criteria whereas 3 studies met ≤ 2 criteria (Table 3.2). With regard to the observational studies, only one study was rated less than 70% (Table 3.3). All studies were included in the systematic review to avoid missing any data from these articles due to the small number of publications identified for each painless and painful procedure. The quality scoring and selection of papers and abstracts was checked by two independent reviewers (BS and HS).

Table 3. 2: Quality assessment criteria of RCTs.

References	Jadad score (out of 5)
Parameswari et al., 2010 [302]	4
Millichap ,1972 [174]	3
Gupta et al., 1972 [128]	3
BOYD, 1973 [303]	3
Page, 1990 [304]	3
Singh et al., 2003 [305]	3
Shabbir et al., 2011 [301]	3
Lindgren et al., 1980 [306]	2
Sharma et al., 1992 [307]	2
Bhatnagar et al., 2012 [308]	1

Table 3. 3: Quality assessment criteria of observational studies.

References	STROBE scoring (out of 22)	%
Jackson et al, 1991[130]	17	77
Stocks et al, 1994[309]	17	77
Rabbette et al., 1991[310]	16	73
Udani et al. 1965[311]	15	68

3.4.1. Painless procedures

Five studies identified recruited 170 children aged from 5 weeks to 14 years. They were conducted in 4 different countries (2 in the UK, and one in each India, Japan, and the USA). Triclofos effectiveness and safety were evaluated for 5 different painless procedures (Table 3.4)

Table 3. 4: Types of painless procedures

Painless procedure	Number of studies
CT	1
EEG	1
Measurement of Hearing-Breuer inflation (HBR)	1
Hypnotic test (psychological test to assess mental state)	1
Lung plethysmography study	1
Total number	5

One randomised double-blind study was published in 1972 [174]. This study compared the safety and effectiveness of oral triclofos with oral chloral hydrate for EEG. 37 children, aged from 4 to 14 years, received (33 mg/kg) triclofos orally and 34 children (22 mg/kg) chloral hydrate orally. The mean time of sedation induction was similar for triclofos, 36.6 minutes and chloral 37.3 minutes respectively. Sedation was successful in 31 patients (84%) given triclofos and 30 patients (88%) with chloral hydrate. 12 AEs (12/37 patients, 32.4 %) were documented during triclofos sedation. The most frequent AEs for triclofos were drowsiness 5 cases/37 patients (13.5%), followed by: ataxia 3 cases/37 patients (8.1%), dizziness 3 cases/37 patients (8.1%) and grogginess 1 cases/37 patients (2.7%) children.

One prospective observational study was conducted in the UK to evaluate safety and effectiveness for Hearing-Breuer inflation (HBR) test in 33 infants aged from 4 to 6

weeks [310]. Triclofos was administered orally in doses of 75 mg/kg. Only one infant (3%) failed to sleep following sedation.

One prospective study conducted in India evaluated triclofos safety and effectiveness for hypnotic test (induce sleep) in 50 paediatric patients aged from 3 months to 12 years [312]. The dose of triclofos was between 22 and 44 mg/kg (maximum 66-88 mg/kg) orally. Mean sedation time was 60 minutes. The only AE was vomiting which occurred in one child. 49 (98%) were successfully sedated.

A prospective study conducted in the UK, assessed the lung plethysmography in 49 infants, aged 5 to 8 weeks [309]. The dose of triclofos was 75 mg/kg orally. The plethysmography study was done successfully for all 49 infants (100%). There was no incidence of any AE.

There was one case report of a 28 weeks old male who developed pedalling-like movements after receiving a dose of 80 mg/kg orally for a CT scan [313].This AE lasted for approximately two hours. Medical interventions were not required.

The following tables (3.5, 3.6) summarise the AEs and clinical effectiveness data of triclofos (PS).

Table 3. 5: Triclofos sedation success rates

Type of procedure	No. of patients	Triclofos dose	Success rate (%)
Lung plethysmography study	49	75 mg/kg	100
Hypnotic test (induce sleep)	50	22 to 44 mg/kg	98
Hearing-Breuer inflation (HBR)	33	75 mg/kg	97
Electroencephalogram (EEG)	37	33 mg/kg	84

Table 3. 6: Triclofos sedation AEs.

Type of procedure	Triclofos dose	Frequency	Incidence of AEs (%)
Electroencephalogram (EEG)	33 mg/kg	12	12/37 patients (32.4%)
Hypnotic test	22 to 44 mg/kg	1	1/50 patients (2%)

3.4.2. Painful procedures

There were 12 studies involving 518 children aged between 0 and 15 years old. Three studies were conducted in India, the USA, and the UK, and one in each Finland, Israel, and Japan (Table 3.7). The majority were RCTs

Table 3. 7: Summary of 12 studies that reported on clinical effectiveness and safety of triclofos for painful procedures in paediatrics

Studies' characteristics	Number of studies	Number of children
Type of study	**N=12**	**N=518**
• Randomised controlled trial	9	506
• Prospective observational	1	10
• Case report	2	2
Type of procedures		
• Dental	4	123
• Minor surgery	8	395
Route of Administration		
• Oral	12	518
Age groups		
• Preterm neonates	0	0
• Term neonates	0	0
• Infants	2	2
• Children	4	185
• Other patient age groups*	6	331

*Including paediatric studies for which the age group was not stated or mixed ages.

3.4.2.1. Triclofos effectiveness

Four RCTs were identified for dental procedures (Table 3.8), all performed in India. The total number of children was 123, with age ranging from 15 months to 9 years. Triclofos was given in combination with other sedative agents (promethazine) in one study [307]. Triclofos was given via the oral route in doses that ranged from 70 to 75 mg/kg (median 70 mg/kg). The success rate ranged between 76 and 100%, median 99% (Table 3.8).

Table 3. 8: RCTs for dental procedures

Reference, country	Study design	Age	No. of patients	Drug	Dose mg/kg	Success rate (%)	Supplementary dose/med (No.)	Sedation (min)	
								Onset	Duration
Sharma et al., 1992, India [307]	Cross-over study	36- 60 months	21 22	TRI TRI+PRO	75 PO 59+1 PO	76 86	NA NA	NA NA	NA NA
Singh et al., 2003, India [305]	Double-blind RCT	15- 45 months	30 30 30	TRI M PRO	70 PO 0.5 PO 1.2 PO	100 100 100	NA NA	Mean 35 Mean 19 Mean 37	Mean 131 Mean 93 Mean 143
Shabbir et al., 2011, India [301]	Cross-over study	3- 9 years	12 12	TRI M	70 0.5	98 100	N N	NA NA	NA NA
Bhatnagar et al., 2012, India [308]	Single-blind RCT	3- 9 years	60	TRI M TR Z	70 PO 0.5 PO 2 PO 0.4 PO	100 100 100 100	NA NA	NA NA	NA NA

HYD=Hydroxyzine, M=Midazolam, MEP= Meperidine, PRO= Promethazine, TR= Tramadol, TRI=Triclofos, Z= Zolpidem

A total of five studies were identified involving administration before anaesthesia minor for surgery. All were published between 1972 and 2010. The studies were performed in four different countries; two in the UK and one in each; Finland, India and the USA. The total number of children involved was 383, in children from birth to fifteen years. The success rate ranged from 50 to 98%, median 80% (Table 3.9).

Table 3. 9: RCTs for minor surgery

Reference, country	Study design	Age	No. of patients	Drug	Dose mg/kg	Success rate (%)	Supplementary dose/med (No.)	Sedation (min)	
								Onset	Duration
Gupta et al., 1972, UK [128]	Double-blind RCT/ preoperative sedation	2- 13 years	95 95	TRI TRI+ HY	75 PO 75+ 0.035 PO	80 80	NA NA	NA NA	NA NA
BOYD and MANFORD, 1973, UK [303]	Double-blind RCT/ preoperative sedation	2-9 years	99 101	TRI D	71 PO 0.2 PO	90 81	NA NA	NA NA	NA NA
Lindgren et al., 1980, Finland[306]	Double-blind RCT/ Otolaryngological surgery	0-15 years	41 87	TRI D+F	70 PO 0.25+0.02 PO	50 100	NA NA	NA NA	NA NA
Page and Morgan-Hughes,1990, USA [304]	Double-blind RCT/day-case surgery	1- 5 years	128 135	TRI P	70 PO	98 98.5	NA NA	90 NA	NA NA
Parameswari et al.,2010, India [302]	Double-blind RCT/elective surgery	1-10 years	20 20	TRI M	75 PO 0.5 PO	65 20	NA NA	90 NA	30 NA

D=Diazepam, F= Flunitrazepam, HY= Hyoscine, P=Placebo, TRI=Triclofos, M=Midazolam

3.4.2.2. Triclofos safety

Two RCTs evaluated Triclofos safety for dental procedures [305, 307]. The total number of children was 51 aged from 15 to 60 months. Triclofos was given in a median dose of 72.5 mg/kg. Only one patient developed vomiting (1/51 patients, 2%).

Six studies evaluated triclofos toxicity for minor surgery [128, 130, 302-304, 306]. They included 393 children aged from 0 to 15 years. Triclofos was given orally, 70 to 100 mg/kg (median 75 mg/kg). 120 AEs with the incidence rate of 30.5% (120 AEs/393 children). Vomiting was the most frequent AE occurring in 60/393 patients (15%) followed by; mild hypoxia in 48/393 patients (12%) and restlessness in 12/393 patients (3%) patients.

There were two case reports of male infants aged two months and ten months who received oral triclofos for sleep induction [314, 315], doses were 1800 mg and 120mg/kg respectively (medication errors). After six hours the first infant developed deep coma, severe hypothermia, hypotension and lack of tendon reflexes. He was admitted to the hospital and was given intravenous fluids and was monitored for more than four days until he became stable. Another 10 months infant developed cyanosis due to upper airway obstruction following oral administration of triclofos. He required medical interventions (oxygen supplementation) and hospitalisation.

Table 3.10 and table 3.11 summarise triclofos safety and effectiveness data in children undergoing painful procedures.

Table 3. 10: Triclofos sedation success rates of all painful procedures

Type of painless procedures	Triclofos dose range mg/kg (median)	Success rate (median)
Dental procedure	70 to 75 mg/kg (70 mg/kg)	76 to 100% (99%)
Minor surgery and sleep induction	70 to 75 mg/kg (71 mg/kg)	50 to 98% (80%)

Table 3. 11: Sedation AES all painful procedures

Type of procedure (No. of patients)	No. of patients	Triclofos dose range mg/kg (median)	Frequency	Incidence of AEs (%)
Minor surgery and sleep induction	393	70 to 100 mg/kg (75mg/kg)	120	120 /393 patients (30.5%)
Dental procedure	51	70 to 75 mg/kg (72.5 mg/kg)	1	1/51 patients (2%)

3.5. Discussion

Triclofos (trichloroethanol) is an active metabolite of chloral hydrate. However, its use is limited in some countries for instance; in the UK, triclofos is not among the sedation agents commonly used in the NHS [80]. The present systematic review suggests that triclofos can be an effective and safe sedative agent for children and young people undergoing certain diagnostic or treatment procedures.

The systematic literature review in this study yielded 17 articles. Surprisingly, these indicated that triclofos was used more frequently for painful therapeutic procedures than painless diagnostic procedures (71% and 29% respectively). This finding contrasts with various guidelines that recommend the use of triclofos as a sedative agent only for painless treatment or diagnostic procedures [316].

Approximately 1 in 5 children (21.9%) experienced an AE with triclofos. The incidence of AEs was significantly higher following triclofos administration for painful procedures, particularly sleep induction before minor surgery, compared with painless procedures (27.3% (121/444) versus 7.7% (13/169)). This result agrees well with the findings obtained by Boyd and Manford (1973) who found a high incidence of AEs after triclofos (PS) for children aged from two to nine years undergoing ear, nose and throat (ENT) surgery [303]. This was thought be due to the administration of intravenous barbiturate medication such as thiopentone and methohexitone for induction and/or procedure itself such as dental treatment procedures [303, 306].

Additionally, these results were comparable with those reported for chloral hydrate in Chapter 2, in which the incidence of AEs was higher in painful procedures than it was in painless procedures (17.3% (313 AEs/1810 patients) versus 13.5% (1,951 AEs/14439 patient) respectively).

According to this systematic review the types of AEs were different according to the type of diagnostic or treatment procedure. The most commonly reported AE was vomiting with the incidence rate of 10% (62/613) children. This AE was higher with painful procedures (minor surgical procedure) compared with painless procedures (hypnotic test) 15% (60/393) versus 2% (1/50) respectively. In a prospective study of ear, nose and throat (ENT) surgical procedures, vomiting was more common in the post-operative period in children receiving triclofos (55.5%) versus (52.5%) in diazepam group [303]. It seemed unlikely that the triclofos premedication was a causal factor since they found that the nature of the vomitus in almost every case was altered blood. Most of the vomiting documented in this review was not severe and did not warrant medical intervention.

The second most commonly reported AE revealed in this review was hypoxia, with a risk of 7.8% (48/613). This AE was reported only in healthy children undergoing painful procedures (minor surgery; 12% (48/393)). This result agrees with those obtained in other studies. In a study of children undergoing triclofos PS for sleep induction prior to elective surgery, Jackson and colleagues (1991) found that administration of triclofos in doses up to 100 mg/kg led to development of mild hypoxia (approximately 70% infant) [130]. All hypoxia cases were mild (SpO2 90-95%) and did not required medical intervention.

In our systematic literature search, only two serious AEs were found. These AEs were due to administration in over dose (1800 mg and 120mg/kg) to two male infants aged two and ten months respectively [314, 315]. Hypotension and lack of tendon reflexes occurred with the first infant, while cyanosis developed in the second infant. Both cases required medical interventions and hospitalisation. One AE (pedalling like movements) was developed after administration of a dose of 80 mg/kg of chloral hydrate to a 28 weeks old infant[313]. Medical interventions were not needed.

The success rate of painless PS compared with painful procedures was found to be higher (ranged from 84% to 100% versus 50 to 100%). This might be because the painful dental treatment procedures required a longer duration of time to be completed or because of inadequate analgesia [307, 317].

3.6. Limitations

The results of this systematic review must be construed with caution because of a number of limitations. Few studies had the clear objective of determining the clinical effectiveness of triclofos as a sedative in either painless or painful procedures. The assessment of outcomes was inconsistent. As well, the statistical methods in the various studies were diverse. Some of the findings were limited by the number of children. Finally, the rarity of noted AEs might be due to inadequate reporting.

3.7. Conclusions

The systematic review suggests that triclofos seems to have a good sedative effect mainly with short painless PS. Vomiting and hypoxia AES were the most commonly reported AEs. However, these findings are limited by low patient numbers and the non-uniformity of outcomes reporting system(s).

CHAPTER FOUR

Paraldehyde Safety and Clinical Effectiveness for Procedural Sedation in Children: A Systematic Review

4.1. Introduction

Several classes of drugs have been used for providing comfort to children during various procedures. In the UK, drugs used for procedural sedation (PS) in children include: Chloral hydrate, Fentanyl, Ketamine, Midazolam, Morphine, Nitrous oxide, Opioids, Propofol and Sevoflurane [318]. In previous chapters chloral hydrate and triclofos safety and effectiveness for PS in children were studied. This chapter discusses an additional drug, paraldehyde.

Currently, in many countries, the use of paraldehyde is limited to the treatment of convulsive episodes in patients with tetanus and status epilepticus [163]. However, in some countries, such as the UK, paraldehyde is still used for PS in children as a part of the local hospital's sedation policy (e.g. Derbyshire Children's Hospital). Moreover, there are concerns about its adverse events (AEs), including respiratory depression and cardiovascular collapse, especially when given in high dose(s). Paraldehyde is still used as an add on agent in the sedation protocol of the Royal Derby Children's Hospital, therefore, we found that evaluating the literature about its safety and effectiveness is very important.

4.2. Methods

A systematic literature review was conducted to identify studies evaluating the efficacy and safety of paraldehyde in paediatric patients aged 18 years and younger. The following databases were searched separately and then combined together to remove duplications: MEDLINE, EMBASE, International Pharmaceutical Abstracts (IPA) and PubMed.

All articles published between 1948 and August 2013 were considered. All languages were included in this systematic literature review.

Selection of the keywords in this systematic review was based on their sensitivity and specificity according to validated age specific search strategy by Hedges Team [166]. Thus it has been found that the most sensitive and specific keywords were as following: paraldehyde and children or infant or pe*diatric* or neonate or adolescence or adolescences or adolescent and sedation (combined with the Boolean operator "OR").

Inclusion criteria were original studies assessing the safety and clinical effectiveness of paraldehyde as a sedative medication in children, up to the age of 18 years, undergoing diagnostic and/or treatment PS.

Exclusion Criteria were:

• Patients who are older than 18 years.

• Paraldehyde not used for sedation.

• Any comment, editorial or review article.

Data extracted from each article included the publication year, study period, study region, study design, number of children exposed, age of children exposed, dose of paraldehyde, route of administration, induction time of sedation, duration of sedation, success rate and AES data.

Assessment of trial quality for each paper was made in order to reduce the risk of bias. The STROBE checklist was used to score both prospective observational studies and retrospective study [169]. Any study with a minimum score of 70% was considered a good quality study. All studies were included in the systematic review to avoid missing any data from these articles due to the small number of articles found which assessed paraldehyde safety and effectiveness for PS. The quality and selection of papers and abstracts were checked by two independent reviewers (BS and HS).

4.3. Results

The initial search revealed 445 references. 266 articles remained after limitation to human and removing the duplication was applied (Figure 4.1), and after reviewing the titles and abstracts of these articles, 234 articles did not fulfil the inclusion criteria. 32 articles were read, but 27 did not meet the inclusion criteria, leaving only 5 articles figure (4.1) and table (4.2).

Three of the 5 included studies were rated above 70%. All studies were included in the systematic review. Meta-analysis was not performed due to the heterogeneity of the studies. The scores for the STROBE checklist for observational studies are illustrated in table 4.1.

Table 4. 1: Quality assessment criteria of included observational studies

References	STROBE scoring (out of 22)	%
Palomo et al. 1988[319]	19	86
Keengwe et al. 1999[320]	18	82
Adenipekun et al. 1997[321]	17	77
Dearlove ,2007[322]	15	68
Sammons et al. 2011[323]	14	64

Figure 4. 1: Flow chart of study

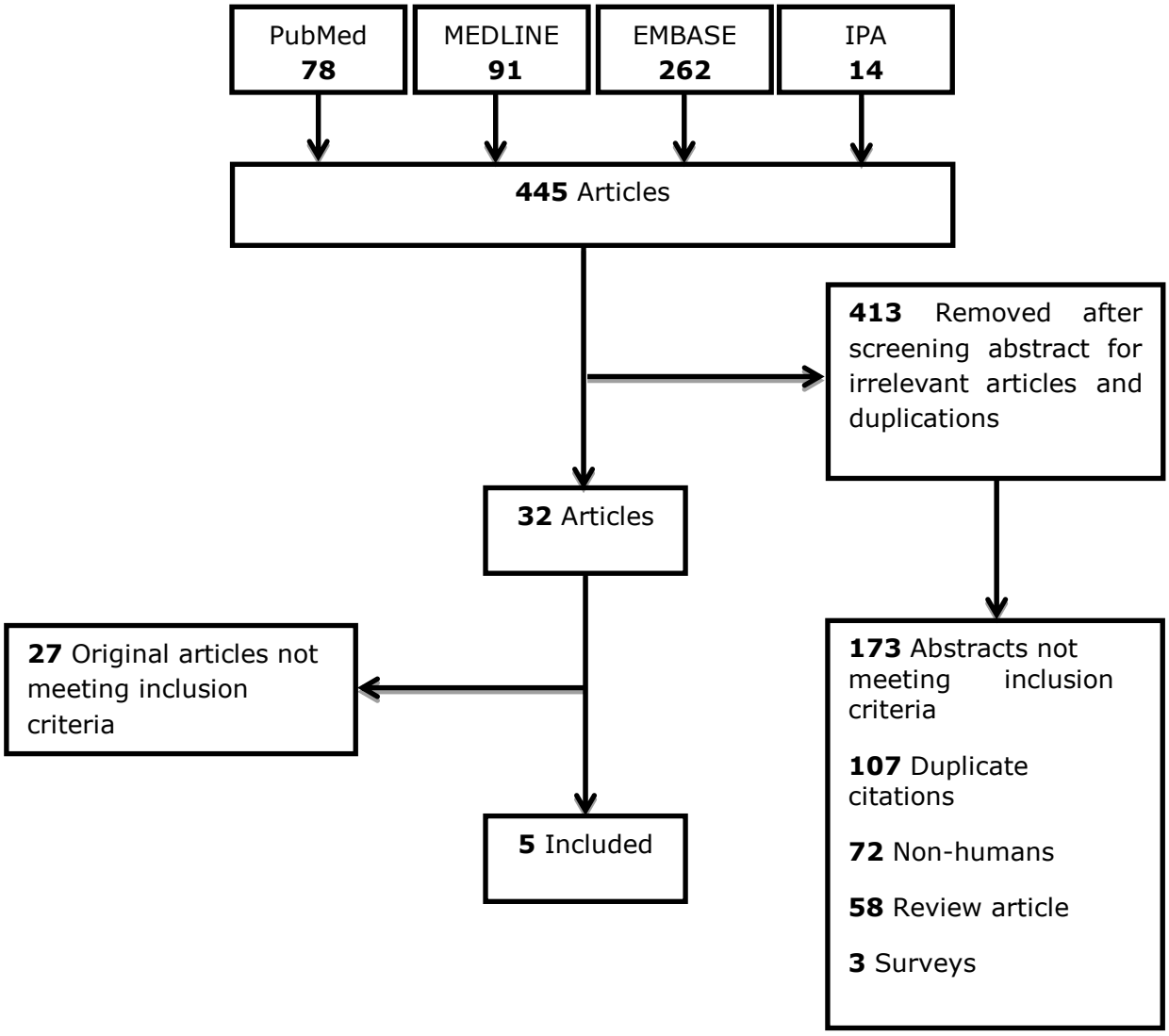


Table 4. 2: Characteristics of the five selected studies

Study/ Country	Type of study	No. of children	Paraldehyde group	Age	No. (%) of AEs
Palomo et al., 1988/Spain [319]	Prospective observational	8	8	18 months to 4 years	2 (25%) vomiting
Adenipekun et al., 1997/Nigeria [321]	Retrospective	84	Not specified	1 month to 6 years	35 (85.4%) injection cellulitis, 3 (7.3) paresis of lower limb, 2 (5%) sterile abscesses, 1 (2.4%) aspiration pneumonia
Keengwe et al., 1999/UK [320]	Prospective observational	1857	Not specified	5 months to 19 years	Not specified
Dearlove and Corcoran, 2007/UK [322]	Prospective observational	4643	Not specified	Not specified	Not specified
Sammons et al.,2011/UK [323]	Prospective observational audit	297	149 (0.5%)	Median 2 years	Not specified

The five studies identified were published from 1988 to 2011. The majority (4) were prospective observational studies. They were performed in three different countries (Nigeria, Spain and the UK) (Table 4.1).

The first study was published in 1988 by Palomo et al. to evaluate the efficacy and safety of paraldehyde when administered rectally to eight paediatric patients, aged from 18 months to 4 years undergoing audiometric tests [319]. The dose of paraldehyde ranged between 0.15 ml/kg and 0.5 ml/kg. Effective sedation was achieved in 6 (75%) of the children, while two children (25%) failed (there was no relation between the paraldehyde dose and sedation duration). The onset of action was reached within 5 to 15 minutes and the duration of sedation was from 4 to 8 hours. The only reported adverse event was vomiting, occurring in 2 cases/8 children (25%) of the patients.

A retrospective study evaluated the occurrence of complications following sedation of children undergoing radiotherapy [321]. The authors reviewed the records of 84 children aged from one month to six years. The doses of sedative agents were 25mg to 50mg chlorpromazine, 6.25mg to 12.5mg promethazine, I.M paraldehyde and I.V diazepam. Complications were observed in 41 children (41/84, 49%). Tolerance was distinguished by the third week of paraldehyde daily I.M injection which led to an increase in the dose or addition of diazepam I.V. Reported AEs included injection cellulitis 35 (35/41, 85.4%), paresis of lower limb 3 (3/41, 7.3), sterile abscesses 2 (2/41, 5%), and aspiration pneumonia 1 (1/41, 2.4%). The authors did not mention how many children received paraldehyde alone or in combination with other drugs.

The following year (1999), Keengwe and colleagues conducted a prospective observational study to assess the efficacy and safety of their structured sedation program [320]. A total of 1857 children aged between 5 months and 19 years undergoing MRI scans received either oral sedation that consisted of chloral hydrate

90 mg/kg (maximum 2g) orally with or without rectal paraldehyde 0.3 ml/kg (in children ≥6 years). All MRI scan requests for paediatric patients who failed oral PS, as well as those diverted for general anaesthesia from the beginning, were allocated to undergo the MRI scan with either general anaesthesia or intravenous sedation after reassessment by a consultant anaesthetist. Sedation was accomplished in 93.1% of the children given oral sedation.

The only adverse events were reported in oral chloral hydrate group alone in which two paediatric patients developed severe respiratory depression necessitating 12 to 18 hours monitoring in the hospital following scanning. No data was given regarding the number of patients receiving paraldehyde.

From 2002 to 2006, the efficacy and safety of the structural sedation programme of Manchester children's hospitals for MRI examination in paediatric patients were evaluated [322]. 4165 children underwent PS. For those <20 kg the agents prescribed were 100 mg/kg up to maximum dose of 2 gm of chloral hydrate with or without 0.3 ml/kg paraldehyde. For those >20 kg quinalbarbital 10mg/kg up to 200 mg orally was prescribed. Additionally, there were 478 children who underwent general anaesthetics due to sedation failure or general anaesthesia referral. The total failure rate was 11% (478 of 4165 children). There were five AEs which were respiratory complications due to PS. Only, one AE developed after general anaesthesia (not specified by authors). Numbers, safety and/or clinical effectiveness data for those that received paraldehyde sedation were not specified as a separate group.

Another observational study evaluated the safety and clinical effectiveness of both sedation and anaesthesia for neuroimaging procedure in children from 2000 to 2004 at the University hospital of Nottingham [323]. The population consisted of 297 patients (median of 2 years of age) given sedation for neuroimaging. The sedation regimen included- Chloral hydrate 50 to 100 mg/kg to a maximum of 2 g, with or

without rectal paraldehyde 0.3 ml/kg for children younger than four years and Quinalbarbitone 7.5 to 10 mg/kg to nearest 25 mg to a maximum of 200 mg, with or without rectal paraldehyde 0.3 ml/kg for children older than four years. Chloral hydrate was given as the first drug to 64%, quinalbarbitone to 35%, paraldehyde to 0.5% and midazolam to 0.5%. A second drug was administered in 16% cases. Successful sedation was achieved in 92% of the children, with median duration time of three hours and 9 minutes. 1.5 % cases failed to achieve sedation. Vomiting occurred in 36% of the paediatric patients and 20% were given supplemental oxygen throughout the neuroimaging scan. Additionally, one serious adverse event occurred, the child required oxygen therapy and hospitalisation. In another group 111 paediatric patients, with median age of 5 years, were given general anaesthesia for neuroimaging procedure, all were completed successfully. Vomiting was developed by one child after awakening from general anaesthesia and two children developed nausea. Median duration time for general anaesthesia was one hour and 30 minutes. The authors concluded that general anaesthesia is more convenient and better tolerated than (PS) for paediatric neuroimaging. No separate data was given for the patients receiving paraldehyde.

4.4. Discussion

The aim of this systematic literature review was to evaluate paraldehyde safety and clinical effectiveness in order to develop evidence based for its use as sedative agent in children. However this systematic review could not find any studies evaluating and/or comparing the safety and /or clinical effectiveness of paraldehyde with other available sedative dugs commonly used for (PS) in children.

The major problem associated with assessing the safety and clinical effectiveness of paraldehyde sedation is the small number of studies, their poor quality and limited data available within them. In Palomo and colleagues (1988), the data is from only

eight subjects, which is too small to evaluate safety, however this was the only study that clearly aimed to evaluate use and safety in children [319]. It found only two cases of vomiting that were self-limiting and required no therapeutic intervention.

The number of children who received paraldehyde, alone or in combination with other sedative agents, and the number and severity of AEs were not mentioned in 2 of the reviewed studies [320, 322]. The studies by Sammons et al. (2011) and Dearlove (2007) evaluated the safety and efficacy of their institutional (PS) guidelines [322, 323]. Paraldehyde was used as a second-line agent and was not separately described.

With respect to secondary outcomes, none of the studies that evaluated the effectiveness of paraldehyde used the Ramsey Sedation Scale (RSS) or another precise measurement system. Palomo et al. (1988) concluded that sedation was effective in 3/4 of the children, however, the study did not describe the exact dose of rectal paraldehyde [319].

The trial by Keengwe and colleagues (1999) compared the efficacy of oral sedation, intravenous sedation and general anaesthesia, but no data was given about clinical effectiveness of paraldehyde sedation alone or as a second line sedative [320].

We do not feel that there is any evidence in the literature that currently supports the use of paraldehyde as a first or second line agent for sedation in children.

4.5. Limitations

Our systematic literature review is limited by the small number of studies that evaluated the outcomes. The data were pooled from only 3 studies that evaluated the AEs and successful PS of paraldehyde. Accordingly, our results regarding safety and clinical effectiveness can only be considered preliminary.

4.6. Conclusions

This systematic review was carried out to evaluate paraldehyde safety and clinical effectiveness for paediatric (PS). The data were limited and available in only 5 studies, and the evidence for the use of paraldehyde in (PS) in children remains questionable. This highlights the importance of further large and well-designed studies to confirm its future use.

CHAPTER FIVE

Midazolam for Sedation of Children during Imaging Procedures: A Systematic Review

5.1. Introduction

Several sedatives are available for procedural sedation (PS) in children[254]. The choice of drug depends on practice, guidelines and physician comfort[324]. Midazolam belongs to a class of benzodiazepines named imidazobenzodiazepines[12]. Clinically, midazolam is primarily used as premedication or as a sedative for minor procedures because it has a relatively rapid onset of action and short half-life [325]. It also has anticonvulsant and muscle relaxant characteristics [326].

Midazolam is extensively used for sedation in children word-wide. In this chapter I will describe a systematic literature review of studies evaluating midazolam effectiveness and safety as a sedative agent in children undergoing imaging procedures. We focused on its use for imaging procedures because midazolam is the recommended drug at the Royal Derby Hospital for imaging diagnostic procedures in children over 15 kg. However, a local hospital audit study (unpublished) conducted at the hospital evaluating the effectiveness of midazolam during imaging procedures in 20 children suggests that midazolam does not work (only 40% of children completed their procedures after sedation was supplemented with paraldehyde, while no children on midazolam alone completed their procedures).

5.2. Method

This systematic literature review was conducted using MEDLINE (1948– September 2014), EMBASE (1980– September 2014), International Pharmaceutical Abstracts (IPA) (1970- September 2014), and PubMed (until September 2014).

In order to select the most specific and sensitive key words for the search strategy, an initial search for related terms was conducted. These terms were used by previous review studies by Lourenço-Matharu et al. in 2012 and Morão et al. in 2011 [327, 328]. Our search terms were also selected according to a validated age-specific search strategy developed by the Hedges Team [166]. These terms included: midazolam and children or infant or pe*diatric* or neonate or adolescence or adolescences or adolescent and Hypnotics or Sedatives or Anti-Anxiety Agents or Conscious sedation or Preanesthetic medication or preanaesthetic medication or sedat$ or Anxiety or anxiety or anxious or fear$ or fright$ or stress$ or distress$ or phobi$ or uncooperative or un-cooperative or unco-operative.

All studies, irrespective of language, which evaluated midazolam safety or adverse events and clinical effectiveness, were included. Letters, comments, editorials, notes, review articles, studies involving patients older than 18 years and studies that did not use midazolam for PS during imaging were excluded.

All selected abstracts were double-checked to ensure that they satisfied the inclusion and exclusion criteria. The included articles were read carefully, and the following data was extracted from each study: sample size, study region, study period, study design, dose of midazolam, adverse drug events of midazolam, other sedative drug(s) used, supplementary dose of sedative drug(s), induction time of sedation, duration of sedation, failure rate and success rate. The children were grouped by age: less than 2

years, from 2 through 11 years, and from 12 through 18 years, according to the guidelines of the International Conference of Harmonization (ICH) [167].

- **Outcome measures**

1. Evaluating the incidence of AEs in children who received midazolam.
2. Evaluating success rate of imaging procedures.

AEs were categorised as either serious or mild, according to the European Medicines Agency guideline [50]

- A serious AE is defined as "any untoward medical occurrence that, at any dose, results in death (or) is life-threatening, (or) requires inpatient hospitalisation or prolongation of existing hospitalisation (or) results in persistent or significant disability/incapacity, or is a congenital anomaly/birth defect".
- A mild AE is defined as "any AE that occurred that did not need any intervention".

Hypoxia was regarded as mild when the value of arterial haemoglobin oxygen saturation (SpO2) fell to between 90 and 95%, moderate between 85 and 89%, and severe when less than 85%[120]. Successful PS was defined as the ability to sedate the child to the target sedation level and the ability to achieve the imaging procedure[262].

All studies were assessed for risk of bias. The Cochrane collaboration's tool was used to evaluate randomized controlled studies (RCTs) [329]. Prospective observational studies, and retrospective studies were assessed using the STROBE checklist [169]. Any study with a minimum score of 70% was considered to be of good quality.

Data from included studies were analysed statistically using SPSS version 22. Incidence was calculated by dividing the number of AEs by the number of children exposed to midazolam, excluding case reports. The clinical efficacy was calculated as the weighted mean difference of the number of children whose procedures were completed successfully with midazolam compared to placebo or other sedative agents. Fisher's exact test was used to compare sedative supplementations between imaging procedures. The differences between imaging procedures was considered significant at $P<0.05$. Meta-analysis was not performed due to the heterogeneity of the studies.

5.3. Results

The total number of articles identified after searching EMBASE, MEDLINE, IPA, and PubMed databases was 4402. After removing duplications and to include only humans, 2903 articles remained (Figure 5.1). During the initial screening of article titles and abstracts, 948 articles were removed, leaving 1955 articles. The inclusion and exclusion criteria were applied to these, resulting in 29 studies, including 17 RCTs, 10 prospective observational studies, 1 retrospective study and 1 case report (Figure 3.1 and Table 3.1).

The final 29 studies were performed in 12 countries and included 6342 children (Table 5.1), who were aged between 0 and 18 years (mean 45 months). The doses given are shown in Table 5.2.

Figure 5. 1: Flow chart of study

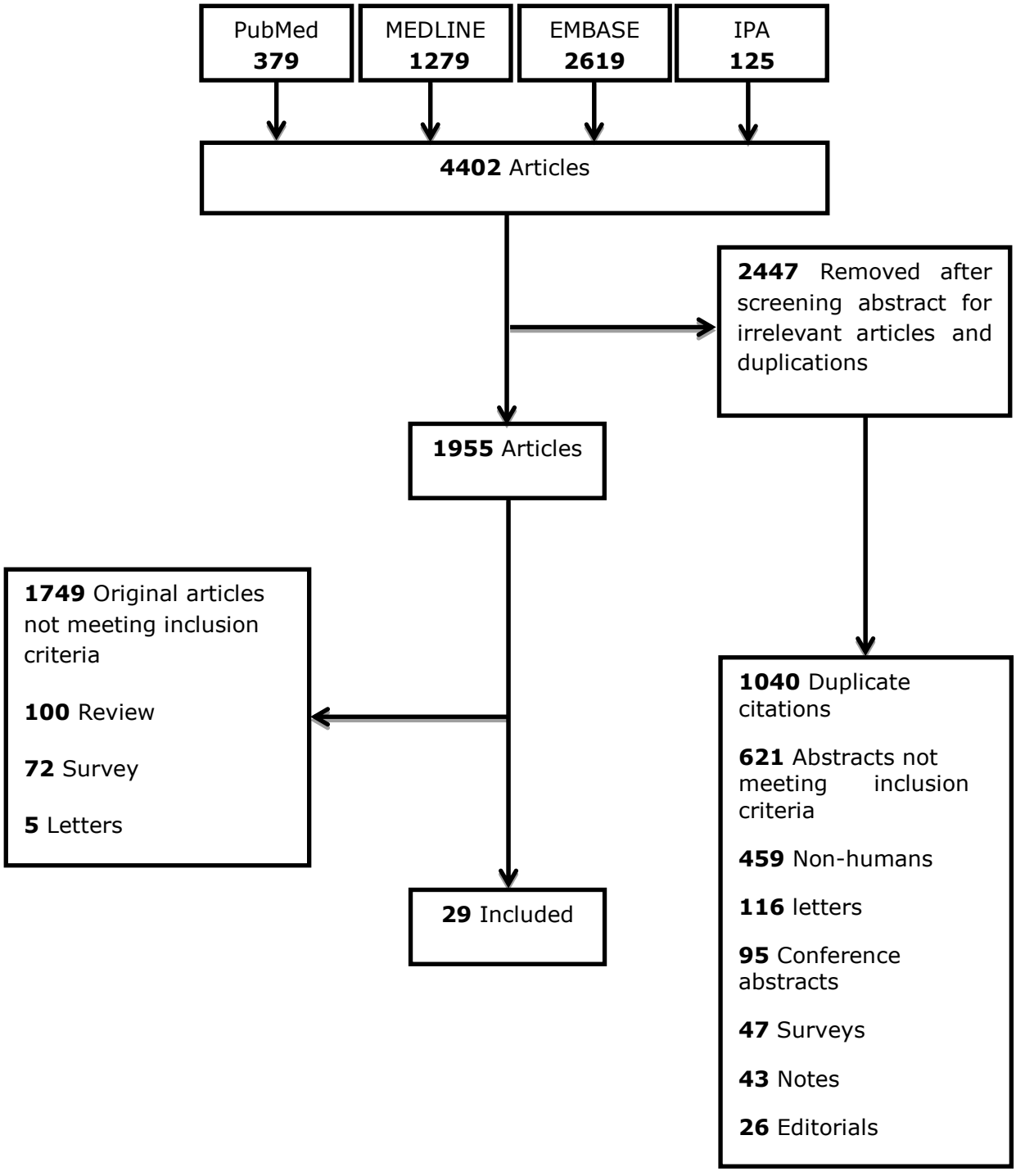


Table 5. 1: Summary of 29 studies that reported on clinical effectiveness and safety of midazolam for imaging procedures in paediatrics

Study characteristics	Number of studies	Number of children
Type of study	**N=29**	**N=6342**
• Randomised controlled trial	17	1269
• Prospective observational	10	4704
• Retrospective	1	367
• Case report	1	2
Type of imaging procedure		
• CT, MRI	19	5576
• MCUG, VCUG	6	271
• ECG	2	162
• EEG	1	100
• Gamma camera examination	1	233
Route of Administration		
• Oral	12	1225
• Intravenous infusion	6	3556
• Intranasal	4	579
• Intravenous bolus	3	376
• Rectal	3	130
• Not reported	1	476
Age groups		
• Preterm neonates	0	0
• Term neonates	2	9
• Infants	0	0
• Children	5	341
• Other patient age groups*	22	5992

MCUG= micturating cystourethrogram, VCUG= voiding cystourethrogram

*Including paediatric studies for which the age group was mixed or not stated.

Table 5. 2: Routes of drug administration and ranges of midazolam doses

Routes of drug administration	Range of doses (median)
By mouth	0.5 to 0.6 mg/ kg **(0.5 mg/kg)**
Intranasal	0.15 to 0.5 mg/ kg **(0.3 mg/kg)**
Intravenous bolus	0.1 to 0.6 mg/ kg **(0.16 mg/kg)**
Intravenous infusion	LD* 0.02 to 0.2 mg/kg **(0.2 mg/kg)** MD** 0.15 to 0.6 mg/kg **(0.3 mg/kg)**
Per rectal	0.3 to 1 mg/ kg **(0.3 mg/kg)**

*LD= loading dose, **MD= maintenance dose

Using the Cochrane risk of bias criteria for quality assessment five RCTs were rated high-risk in their blinding of participants and personnel [177, 271, 330-332]. The assessment of incomplete outcome was inadequately described in 5 RCTs [330-334]. The risk of bias in the blinding of outcome assessment was high in 4 RCTs [177, 330, 331, 335]. Three RCTs were rated high risk in selective reporting bias [177, 332, 334] (Figure 5.2). Nine of the 11 observational studies were rated as meeting 70% of the criteria or higher. The remaining two were rated 68% [3, 336] (Table 5.3). All studies were included in the systematic review in order to avoid missing any data due to the small number of articles identified for each imaging procedure.

Figure 5. 2: Cochrane risk of bias criteria for quality assessment of RCT

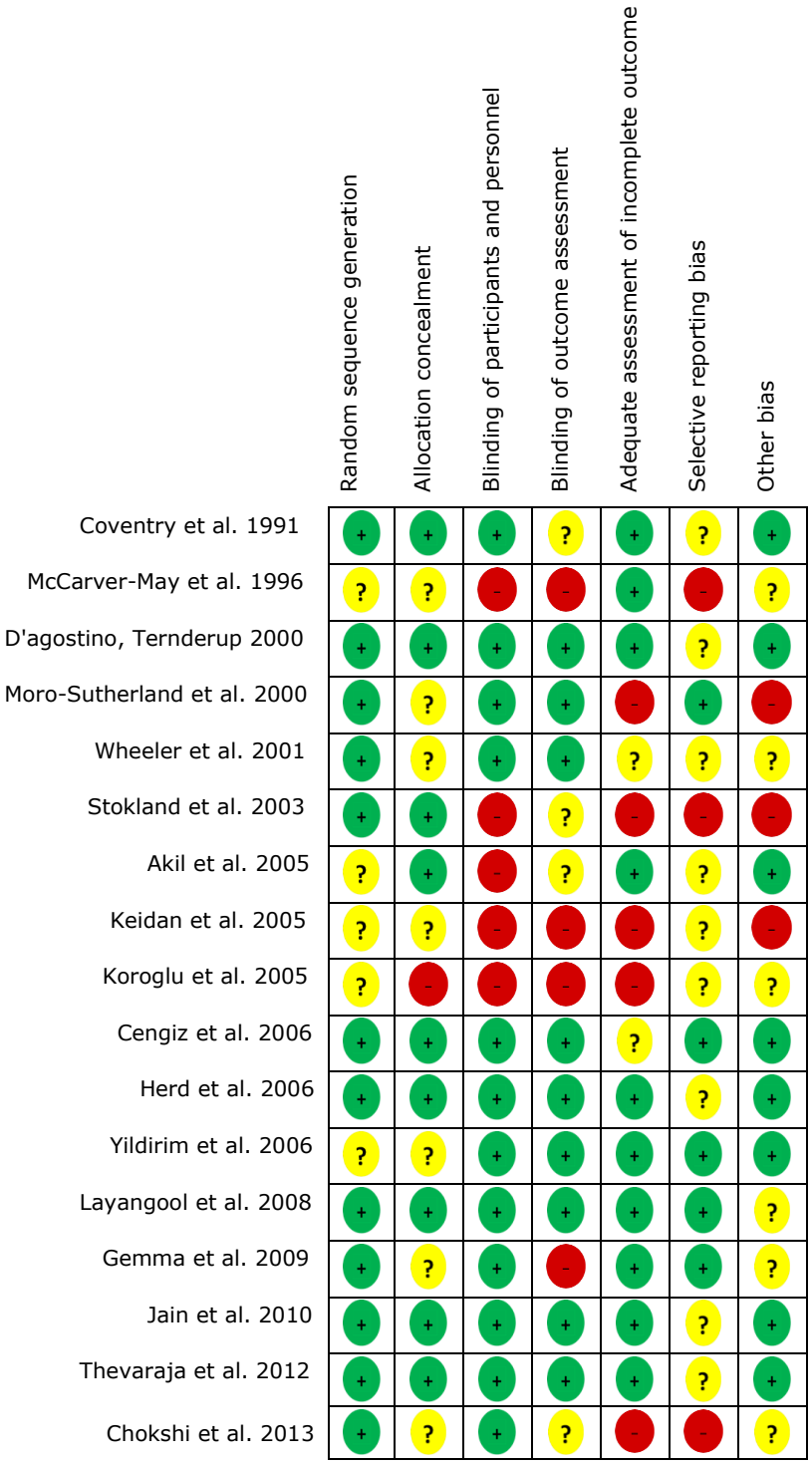


Table 5. 3: Quality assessment criteria of included observational studies

References	STROBE scoring (out of 22)	%
Singh et al. 2009[337]	19	86
Ashrafi et al. 2013[338]	18	82
Elder, 1995[339]	18	82
Szczepaniak et al. 2004[340]	18	82
Solvis et al. 1993[202]	17	77
Ljung, 1996[341]	16	73
Malviya et al. 2000[207]	16	73
Mekitarian et al. 2013[342]	16	73
Koroglu et al. 2005[331]	16	73
Doganay et al. 2001[336]	15	68
Alp et al. 2002[3]	15	68

5.3.1. Midazolam Effectiveness

All included studies were classified according to five types of imaging procedure (Table 5.1). The measures of effectiveness in this systematic review included procedural success, induction time of sedation, and duration of sedation, as reported by the original investigators.

Twenty three articles evaluated the clinical effectiveness of midazolam for imaging procedure sedation: 8 computed tomography (CT), 6 magnetic resonance imaging (MRI), 6 micturating urethrograms (MCUG) or voiding urethrograms (VCUG), 2 electrocardiograms (ECG), and 1 electroencephalogram (EEG).

5.3.3.1. CT scanning

Eight studies (5 RCTs and 3 prospective studies) evaluated midazolam effectiveness for CT scanning in 650 children (Table 5.4).

The success rate of midazolam procedural sedation was variable and ranged from 19% in one study to 100% (median 69%). Fifty four patients (8.3%) required supplementary dose(s) of either midazolam 0.2mg/kg, pentobarbital 2.5 to 5 mg/kg

(mean 3.75 mg/kg), or ketamine/lignocaine 5 mg/kg +2 mg/kg. The onset of sedation for the intravenous route ranged from 3 to 15 minutes and for the rectal route ranged from 16 to 20 minutes. The duration of sedation for the intravenous route ranged from 4.8 to 55 minutes, for the oral route ranged from 4.1 to 76 minutes and for the rectal route ranged from 66 to 157 minutes (Table 5.3).

Table 5. 4: RCTs and observational studies for CT scanning

Reference, country	Study design	Age	No. of patients	Drug	Dose mg/kg	Success rate (%)	Supplementary dose/med (No.)	Sedation (min)	
								Onset	Duration
Coventry et al. 1991, UK[343]	Double-blind RCT	5 months-5 years	15 15	M M	0.3 PR 0.6 PR	87 80	Y (5) Y (5)	16 10	157 NA
McCarver-May et al. 1996, USA[177]	Single-blind randomised cross-over	Median 14 days	7 7	M CH	0.2 IV 75 PO	43 100	N N	3-15 9-40	15- 55 15- 55
D'Agostino & Terndrup 2000, USA[171]	Double-blind RCT	2 months–8 years	22 11	M CH	0.5 PO 75 PO	50 100	Y (12) Y (1)	NA NA	76 95
Morp-Sutherland et al. 2000, USA[333]	Single-blind RCT	6 months-6 years	26 29	M PEN	0.2 IV infusion 5 IV infusion	19 97	Y (16) N	NA 6	NA 86
Jain et al. 2010, India[344]	Double-blind RCT	1-5 years	29 31 32	M M+K P	0.5 PO 0.25 PO+ 1 PO	100 100 100	NA NA NA	NA NA NA	4.1 4.5 5.2
Doganay et al. 2001, Turkey[336]	Prospective observational study	1-18 years	30	M	0.35 PR	100	NA	NA	NA
Alp et al. 2002, Turkey[3]	Prospective observational study	2- 78 months	20 30 20	M T C	1 PR 50, 35, 25 PR 0.1 ml/kg IM	36.6 39 24.4	NA	20 15 22	66 94 118
Singh et al. 2009, India[337]	Prospective observational study	6 months-6 years	516	M	0.2 IV infusion	98	Y (16)	5.9	4.8

CH= chloral hydrate, IV= intravenous, K= ketamine, M= midazolam, P= placebo, PEN= pentobarbital, PO= Orally, PR= per rectum (by rectum), T=Thiopental, C=Cocktail

5.3.3.2. MRI

Three RCTs and two prospective observational studies evaluated midazolam in 143 children aged from 1 to 18years during MRI (Table 5.5). The success rate varied from 0 to 100% (median 67%). Success was lower after a single dose (20%) and increased significantly (up to 100%) after supplemental IV boluses of 0.5 mg/kg propofol[331, 335]. 35 children (24.5%) required supplementary sedatives (midazolam 0.2 mg/kg or propofol 0.5 mg/kg) to complete the procedures. The onset of sedation varied from 15 to 43 minutes and the duration of action ranged from 2.5 to 118 minutes.

Patients receiving CT scans were less likely to require supplemental doses of sedative compared to those receiving MRI (RR= 27.6, 14% CI: 33-53.15, P=0.0001).

Table 5. 5: RCTs and observational studies for MRI

Reference, country	Study design	Age	No. of patients	Drug	Dose mg/kg	Success rate (%)	Supplementary dose/med (No.)	Sedation (min)	
								Onset	Duration
Koroglu et al. 2005, Turkey[331]	Single-blind RCT	1-7 years	40 40	M Dext	0.6 IV infusion 0.5 µg IV infusion	97.5 97.5	Y (30) Y (8)	35 19	25 24
Cengiz et al. 2006, Turkey[345]	Double-blind RCT	1-7 years	48 48	M + P M + Diph	0.5 PO 0.5 + 1.25 PO	59 82	NA NA	15- 30 15- 43	15-43 14-45
Gemma et al. 2009, Italy[335]	Single-blind RCT	3-7 years	5 7	M Pro	0.6 IV infusion 4 IV infusion	100 100	Y (5) Y (5)	NA NA	2.5-15 2-15
Doganay et al. 2001, Turkey[336]	Prospective observational study	1-18 years	30	M	0.35 PR	67	NA	NA	NA
Alp et al. 2002, Turkey[3]	Prospective observational study	2- 78 months	20 30 20	M T C	1 PR 50, 35, 25 PR 0.1 ml/kg IM	0 76.5 23.5	NA	20 15 22	66 94 118

IV= intravenous, K= ketamine, M= midazolam, P= placebo, PEN= pentobarbital, PO= orally, PR= per rectum (by rectum), Diph= Diphenhydramine,

Dext= Dexmedetomidine

- **RCTs comparing effectiveness to other agents in CT and MRI**

Seven RCTs compared midazolam effectiveness with other sedative agents for CT and/or MRI (Tables 5.4 and 5.5). In 4 RCTs, midazolam was less effective than the comparator [171, 177, 333, 345].

Coventry et al. (1991) compared midazolam in different doses and found that midazolam given rectally as the sole agent during CT scanning was effective in approximately half of the children[343]. After supplementary doses of ketamine 5 mg/kg or lignocaine 2 mg/kg, midazolam 0.3 mg/kg and 0.6mg /kg produced adequate sedation for the procedure to be completed in 87% and 80% of the children respectively. The authors found that midazolam 0.3 mg/kg and 0.6mg/kg were not different in effectiveness for sedation for CT.

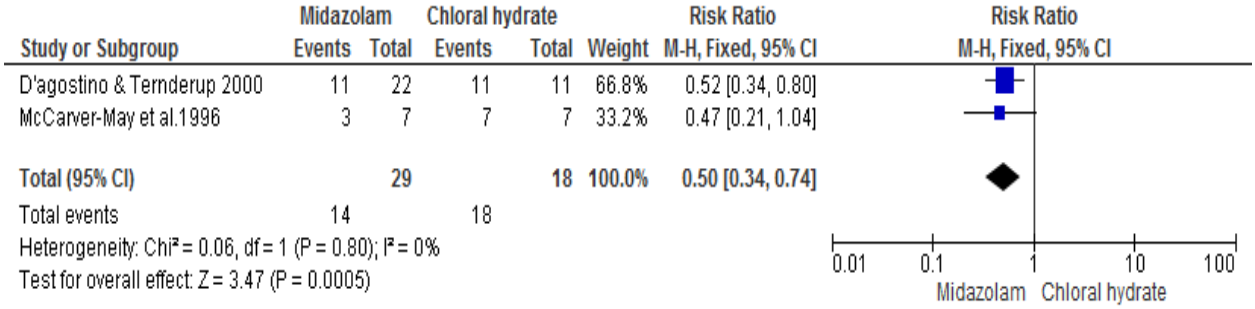
In a crossover study by McCarver-May et al. (1996) 7 infants (median 14 days) undergoing CT scanning were successfully sedated with a single dose of oral chloral hydrate 75 mg/kg. After 48 hours these same 7 infants underwent a second episode of imaging and instead received IV midazolam 0.2 mg/kg; only three were successfully sedated with a single dose (p=0.04)[177]. Another study by D'Agostino and Terndrup found that oral midazolam 0.5 mg/kg was ineffective in 11 of 22 children (50%) undergoing MRI and CT scanning[171]. The authors discussed the duration of the diagnostic procedure, which might have precluded the efficacy of midazolam as a sedative[171]

Midazolam was associated with a faster onset of sedation in two RCTs[177, 345] and slow onset of action in one RCT[331].

Two RCTs compared midazolam procedural success with chloral hydrate during CT scanning in children aged 2 months to 8 years[171, 177] (Figure 5.3).

The pooled risk ratio (RR) of the procedural success rates for midazolam versus chloral hydrate was 0.50 (95% CI: 0.34, 0.74) (P= 0.0005), favouring chloral hydrate.

Figure 5. 3: Midazolam versus chloral hydrate



5.3.3.3. MCUG/VCUG

Six RCTs reported midazolam effectiveness for MCUG/VCUG procedural sedation. The number of children recruited was 271, and their ages ranged between birth and 15 years (median 5 years). In four of these studies, midazolam was administered orally. In one, it was given intranasally, and in another, by intravenous injection (Table 5.6). The onset of action ranged between 10 and 35 minutes. The procedural success rate ranged from 94% to 100%. All procedures were performed successfully. Midazolam was effective for all the children in 5 of the 6 studies. In one study, it was less effective than chloral hydrate. In three studies, both agents were effective in all children.

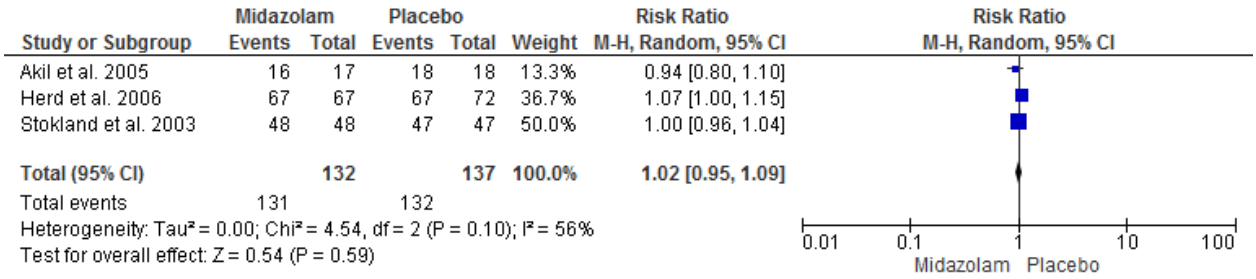
Table 5. 6: RCTs and observational studies for MCUG/VCUG

Reference, country	Study design	Age	No. of patients	Drug	Dose mg/kg	Success rate (%)	Supplementary dose/med (No.)	Sedation (min)	
								Onset	Onset
Stokland et al. 2003, Sweden[332]	Double-blind RCT	0.5-9.0 years	48 47	M P	0.2 IN	100 100	NA NA	NA NA	15-105 15-85
Akil et al. 2005, Turkey[271]	Single-blind RCT	0.8-14.5 years	17 18 18	M CH P	0.6 PO 25 PO	94 100	NA NA	10-35 10-20	40-105 20-35
Keidan et al. 2005, Israel[330]	Single-blind RCT	3–15 years	24 23	M N2O	0.5 PO 50% inhaled	100 100	NA NA	NA NA	20 23
Herd et al. 2006, New Zealand [346]	Double-blind RCT	1-14 years	67 72	M P	0.5 PO	100 93	NA NA	NA NA	NA NA
Thevaraja et al. 2013, India[347]	Double-blind RCT	4-8 years	17 17	M K	1-2 µg IV infusion 10-20 µg IV infusion	100 100	N N	9.40 6.80	36 33.7
Elder, Longenecker 1995, USA[339]	Prospective observational	23 months-9 years	98	M	0.6 PO	100	N	10-15	NA

CH= chloral hydrate, IN= intranasal, IV = intravenous K= ketamine, M= midazolam, NA= not available, N2O= nitrous oxide, P= placebo, PO= per oral,

The pooled risk ratio (RR) of procedural success rate using midazolam versus placebo was 1.02 (95% CI: 0.95, 1.09) (P= 0.59). This shows no statistical difference between the use of midazolam and placebo in the success of the procedure (Figure 5.4).

Figure 5. 4: Midazolam versus placebo



5.3.3.4. ECG

Three RCTs evaluated midazolam for sedation during ECGs in 344 children aged from 6 months to 5 years. Midazolam was given orally in all studies.

The mean onset of action was 11 minutes; the mean duration of action was 40 minutes. The success rate was reported between 36% and 100% (median 95%). Twenty children (8.4%) needed a supplemental dose of 0.5 mg/kg midazolam (Table 5.7).

Table 5. 7: ECG RCTs

Reference, country	Study design	Age	No. of patients	Drug	Dose mg/kg	Success rate (%)	Supplementary dose/med (No.)	Sedation (min)	
								Onset	Onset
Wheeler et al., 2001, USA[175]	Single-blind RCT	1- 5 years	25 15	M CH	0.5 PO 75 PO	36 93	Y (13) Y (5)	mean 27.3 mean 25	mean 21.69 mean 25.6
Yildirim et al. 2006, Turkey[348]	Single-blind	6 months- 3 years	30 30 20	M M control	0.4 PO 0.2 IN	100 100	NA NA	10 NA	NA 10
Layangool et al. 2008, Thailand[173]	Double-blind	6 months-5 years	132 132	M CH	0.5 PO 50 PO	95 89	Y (7) Y (14)	11.13 25.1	40.10 78.9

CH= chloral hydrate, IN= intranasal, M= midazolam, NA= not available, PO= per oral

5.3.3.5. EEG

A prospective observational study by Ashrafi et al. (2013) compared oral midazolam 0.5 mg/kg to 5% oral chloral hydrate 1 ml/kg [338]. There were 100 children in the midazolam group versus 98 in the chloral hydrate group, aged from 2 months to 9 years (median 4 years). Sleep onset was significantly shorter in children who received chloral hydrate, at 20 to 95 minutes (median 32 minutes) versus 45 to 98 minutes (median 58 minutes) in the midazolam group ($p<0.001$). The duration of sedation was significantly shorter in the midazolam group, at 12 to 38 minutes (median 25.5 minutes), versus 56 to 98 minutes (median 66.5 minutes) in the chloral hydrate group ($p<0.001$).

- **Summary of midazolam clinical effectiveness**

We found 23 articles evaluating the use of midazolam for imaging sedation. The following table illustrates the success rates per type of imaging procedure (Table 5.8).

Table 5. 8: Success rate (%) of all types of imaging procedure

Procedures	Midazolam dose Range (median dose)	Success rate Range (median success)
MCUG/VCUG	▪ Oral, 0.5 to 0.6 mg/kg (0.55mg/kg) ▪ IV infusion, 0.1 to 0.2 mg/kg/min ▪ IN, 0.2 mg/kg	94 to 100% (97%)
ECG	▪ Oral, 0.4 to 0.5 mg/kg (0.45 mg/kg)	36 to 100% (95%)
CT	▪ Oral, 0.5 mg/kg ▪ rectal, 0.3- 0.6 mg/kg ▪ IV infusion, 0.2 mg/kg over 2-4 min	19 to 100% (69%)
MRI	▪ Oral, 0.5 mg/kg ▪ IV infusion, 0.2- 0.6 mg/kg/min (median 0.55 mg/kg)	0 to 100% (67%)

IN= intranasal, IV = intravenous MCUG= micturating cystourethrogram, VCUG= voiding cystourethrogram

5.3.2. Midazolam safety

Twenty five studies evaluated midazolam safety. They were published between 1991 and 2013 and included 6145 children aged from birth to 18 years. RCTs were the most common type of study, but most AEs were reported in the prospective observational studies (Table 5.9).

Table 5. 9: Summary of 26 studies that reported on safety of midazolam

Type of study	No. of studies (N=25)	Age of children (range)	Children receiving midazolam (N=2046)	Adverse Events (N=301)
Randomised controlled trial	14	0-15 years	1220	26
Prospective observational	10	0-18 years	459	244
Retrospective population based	1	2 months-14 years	367	31

Of the 25 studies that monitored AEs, 15 reported one or more. The other 10 studies reported no AE (Tables 5.10 & 5.11). The mean age of the children receiving midazolam was 41 months, excluding 2 studies which did not report the mean age [202, 337]. In total, 2046 children were exposed to midazolam, and there were 301 reported AEs. This gave an estimated risk of AE as 15 in every 100 patients, or 1 AE in every 6 patients. Other than nasal discomfort, the most frequently occurring AEs were hypoxia, vomiting, paradoxical reaction and prolonged sedation (Table 5.12). No severe AEs or medication-related deaths were reported.

Table 5. 10: Summary of 15 studies that reported AEs

Reference	Study design	Age	No. of patients receiving midazolam N= 1832	No. of AEs N=301
McCarver-May et al. 1996[177]	RCT	Median 14 days	7	8
D'Agostino, Terndrup 2000[171]	RCT	2 months-8 years	22	1
Keidan et al. 2005[330]	RCT	3-15 years	24	1
Cengiz et al. 2006[345]	RCT	1-7 years	48	8
Herd et al. 2006[346]	RCT	1-14 years	67	2
Layangool et al. 2008[173]	RCT	6 months-5 years	132	6
Solvis et al. 1993[202]	Prospective observational	8-18 years	80	16
Elder, 1995[339]	Prospective observational	23 months-9 years	98	11
Ljung, 1996[341]	Prospective observational	6 months-15 years	233	136
Malviya et al. 2000[207]	Prospective observational	0-18 years	40	14
Koroglu et al. 2005[331]	Prospective observational	1-7 years	40	3
Singh et al. 2009[337]	Prospective observational	6 months-6 years	516	57
Ashrafi et al. 2013[338]	Prospective observational	2 months-9 years	100	2
Mekitarian et al. 2013[342]	Prospective observational	1 month-5 years	58	5
Szczepaniak et al. 2004[340]	Retrospective population-based	2 months-14 years	367	31

Table 5. 11: Summary of 10 studies that reported no AEs

Reference	Study design	Age	Patients receiving midazolam (N= 214)
Coventry et al. 1991[343]	RCT	5 months-5 years	15
Moro-Sutherland et al. 2000[333]	RCT	6 months-6 years	26
Akil. et al. 2005[271]	RCT	Mean 6 years	17
Yildirim et al. 2006[348]	RCT	6 months-3 years	30
Gemma et al. 2009[335]	RCT	3-7 years	5
Jain et al. 2010[344]	RCT	1- 5 years	29
Thevaraja et al. 2013[347]	RCT	4- 8 years	17
Chokshi et al 2013[334]	RCT	Not available*	25
Doganay et al. 2001[336]	Prospective observational	1-18 years	30
Alp et al. 2002[3]	Prospective observational	2- 78 months	20

* Authors documented the weight of children and it was <10 kg were included

Table 5. 12: Reported AEs from 15 studies

Body system	Adverse effects	Frequency	Incidence (%)
Respiratory	Hypoxia	74	3.62
	Apnoea	3	0.15
Gastrointestinal	Vomiting	21	1.02
Central nervous	Paradoxical reaction	16	0.78
	Motor imbalance	7	0.34
	Agitation	4	0.20
	Anger/screaming	3	0.15
	Restlessness	3	0.15
	Aggression	2	0.10
	Irritability	2	0.10
	Lack of consolability	2	0.10
	Crabbiness	1	0.05
	Mood swings	1	0.05
	Wildness	1	0.05
Cardiovascular	Decreased mean arterial pressure (MAP)	3	0.15
	Tachycardia	1	0.05
Other	Nasal discomfort*	122	5.96
	Prolong sedation	14	0.68
	Hiccup	10	0.49
	Split vision	10	0.49
	Headache	1	0.05
Total		301	15.0

***Reported by one study only in children who received intranasal midazolam

Hypoxia was the most commonly reported AE. 74 children were documented to have had hypoxia with an estimated risk of 3.6 per 100 patients who received midazolam. Most cases of hypoxia were mild (SpO2 90-95%) in 42 cases (41/2046, 2.1%) or moderate (SpO2 <90%) in 32 cases (32/2046, 1.6%). No imaging procedures were discontinued as a result of hypoxia and cases of mild hypoxia were self-limiting. All patients with moderate hypoxia responded to supplemental oxygen. One case required nebulised salbutamol.

Three studies reported 32 children who experienced moderate hypoxia, which was defined as SpO2<90%. In two of these studies, midazolam was given as an IV bolus in doses ranging from 0.1 to 0.2 mg/kg (median 0.15 mg/kg) [177, 340]. The route of administration of midazolam was not mentioned in the other study [207]. The mean age of the children with moderate hypoxia was 50 months. This is similar to the mean age of children in all the studies (Table 5.13). Twenty seven of the 32 children were in one large retrospective cohort study [340].

Table 5. 13: Summary of the 32 children who developed moderate hypoxia

References	Study design	Patients receiving midazolam	Patients with moderate hypoxia	Age	Dose	Monitoring device(s) and intervention(s)
McCarver-May et al. 1996[177]	Double blind cross-over	7	4	Median 14 days*	0.2 mg/kg IV bolus	▪ Continuously monitored hemoglobin oxygen saturation ▪ Supplemental oxygen therapy ▪ Administration of albuterol nebulization (in one patient)
Malviya et al. 2000	Prospective	40	1	<18 years, mean 50 months*	Mean 0.15 ±0.13 mg/kg, route of administration not mentioned	▪ Pulse oximetry ▪ Supplemental oxygen therapy
Szczepaniak et al. 2004	Retrospective population-based	367	27	2 months to 14 years, mean 46 months*	0.1 mg/kg iv bolus	▪ Continuously monitored saturation (SaO2) and end-expiratory carbon dioxide concentration (ETCO2) ▪ Supplemental oxygen therapy

* Individual patient ages were not given

Vomiting was the second most reported AE, affecting 21 children (21/2046, 1%). It was reported in 16 studies (10 prospective observational studies, 5 RCTs and 1 retrospective cohort study). All the cases were self-limiting and none required medical intervention.

Nasal discomfort was reported in one prospective observational study in which 233 children received 0.3 mg/kg midazolam nasal drops and 143 children received 0.2 mg/kg midazolam nasal spray. Nasal discomfort was seen in 66 children (66/233, 28.3%) in the drops group versus 56 (56/143, 39.2%) in the spray group [341].

This systematic review identified one case report by Zaw et al. (2001) that discussed two cases of full-term neonates [349]. The first was a 4-day-old who developed

myoclonic-like movement of upper and lower extremities, 45 minutes after administration of 160 μg/kg IV bolus midazolam. The abnormal movements lasted for 90 seconds, then the infant became very irritable for about 10 minutes prior to failing asleep and received no medical intervention. The other case was a 2-day-old neonate who developed myoclonic-like movement of upper and lower extremities 30 minutes after administration of 500 μg/kg oral midazolam. The abnormal movements were controlled successfully by immediate administration of 20 mg/kg IV phenobarbital.

5.4. Discussion

This review showed that the success rate for midazolam PS varied across the different imaging procedures, with the success rate ranging from 0 to 100%. Midazolam was relatively ineffective for both MRI and CT, as the median success rate was 67% and 69% respectively. This could be because midazolam has a short duration, and these types of procedures usually require more time[343].

Conscious sedation using midazolam was found to be effective in children undergoing MCUV/MCUG in five RCTs involving 254 children. This finding supports the results of the retrospective observational study published by Elder and Longenecker (1995), which found that sedation with midazolam increased the success of VCUG/MCUG procedures by reducing anxiety in the children undergoing these procedures[339].

Our results indicate that midazolam is less effective than other sedative agents, including chloral hydrate, pentobarbital, and thiopental. In comparison with the effectiveness of chloral hydrate for imaging procedures (94% and 81% for CT and MRI, respectively), as shown in the previous chapter (Chapter 2, Part 2.1), the sedation success of midazolam is substantially lower.

With regards to the safety of midazolam, the previous studies differed widely in the number of reported AEs; some reported none, while others reported that a high percentage of patients (up to 45%) experienced them. In general, AEs were less frequently recorded in the RCT studies than in the cohort studies.

Respiratory complications were the most commonly reported AEs. Hypoxia was the most frequently reported AE, with 32 cases (32/2046, 1.6%) defined as moderate (SpO2 85–89%) and requiring an intervention. It is difficult to determine if the dosage or the age of patients were influencing factors for moderate hypoxia, as individual data was not provided for individual children in many studies. The frequency of moderate hypoxia emphasises the importance of having adequate and continuous monitoring during (PS). The incidence of other AEs was lower.

Hypoxia was also found to be the most commonly reported AE for chloral hydrate, as shown in the safety results in the previous chapter (Chapter 2, Part 2.1). However, it was reported more often with chloral hydrate PS (774/14439, 5.3%) than with midazolam sedation (74/2046, 3.6%). This is consistent with the results of Layangool et al. (2008), who found that 13 (9.9%) of the children in the chloral hydrate group experienced hypoxia, while only 4 (3%) of the children in the midazolam group experienced hypoxia [173].

Our review found that vomiting was the second most common AE (with an incidence of 1% (1/2046)) after hypoxia. There is some evidence that midazolam reduces the incidence of post-diagnostic or post-treatment nausea and vomiting in children [350, 351]. However, the high incidence of vomiting could be due to the bitter taste of midazolam itself [345].

In our systematic literature search, we tried to find as many AEs as possible in order to avoid missing serious AEs. In this extensive search, only one serious AE was found:

myoclonic-like movement of the upper and lower extremities. This AE was found in two neonates and required medical intervention (administration of 20 mg/kg IV phenobarbital) [349].

5.5. Limitations

The studies included in this systematic review have a number of limitations. Some RCTs were not double-blind studies, which means there is a potential for bias in the recording of results. In general, the number of studies included in the review was relatively small and the type of imaging procedure varied between studies, which led to differences in the midazolam dosages and the route of administration. Moreover, the definitions of sedation AEs and the effectiveness and outcome measures for (PS) varied between trials, which make meta-analysis difficult. It is also possible that the rarity of severe AEs with midazolam in some of the reviewed studies could be due to improper documentation of the safety data. The difficulty in reporting the safety data was compounded by the heterogeneous reporting style of the authors. Many did not use a standardized definition for AEs or standardized measures for reporting the outcomes.

5.6. Conclusions

The success rate for midazolam varies, and the rate is poor with both MRI procedures and CT scans. However, midazolam is effective for imaging procedures, such as MCUV/MCUG, that require a sedative agent with anxiolytic and amnesic effects. Midazolam seems to have a low incidence of AEs, although the occurrence of mild/moderate hypoxia emphasises the necessity of monitoring children during sedation. Serious AEs associated with PS using midazolam appear to be rare.

CHAPTER SIX

Assessing the Palatability of Chloral Hydrate and Midazolam in Children: A literature Review

6.1. Introduction

Palatability of an oral medicine has been recognised as one of the most important factors in drug treatment adherence as it increases the chance of successful drug administration during a therapeutic course [96]. It differs from one drug to another, as well as from brand to brand for the same drug, and it also varies from child to child [89]. Palatability is influenced by a mixture of sensory perceptions including taste, smell, appearance, and temperature. When taking into account the important role of the palatability of drugs, particularly oral preparations, taste therefore should be an essential issue in the development of medicine [352].

There have been relatively few studies of adherence and palatability in children. A study by Venables et al. (2015) identified taste as the most frequently reported barrier to adherence with long term treatment ($p<0.001$) [353]. It is reasonable to presume that a better tasting medication is easier to administer to young patients[354]. The importance of studying the palatability of children formulations has been endorsed in the European Paediatric guideline on pharmaceutical development of formulations for paediatric use [355]. The FDA also, highlights the importance of producing new medications and making them more acceptable [356]. In the previous chapters (Chapter 2 and Chapter 5) the effectiveness and safety of chloral hydrate and midazolam were evaluated. In this chapter the palatability of these two oral sedatives will be evaluated.

6.2. Aim

This literature review aimed primarily to evaluate the current published clinical evidence concerning the palatability of the oral sedatives chloral hydrate and midazolam in children. A secondary aim was to review the methodology used in previous studies of these sedative agents to inform the protocol for a future planned study (chapter 7).

6.3. Methods

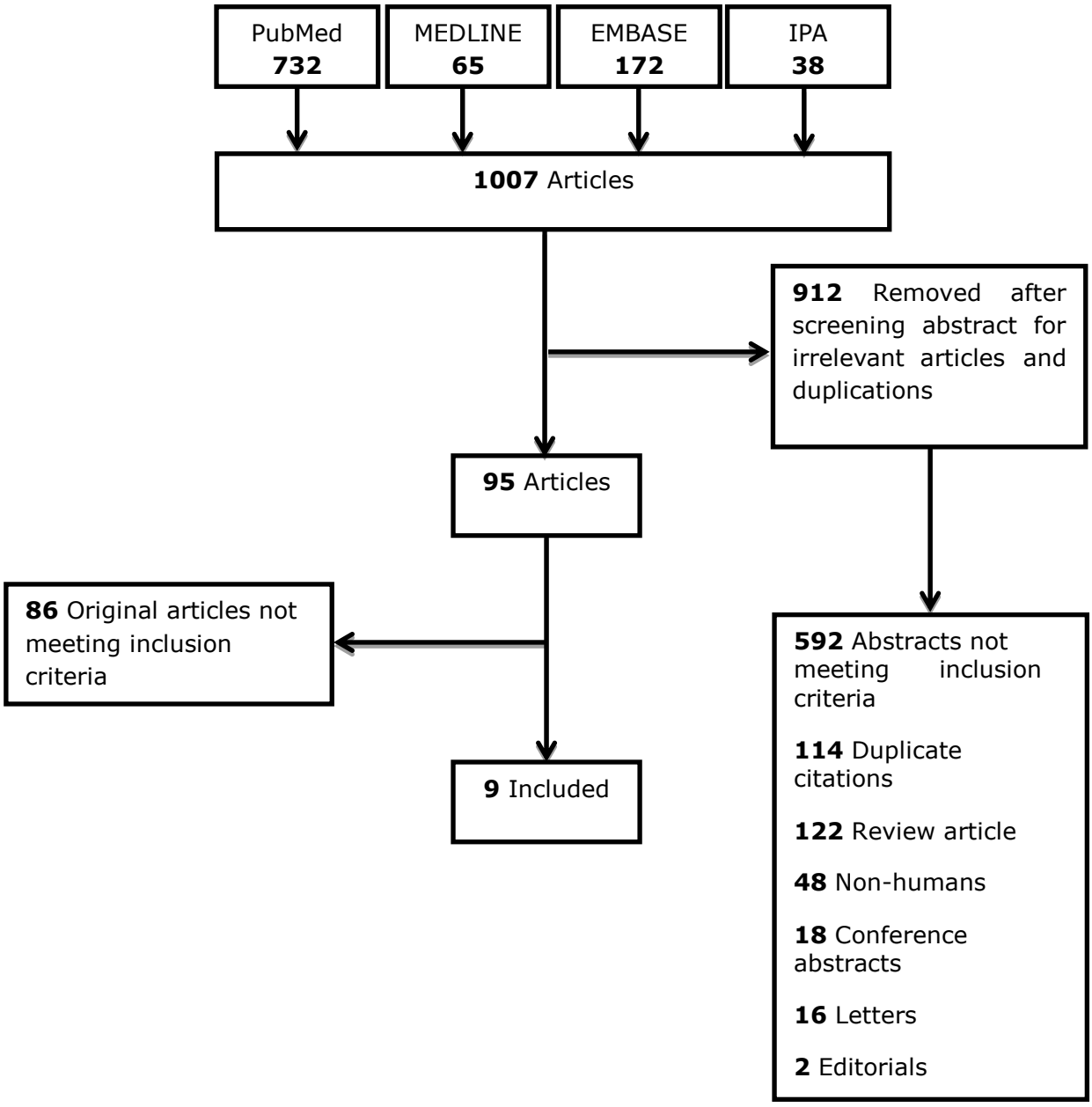
A literature search was performed on MEDLINE (1948–January 2014), EMBASE (1980–January 2014), International Pharmaceutical Abstracts (IPA; 1970–January 2014) and PubMed (until January 2014). Search terms were 'chloral hydrate', 'midazolam', 'palatability' or 'taste'. All studies evaluating chloral hydrate and/or midazolam use in children up to 18 years undergoing procedural sedation (PS) published in all languages were included, if they evaluated or reported palatability and/or taste outcomes. The following data were extracted from each study: study region, study period, study design, number of children, age group, dose of chloral hydrate and midazolam, palatability measurement method, sedation scoring method and procedural success rate. Comments, editorials, letters, notes, review articles and studies that did not evaluate chloral hydrate and/or midazolam palatability for PS were excluded.

6.4. Results

A total of 1007 articles were identified after searching the databases. After limiting the results to publications dealing with humans and removing duplicates, 845 articles were identified. Following this, 750 articles were removed after initial screening of the article title and abstract. The full text of the remaining articles (95) was obtained. Nine articles remained after applying the inclusion and exclusion criteria (Figure 6.1).

The selected 9 articles included a total of 1059 children, published between 1988 and 2012. Eight were randomised trials and one was a prospective observational study. They were conducted in 6 different countries, most originated from the USA (3) [184, 357, 358]. Sample sizes in these nine studies ranged from 16 to 397 and the age of participants ranged from birth to 16 years old. All studies were performed in patients with a clinical indication for PS. The number of sedatives evaluated per study varied from 1 to 2.

Figure 6. 1: Flow diagram of the search and review process



6.3.1. Scales to assess palatability

A few different tools were used in the included studies (Table 6.1, Table 6.2). One third (3/9) of the studies assessed children' opinion using various palatability assessment scales. Two studies involved children aged from 1 to 6 years[359, 360]. One study used a 3-point scale[359] and the other used the verbal responses of the children[360]. Neither study adequately described how they assessed the palatability in children less than 2 years old. In the study by Wilson et al. (2007) children aged from 10 to 15 years old assessed the palatability of the study sedative agent by answering the open-ended question (liked ''best'' or ''least'') about the acceptance of the sedative that they had taken [361].

Table 6. 1: Palatability assessment method used with paediatric patients

Palatability measurement method	Age group	Reference
3-point scale ((1) good, (2) indifferent, and (3) bitter)	1– 6 years	Almenrader et al. 2007[359]
Questionnaire response Liked ''best'' or ''least''	10- 15 years	Wilson et al. 2007[361]
Verbal response The drug has ''Bitter Taste'' or "not"	2- 6 years	Kumar et al. 2012[360]

Most of the studies (6 out of the 9) used parents or nurses to assess palatability. Half of the studies used a 4-point scale [357, 358, 362].

In two studies, in children aged from 6 months–16 years[357, 358], the observers used the same scale:

- Accepted readily,
- Accepted with facial grimace,

- Accepted with verbal complaint, and
- Rejected entirely

In another study in patients as young as 4 years old [362] the scale was

- Totally refused,
- Refuses to accept,
- Dislikes, and
- The child liked the medicine

In three studies, nurses assessed the child to estimate the palatability [184, 269, 363]. The scales used by the nurses ranged from a five point scale to simple subjective assessment (Table 6.2)

Table 6. 2: Measurement method used for parents/nurses interpretation

Palatability measurement method	Age group	Reference
Observer opinion on acceptability using 4-point scale ((1) accepted readily, (2) accepted with facial grimace, (3) accepted with verbal complaint, and (4) rejected entirely)	1–15 years	Marshall et al. 2000[357]
	6 months–16 years	Cote et al. 2002[358]
Observer opinion on acceptability using 4-point scale ((1) totally refused, (2) refuses to accept, (3) dislike, and (4) the child liked the medicine)	0- 4 years	Kapur et al. 2004[362]
Nurse and parent's opinion on acceptability using 5-point scale ((1) yucky, (5) yummy)	2–13 months	Chung et al. 2000/ USA[184]
Nurse opinion on taste acceptance ''cooperative'' or ''agitated''	2–8 years	Isik et al. 2008[363]
Nurse opinion on acceptability ((1) grimacing and struggling, (2) spitting out sedative)	1-8 years	Saarnivaara et al. 1988[269]

6.3.2. Studies that assessed palatability

Nine studies evaluated the palatability and/or effectiveness of midazolam. Two evaluated midazolam in different doses[357, 358], one by different routes[360] and one by different added flavours [363]. Three studies compared midazolam with other oral sedatives [269, 359, 361], and only one study compared midazolam with placebo[362].

Two studies evaluated chloral hydrate. One study evaluated chloral hydrate and midazolam[269], the other evaluated chloral hydrate and pentobarbital [184] (Tables 6.3 and 6.4).

Table 6. 3: Studies that used children's opinion to assess palatability

Reference/ country	Design	Number of children	Age	Procedure	Drugs	Dose(s) mg/kg	Palatability assessment	Sedation-scoring method	Results
Almenrader et al. 2007/ Italy[359]	Single-blind RCT	34 30	1–6 years	Preoperative (repair of hernias, circumcision, orchidopexy)	Midazolam Clonidine	0.5 PO 4 Mcg PO	3- point scale	5-point sedation-scoring system	15% (5/34) children refused oral midazolam versus (zero) in clonidine group (P = 0.06) Success rate was 86% in the midazolam versus 83% in clonidine group (P = 0.5)
Wilson et al. 2007/ UK[361]	Single-blind randomised cross-over	36 36	10- 15 years	Dental procedure	Buccal midazolam N2O/O2	0.2 30% / 70%	Verbal response Liked ''best'' or ''least''	Houpt Behaviour Rating Scale	Midazolam was accepted by (23, 66%) versus (32, 89%) patients in N2O/O2 group Success rate was 100% in both group
Kumar et al. 2012/ India[360]	Double-blind RCT	30 30	2- 6 years	Dental procedure	Intranasal midazolam sublingual midazolam	0.3 PO 0.3 PO	Verbal response ''Bitter Taste or not''	5-point sedation-scoring system	A bitter taste was observed in 45% (14/30) of the sublingual group Success rate was 100% in both group

Table 6. 4: Studies that used nurse's/parent's opinion to assess palatability

Reference/ country	Design	Number of children	Age	Procedure	Drugs	Dose(s) mg/kg	Palatability assessment	Sedation-scoring method	Results
Saarnivaara et al. 1988/ Finland[269]	Double-blind RCT	126 122	1–8 years	Preoperative (adenoidectomy, tympanostomy, tonsillectomy)	Midazolam Oral chloral hydrate	0.4, 0.5, 0.6 PO + 0.7 ml/kg fruit juice 25,50, 75 PO + 0.7 ml/kg fruit juice	Nurse's opinion on acceptability using ((1) grimacing and struggling, (2) Spitting out sedative)	4-point sedation-scoring system	Midazolam was more palatable than chloral hydrate (12% versus 6%) (P < 0.001). Sedation effect of all doses was more effective in children >5 years in both (P <0.001)
Chung et al. 2000/ USA[184]	Prospective observational	38 16	2–13 months	CT/MRI	Pentobarbital + Cherry syrup chloral hydrate + Cherry syrup	4- 6 PO 50- 100 max 2000 mg PO	Nurse's and parent's opinion 5-point scale using ((1) yucky, (5) yummy)	Not specified	Pentobarbital was more acceptable than chloral hydrate (3.2% versus 1.7%) (P < 0.0001). Success rate was 100% in chloral hydrate versus 97% in pentobarbital group
Marshall et al. 2000/ USA[357]	Double-blind RCT	28 24 33	1–15 years	Invasive procedures	Midazolam (cherry flavoured)	0.25 PO 0.5 PO 1.0 PO	4-point scale	5-point sedation-scoring system	99% (84/85) of children accepted the syrup Overall 81% of patients achieved satisfactory sedation within 30minutes

Table 6.4: Studies that used nurse's/parent's opinion to assess palatability

Reference/ country	Design	Number of children	Age	Procedure	Drugs	Dose(s) mg/kg	Palatability assessment	Sedation-scoring method	Results
Cote et al. 2002/ USA[358]	Double-blind RCT	132 132 133	6 months–16 years	Preoperative (elective surgery)	Midazolam (cherry flavoured)	0.25 PO 0.5 PO 1.0 PO	4-point scale	5-point sedation-scoring system	95% of children accepted the syrup Overall 97.5% of patients achieved satisfactory sedation within 30 minutes
Kapur et al. 2004/ India[362]	Double-blind RCT	20 20	4 years	Dental procedure	Midazolam (strawberry syrup) placebo	0.5 PO Normal saline + strawberry syrup	4-point scale	5-point sedation-scoring system	Acceptability score was 80% in midazolam group versus 70% in placebo group Success rate was 90% in midazolam group versus 35% in placebo group
Isik et al. 2008/ Turkey[363]	Double-blind RCT	75	2–8 years	Dental procedure	Midazolam mixed with 4 different drinks Pepsi Cola, 10% sodium citrate, pomegranate juice grapefruit juice Midazolam alone	0.75 PO	Verbal response ''Cooperative'' or ''Agitated''	Ramsay Sedation Scale (RSS)	Pepsi Cola and 10% sodium citrate formulation were more acceptable than others (53% & 53% versus 20%, 40% & 47%) ($P < 0.05$). Sedation scores were higher in children receiving 10% sodium citrate ($P < 0.05$)

6.3.3. Summary of palatability results

We found 9 articles evaluating the palatability of chloral hydrate and/or midazolam. Midazolam was acceptable to most children (median 53%). Chloral hydrate however was poorly tolerated (median 3.85%) (Table 6. 5).

Table 6. 5: Acceptability scores (%) of chloral hydrate and midazolam

Sedative	**Acceptability scores** **Range (median acceptability)**
Chloral hydrate	1.7% to 6% (3.85%)
Midazolam	12 to 99% (53%)

6.5. Discussion

There were surprisingly few studies of the palatability of the oral sedatives chloral hydrate and midazolam in children. The majority of the studies evaluated midazolam palatability. Only two studies evaluated chloral hydrate palatability.

Midazolam was found to be palatable in most of the studies. In contrast, chloral hydrate was not palatable. Poor acceptance of chloral hydrate might be due to greater volume and more bitter taste than midazolam [173, 364].

This literature review showed that, almost all palatability studies were randomised. Great variability in the tools used for assessment of palatability was found. Most of the studies used parents or nurses to assess palatability in children. Older children (6 years and older) were considered able to articulate themselves. This was found to be in line with the results from previous studies that used children and parental questionnaires response to evaluate taste and acceptability of antibiotic preparations[365, 366] .

The 10 mm VAS scale was the most commonly uses for assessing palatability in children [95, 367-369].

6.6. Conclusions

In spite of the relatively small number of studies in this literature review, we found higher patient acceptance of oral midazolam than oral chloral hydrate. There was variability in the tools used for palatability assessment. Further investigation evaluating the palatability and effectiveness of the two sedatives will be undertaken in the next chapter (Chapter 7).

CHAPTER SEVEN

Pilot Study to Assess the Palatability of Two Commonly Used Sedative Medicines in a Children's Hospital

7.1. Introduction

Chloral hydrate and midazolam are widely used as sedative agents in children. Both are often regarded as unpleasantly bitter tasting, which may alter their acceptance and the consequent success of the sedation procedure. A prospective study in Italy of 64 children who were given oral midazolam for procedural sedation (PS) found that 15% of the children refused the drug entirely[359].

The taste of oral medicines and the ability of paediatric patients to tolerate them, though widely mentioned, are often not taken into consideration[352]. Several studies describe the assessment of the palatability of medication used in children, however many of these studies were undertaken in adults[90, 96]. It is now recommended that assessment of the palatability of drugs that will be administered to paediatric patients should be undertaken in children [90].

In the previous chapter, we identified that midazolam appears to be palatable to most children. Chloral hydrate, however, appears to be less palatable. There were however only two studies with chloral hydrate. This study aimed to investigate the palatability and acceptability of these two oral sedative agents in children in Derby in the UK, to help evaluate current practice.

7.2. Study aim and objectives

7.2.1. Primary objective

The primary objective of this study was to examine children's opinions of the taste and acceptability of chloral hydrate and midazolam when administered for routine PS.

7.2.2. Secondary objectives

The secondary objectives of this study were:

1- To examine the opinions of parents on the taste and acceptability of the sedative agents immediately after their administration.
2- To examine nurses' opinions on the taste and acceptability of the sedative agents immediately after their administration.
3- To document any manipulation of medication that is performed by nursing staff to encourage children to take the medication.
4- To assess if there could be a relationship between the acceptability of the medicine to children and the success rate of PS.
5- To record any further sedative agents given required the procedure.
6- To ask parents, nursing staff and children open questions about what they think would make administration of these medicines easier.

7.3. Study method

This study was conducted at the Derbyshire Children's Hospital, which is part of the Royal Derby Teaching Hospitals NHS Foundation Trust, providing healthcare to more than 100,000 children each year. The hospital consists of out-patient, emergency, and in-patient departments. This study was conducted in the day-case unit.

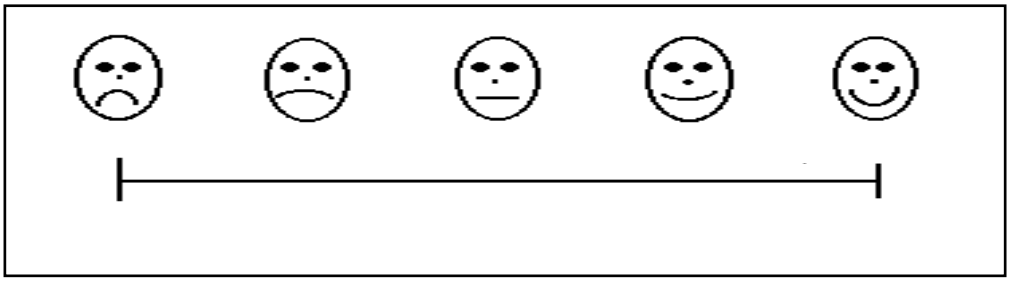
The study's protocol and ethics application were written by Co-investigator (Badriyah Alotaibi) and reviewed by Chief investigator (Dr. Helen Sammons).

7.3.1. Study design

Palatability was assessed using a modified 10 cm visual analogue scale (VAS) incorporating a facial hedonic scale for children aged from 3 to 5 years. Studies have shown that this scale is widely accepted in paediatric patients as young as 4 years and they can easily understand and use it to give their opinion about the taste of medicines by choosing the faces that reflect their opinion [100, 370] (Figure 7.1).A modified 10 cm VAS was used for children aged from 6 to 16 years as children of this age are known to be able to mark their opinion about the taste of the drug that they have taken on the line of the 10 cm VAS scale [102] (Figure 7.2). The two studied medicines were chloral hydrate and midazolam (Table 7.1). The primary end point for the study was to examine the children's opinions on the palatability of each sedative agent as measured on the VAS. "Acceptable" was defined as any score higher than "bad" or measuring more than 2 cm from 0 on the scale.

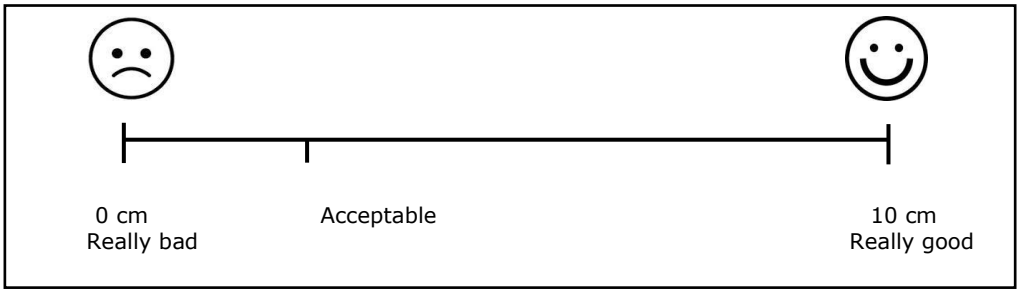
The secondary end points were to assess the relationship between the palatability of the sedative medicine to children, and the success rate of PS.

Figure 7. 1: 10 cm VAS combined with facial hedonic scale for ages 3 - 5



This figure adapted from Matsui (2007) [90].

Figure 7. 2: 10 cm VAS combined with facial hedonic scale for ages 6 - 16



This figure adapted from Matsui (2007) [90].

Table 7. 1: Composition of medicines under study

Medicine	Composition
Chloral Hydrate 500mg/5 mL oral syrup (Rosemont Pharmaceuticals Ltd)	Each 5 mL contained chloral hydrate 500 mg (equivalent to 100mg/mL), propylene glycol (E1520), methyl parahydroxybenzoate (E218), glycerol (E422), colour E110 and sucrose 3g/5mL.
Midazolam 5mg/mL solution for injection/infusion (Hypnovel, Roche)	The ampoules contained, per mL: midazolam 5 mg (as hydrochloride), sodium chloride, hydrochloric acid (to produce hydrochloride) and sodium hydroxide in water for injection, adjusted to pH 3.3

7.3.2. Participant selection and recruitment

When sending appointment letters to parents, the paediatric secretaries and booking clerks included information about the study, and, if age-appropriate, included information to be read by the children.

On the day of admission, the researchers approached ward nurses to assess the suitability of patients who were scheduled for diagnostic PS or botulinum toxin injection, and checked if the patients had been prescribed one of the study medicines. On the patients' arrival at the day case ward, eligible families were asked by the nursing staff if they would be happy to speak to one of the researchers. The researcher explained the study to the child and parents, confirmed that the family had received a child-and-parent information sheet and reviewed this with them. The parent(s) were asked by the researcher for written consent for the child to participate in the study, and the child's assent was taken if the child was aged more than 6 years. The parents and children were advised that they could withdraw from the study at any time.

Consent of parents and assent of children were monitored through the recording of a unique subject number on each consent and assent form. This subject recruitment number was written on the data collection form in order to ensure that the patient's details remained anonymised. The chief investigator kept a key to a locked filing cabinet where the patient's name and hospital number were stored. The consent forms were stored separately from the data collection forms, in case of later enquiries.

All participants (parents and children) were interviewed for approximately 10 minutes, depending on the length of time the child took to swallow the drug and decide on their answers to the study questions. Data was collected immediately after the drug was

administered. Patients were observed for the first 5 minutes after administration to record any immediate adverse events, such as vomiting. Further data was collected from the sedation record sheet via the nursing staff to gauge the outcome of the sedation and success of the procedure.

We did not use hospital interpreters or translator services in this study because the participating children needed to understand verbal explanations or written information in English.

Each potential parent and child were advised that entry into the study was entirely voluntary, and that their treatment and care would not be affected by their decision, and that they could withdraw at any time without being coerced to remain part of the study.

Children who were included in the study were aged from birth to under 16 years and were scheduled for PS or botulinum toxin injection on the wards of the Derbyshire Children's Hospital. This included children who had neurological developmental disabilities but were able to understand the study and use the scoring faces scale.

The children had been prescribed either chloral hydrate or midazolam as a sedative agent, using the dosages recommended in the British National Formulary for Children and/or the local hospital's policies.

The exclusion criteria for this study were:

- Children who were non-English speaking.
- Children receiving sedation agents that were not chloral hydrate or midazolam.

Data collection was performed between November 2014 and April 2015.

This study did not interfere with the normal running of the ward or the care given to the patients. Therefore, no attempt was made to control for potential confounding variables such as whether the child's mouth was free of conflicting tastes. The child was asked to rate the medicine at the place of drug administration, if they were happy with this, or at their bedside.

Immediately after receiving the oral sedative, each participant was asked to mark his or her impression of the taste of the medicine on the 10 cm VAS line (Figure 7.1, Figure 7.2).

The researcher recorded the acceptability of the medicine, length of time between preparation of the medication by nurses and administration to the patient, adverse events during the first 5 minutes after administration (such as vomiting), and parental comments. The success of the sedation and completion of the procedure were rated by the health care professional (nurse or physician).

A data collection form (DCF) (see appendix B) specific to this study was used for each patient. The researcher completed the front page of the DCF, then asked the children to rate the palatability of the drug and marked the child's rating. The remainder of the DCF was filled in by the investigator who questioned the child together with the parent(s).

The DCF included the following information:

- Patient unique identification number
- Date of completion of the study
- Age at study entry, in years and months
- Sex
- Procedure

- Sedative agent, its strength and formulation
- History of given sedative agent
- Child's thoughts about the taste of the drug, on a modified 10 cm VAS
- Time taken to administer the medication, from when the nurse picked up the syringe, through approaching the child, to the point when all of the medicine was swallowed[103].
- The parents' opinion regarding the acceptability of the sedative agent, for children with developmental disabilities, or aged 2 years or younger, according to the facial expression of the child, on a modified 10 cm VAS that incorporated a 5-point facial scale.

- Responses to the open-ended question 'How palatable, including easy to swallow, do you feel the study medication is? 1 = really good, 2 = good, 3 = not sure, 4 = bad, 5 = really bad' [371].
- The nurse's opinion on the acceptability of the given medicine to the patient, recorded as a subjective score from 1 to 4 (Table 7.2)[103].
- Success rate of the procedure post sedation, assessed by recording the children's behavioural responses following a completed procedure, using the Houpt scale for all age groups and measuring the degree of sleep, body movements, crying and overall behaviour (Table 7.3)[372].

Table 7. 2: Acceptability score used by nurse

1. Totally refused
2. Refuses to accept, but forced
3. Dislike, but accepts
4. The child liked the medicine

This figure adapted from Uhari et al. (1986) [103].

Table 7. 3: Scoring criteria for sedation

a. Rating Scale for Sleep Score
1. Fully awake, alert
2. Drowsy, disoriented
3. Asleep
b. Rating Scale for Movement
1. Violent movement that interrupts treatment
2. Continuous movement that makes treatment difficult
3. Controllable movement that does not interfere with treatment
4. No movement
c. Rating Scale for Crying
1. Hysterical crying that interrupts treatment
2. Continuous, persistent crying that makes treatment difficult
3. Intermittent, mild crying that does not interfere with treatment
4. No crying
d. Rating Scale for Overall Behaviour
1. Aborted - No treatment
2. Poor - Treatment interrupted, only partial treatment completed
3. Fair - Treatment interrupted but eventually all completed
4. Good - Difficult, but all treatment performed
5. Very Good - Some limited crying or movement
6. Excellent - No crying or movement

This figure adapted from Houpt et al. (1986) [372].

Ethical approval was obtained from the Officer for Research Ethics Committee Northern Ireland (ORECNI) (Ref: 14/NI/1061 14075). In addition, approval was obtained from the Derbyshire Hospital's NHS Foundation Trust Research and Development (R&D) department (Ref: DHRD/2014/078) (see appendix A).

The data was analysed using the Statistical Package for Social Sciences software (SPSS version 22, IBM United Kingdom Limited, Hampshire, UK) to generate simple descriptive statistics. Histograms and the Kolmogorov–Smirnov test were used to test the distributions of the continuous variables. The results were estimated as mean inter-quartile ranges (IQR).

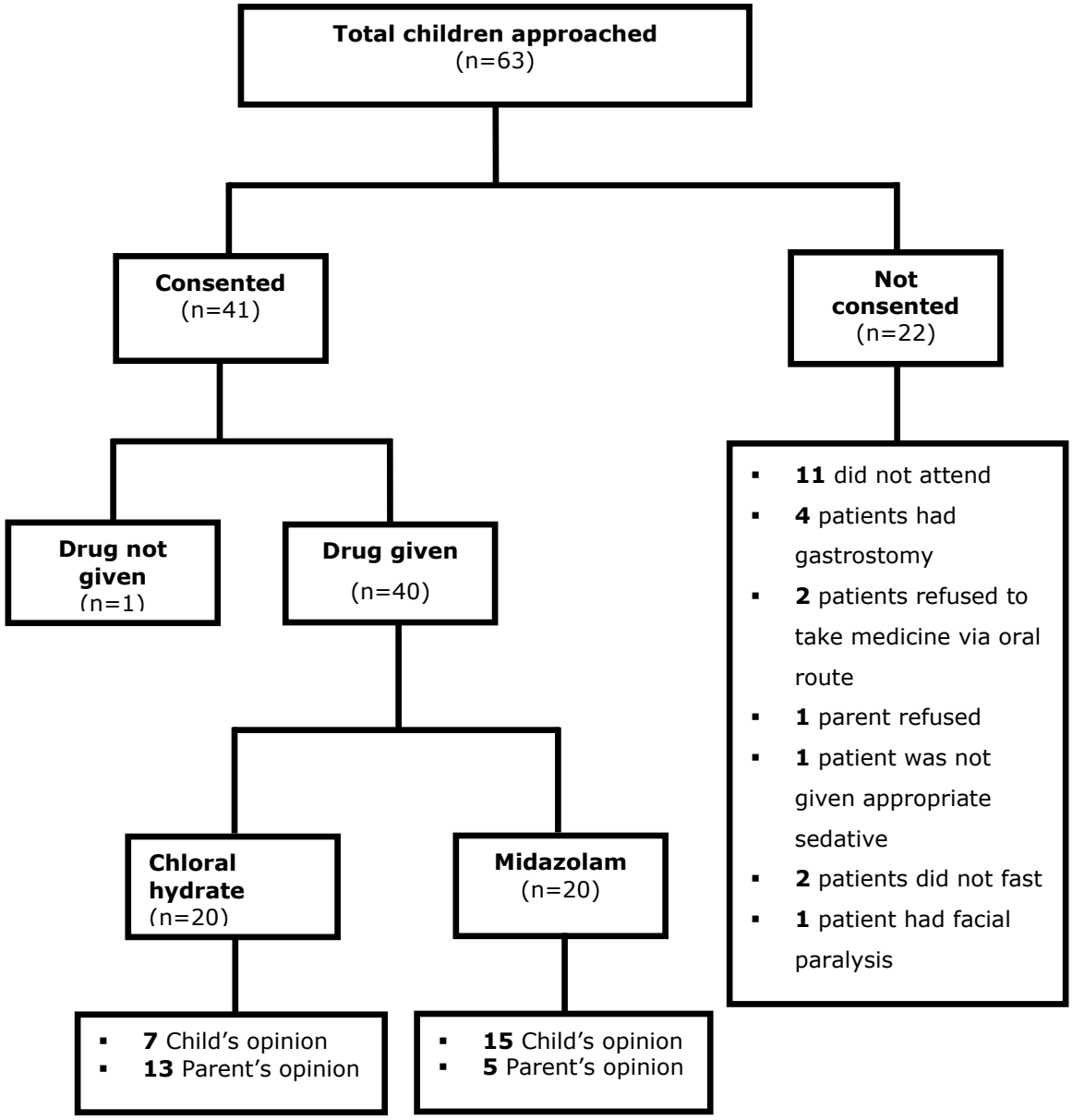
The palatability scores between any two drugs were compared using the Mann–Whitney U test. Spearman's correlation coefficient was used to test the effect of the children's age and number of times a medicine was taken.

7.4. Results

63 children were approached during the period from November 2014 to April 2015.

41 consented to participate. 40 were given a study medicine and provided data. One child did not receive medicine due to an upper respiratory tract infection (Figure 7.3).

Figure 7. 3: Recruitment flow chart



7.4.1. Demographic data

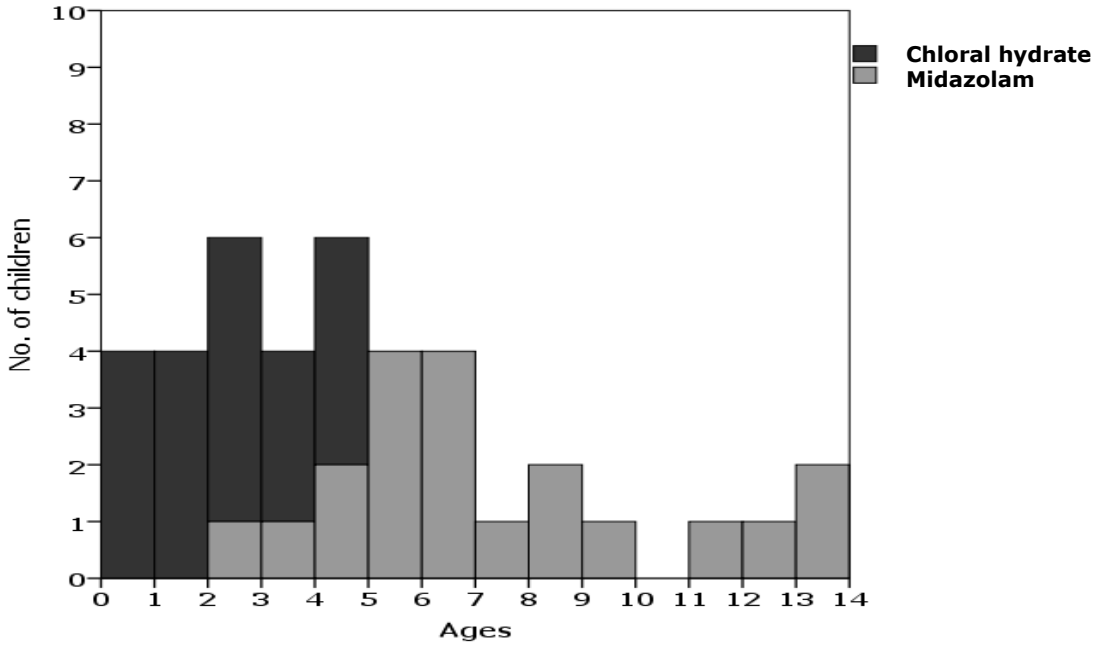
Of the 40 recruited children, the majority (30, 75%) were male. There were 20 patients in each group. The patients underwent the procedures in the following numbers: MRI (24), botulinum injection (10), brainstem auditory evoked potential (4), and CT (2). There were no adverse effects.

The children who received chloral hydrate were younger than those who received midazolam Figure (7.4) ($p = 0.0001$). The median age of children in the chloral hydrate group was 2.4 years, (IQR 1 - 3.6), and for children sedated with midazolam, it was 6.6 years (IQR 5.1 - 9.2). This is because chloral hydrate is recommended by the NICE guideline (2010) for children under 15 kg undergoing painless imaging procedures and midazolam in children from 1 month to 18 years undergoing painful procedures[80]. Thus the results of this study were analysed separately for each drug group in the next sections due to the differences in the patient groups and ages. There was a higher number of children in the midazolam group with developmental disabilities (n=7) than in the chloral hydrate group (n=1) ($p = 0.01$) (Table 7.4).

Table 7. 4: Patient demographics (N = 40 Patients)

Patients	Chloral hydrate	Midazolam	Total No.
Gender	**N= 20**	**N= 20**	**N = 40**
Male	14	16	**30**
Female	6	4	10
Age			
Infant (0-< 2 years)	8	0	8
Children (2- ≤11 years)	12	16	**28**
Adolescent (12 - < 16 years)	0	4	4
Development			
Normal	19	13	**32**
Developmental disabilities	1	7	8
Procedures			
MRI	17	7	**24**
Botulinum injection	0	10	10
Brainstem auditory evoked potential	1	3	4
CT	2	0	2

Figure 7. 4: Distribution of ages of children in both study groups



7.4.2. Acceptability of the study agents

7.4.2.1. Manipulation of medication

The nurses mixed midazolam with blackcurrant juice for 12 children and with orange juice for 2 children. The doses of midazolam for the remaining 6 children were not mixed with any juice because in 4 patients the doses were high so if mixed with juice this would produce a large volume, while in the other 2 patients the nurse did not specify.

Chloral hydrate was given to children without mixing it with any juice or flavour. It was not possible to add juice to the chloral hydrate due to the large volume of liquid required for the dose of chloral hydrate. As the Chloral hydrate's concentration is

100mg/ml and the dosage ranged 50- 100 mg/kg, for example for 15 kg child, the dose of chloral hydrate is 1500 mg (15 mls).

To increase the acceptance of both studied medicines, the nurses tried to verbally motivate the children to swallow the prescribed sedative.

7.4.2.2. Patients' opinions

The child's opinion about the taste of the prescribed sedative was recorded for children aged 3 years and older, while the parents' opinion was taken for children with significant developmental disabilities and children 2 years and younger (section 7.3.2). Table (7.5) and Table (7.6) present the individual data for chloral hydrate and midazolam groups.

Table 7. 5: individual data including drug acceptance and sedation success for children and parents in chloral hydrate group

Opinion	Patients	Taste scores in mm	Additional sedation	Successful procedures
Children	C1	0	Yes	Yes
	C2	20	NO	Yes
	C3	100	NO	Yes
	C4	0	NO	Yes
	C5	20	Yes	Yes
	C6	0	NO	Yes
	C7	0	Yes	Yes
Parent	C8	0	Yes	Yes
	C9	15	NO	Yes
	C10	50	NO	Yes
	C11	0	NO	Yes
	C12	0	NO	Yes
	C13	0	NO	Yes
	C14	0	NO	Yes
	C15	18	NO	Yes
	C16	18	NO	Yes
	C17	0	Yes	NO
	C18	0	NO	Yes
	C19	0	NO	Yes
	C20	50	NO	Yes
Total	**20**	**-**	**-**	**19**

Table 7. 6: individual data including drug acceptance and sedation success for children and parents in midazolam group

Opinion	Patients	Taste scores in mm	Additional sedation	Successful procedures
Children	M1	0	NO	NO
	M2	25	NO	NO
	M3	16	Yes	Yes
	M4	0	NO	Yes
	M5	10	NO	Yes
	M6	50	Yes	NO
	M7	0	NO	Yes
	M8	0	NO	NO
	M9	0	NO	NO
	M10	0	NO	NO
	M11	50	Yes	Yes
	M12	50	Yes	NO
	M13	80	NO	Yes
	M14	75	NO	Yes
	M15	100	NO	Yes
Parent	M16	0	NO	Yes
	M17	50	NO	Yes
	M18	50	NO	Yes
	M19	25	Yes	NO
	M20	50	NO	Yes
Total	**20**	**-**	**-**	**12**

1. Chloral hydrate group

The child's opinion was recorded for 7 children aged from 2.5 to 4.8 years (mean 3.7 years, (IQR 2.8- 4.7). The mean VAS measurement was 20 mm (IQR = 0- 20 mm). Parents' thought about taste was recorded from 13 parents (one child with developmental disabilities) aged from 0.5 to 4 years old (mean 1.6, IQR= 0.8 and 2.2). The mean VAS measurement was 11.62 mm (IQR = 0- 18 mm).

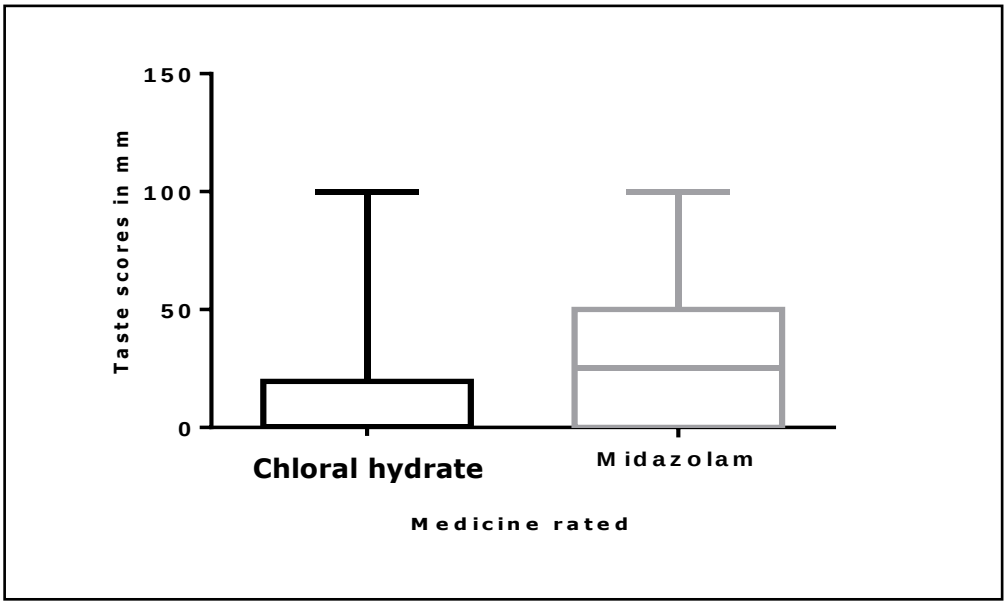
The mean VAS measurement for chloral hydrate taste for both children's and parents' opinion was 14.55 mm (IQR = 0- 19.5 mm) (Figure 7.5).

2. Midazolam group

Children's opinion about the taste was recorded from 15 patients (4 children with developmental disabilities) aged from 4 to 13.9 years (mean 7.4 years, (IQR 5.4- 8.8)). The mean VAS measurement was 30.40 mm (IQR 0- 50 mm). Parents' thought about taste was recorded from 5 parents for children (3 children with developmental disabilities) aged from 2.4 to 12 years old (mean 7.1, IQR= 2.7- 12). The mean VAS measurement was 35 mm (IQR 12.5 - 50 mm).

The mean VAS measurement for midazolam taste was for both children's and parents' opinion was 31.55 mm (IQR 0- 50 mm) (Figure 7.5).

Figure 7. 5: Rated taste in mm for the medicines under study



7.4.2.3. Nurses' opinions

1. Chloral hydrate group

The time required to administer chloral hydrate by the nurse ranged from 35 to 600 seconds (mean 162, IQR 53 – 270)

Scores of acceptability showed that, 10 (50%) of children disliked the medicine but still agreed to take it, 8 (40%) children rejected the medicine, but were forced to take it by nurses and one patient completely refused chloral hydrate. There was only one child who liked the taste of chloral hydrate.

2. Midazolam group

The time required to administer midazolam by the nurse ranged from 10 to 900 seconds (mean 116, IQR 42- 71)

Assessment of palatability found that 15 (75%) children disliked the medicine but still accepted it. No children totally refused to take midazolam; however, 5 children refused the medicine, but were forced to take it. There were no children who liked the taste.

7.4.3. Procedural success

No patient in the chloral hydrate group were undergoing painful procedures, while 10/20 patients in midazolam group were having painful procedures. This is because chloral hydrate has only a hypnotic effect and is therefore recommended by the NICE guideline for painless imaging procedures for children < 15 kg. Midazolam however is recommended for either painless imaging painless procedures for children ≥ 15 kg and also for painful procedures due to its anxiolytic effect [80].

In the chloral hydrate group 19 of the 20 procedures were performed successfully (Table 7.5). In contrast, only 12 of the 20 procedures in the midazolam group were performed successfully (Table 7.6). Five patients from each group required additional sedation (paraldehyde) to augment the sedation effect. Procedural success was also measured on the Houpt sedation scale (Table 7.3) which included the degree of sleep, crying, body movements, and overall behaviour. The overall evaluation data was dichotomised to represent the success of (PS), which was defined as the ability to complete the designated procedure.

1. Chloral hydrate group

For sleep evaluation, three quarters (15) of children were given a score of 3 (asleep) and movement evaluation showed that 13 (65%) of children scored a 4 (no movement). 15 (75%) of children scored a 4 for no crying and 16 (80%) of the chloral hydrate group scored a 5 (very good) or higher for overall behaviour. Table (7.7) shows the mean scores and IQR for sleep, crying, body movements, and overall behaviour in chloral hydrate group.

5 children required additional sedation (rectal paraldehyde). The age of these children ranged from 3 to 5 years (mean 3.46 years, IQR = 2.3 - 4.35). Four children completed their procedures successfully.

Table 7. 7: Mean sedation scores, IQR for chloral hydrate groups

Rated score	Mean	IQR
Sleep	2.75	2.25 - 3
Movement	3.55	3 - 4
Crying	3.70	3.25 - 4
Overall behavior	5.25	5 – 6

2. Midazolam group

Just over half (11, 55%) of the midazolam group scored a 2 (drowsy) for sleep, while for movement evaluation (8, 40%) of subjects scored a 3 (controllable movement). Eight children 40 per cent in midazolam group scored a 4 for no crying and only 7 (35%) scored a 5 (very good) or higher for overall behaviour. Table (7.8) shows the mean scores and IQR for sleep, crying, body movements, and overall behaviour in midazolam group.

5 children required supplemental sedation with paraldehyde (PR). The age of these children in the ranged from 5 to 14 years (mean 7.46 years, IQR = 5.25 - 10.25). Only two of these 5 children completed their procedures successfully.

Table 7. 8: Mean sedation scores, IQR for midazolam groups

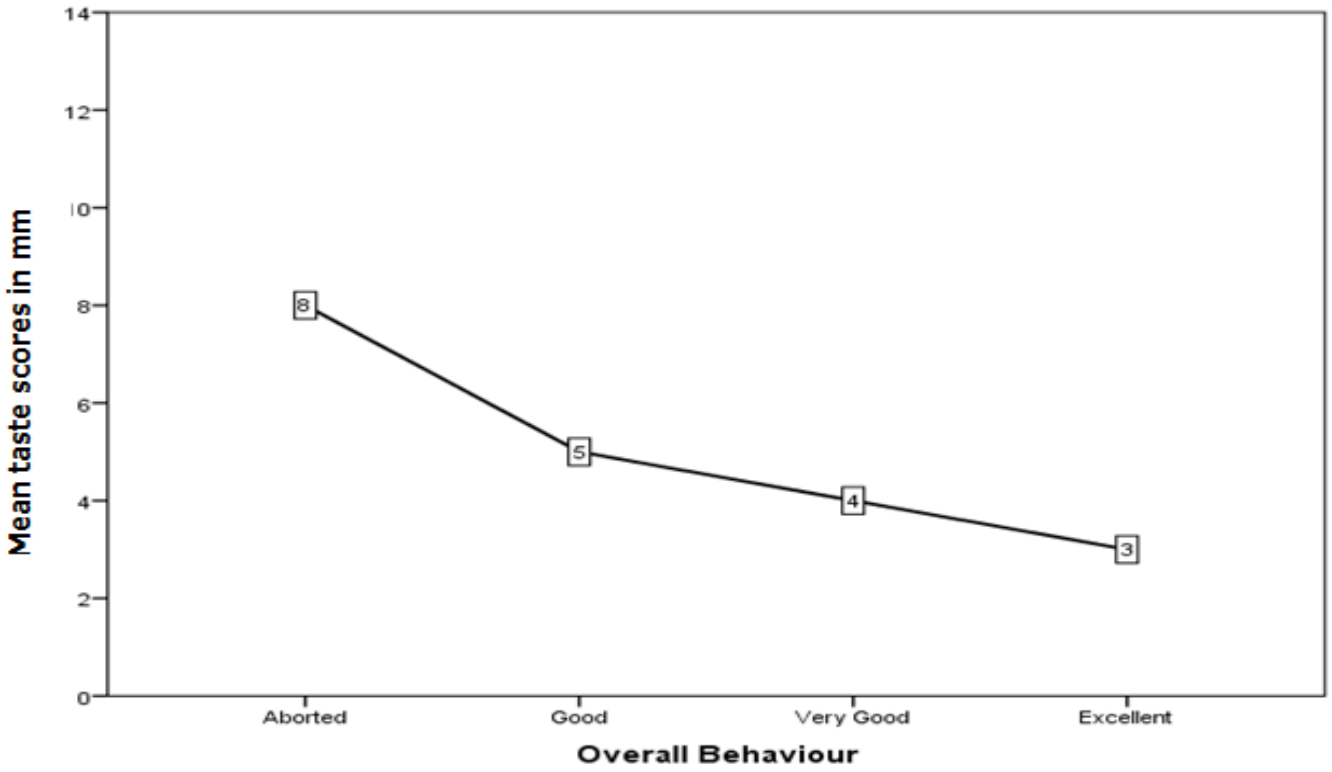
Rated score	Mean	IQR
Sleep	1.65	1 - 2
Movement	2.70	2 - 3
Crying	3.05	2 - 4
Overall behavior	3.30	1 - 5

7.4.4. Acceptability and sedative effect

When drug acceptance and overall behaviour for sedation success were evaluated for each group, in the chloral hydrate group a direct trend was seen for better (PS) effect with higher taste scores (Figure 7.5). However in the midazolam group there is an inverse relationship between (PS) effect and the taste scores (Figure 7.6).

Figure 7. 6: Medicine acceptance and procedural success in chloral hydrate group

Figure 7. 7: Medicine acceptance and procedural success in midazolam group



7.4.5. Comments on improving medicine acceptability

23 answers were collected from the patients and their parents when they were asked what would make administration easier for these medicines. The differences between age or gender for each drug group were not statistically significant. Thirteen of the patients suggested making the medicines sweeter and six suggested making the taste fruitier. Strawberry flavour was preferred by girls, but the difference was not significant. One patient in each group found the taste better than expected. The remaining participants asked to improve the taste of the medicine and make it better without specifying the taste or flavour.

7.5. Discussion

Palatability

In the present pilot study, no extra flavour was used to make chloral hydrate suitable for oral ingestion. This is because of the large volume of most calculated doses. In order to mask the taste with sweetened syrup, the total volume required would be excessive. The coercion of children to take the whole dose of chloral hydrate may result in spitting out or vomiting, leading to not only children's distress, but also the possibility for lower or higher dosing.

The acceptance of oral chloral hydrate was shown to be poor as judged by the children, the children's parents and nursing staff. Those who were seen to have excellent sedation showed a trend to having scored the taste better. Chloral hydrate is one of the most commonly used sedatives, however, bitter taste and gastric irritation are the most common drawbacks [121, 268]. Chung et al. in a prospective study of oral chloral hydrate and pentobarbital for imaging procedures, observed that acceptance of pentobarbital was always superior to that of chloral hydrate [184]. Results published by Millichap show that triclofos was significantly more palatable in a greater percentage of children than chloral hydrate [174].

Oral midazolam was prepared using parenteral midazolam by mixing it with a blackcurrant juice or orange juice as has also been done in previous studies [373, 374]. It has been found that midazolam has relatively good acceptance and the opinions of parents were more likely to prefer midazolam. There was no obvious link between taste score and sedation success. Saarnivaara et al. (1988) evaluated the palatability of chloral hydrate and midazolam in three different sedative doses (25, 50, 75 mg/kg) and (0.4, 0.5, 0.6 mg/kg) respectively[269]. Chloral hydrate was always significantly less palatable than midazolam 12% versus 6.4% respectively ($P < 0.001$).

Effectiveness

In this study 50- 100 mg/kg chloral hydrate provided satisfactory effectiveness and 5 children were administered supplementary sedation. Most of these children completed their procedures successfully. This is in line with the study by Rooks et al. (2003) who found that the 75 mg/kg dose of chloral hydrate provided good effectiveness (100%), while midazolam in the 0.5 mg/kg dose produced low effectiveness (50%) in children aged from 2 months and 8 years old [194]. Only one child in the chloral hydrate group required supplementary sedation; however, 12 children in the midazolam group were given sedation supplementations [194]. Chung et al. (2000) in a prospective study showed that chloral hydrate in doses ranging from 50 to 100 mg/kg provided good sedation for children aged up to 13 months and none of the patients required supplementations [184]. A study by Marchi et al. (2004) found that chloral hydrate for diagnostic procedures was effective in 99% of children aged 3 months to 12 years [217].

With regards to midazolam, the present results showed low success rate with midazolam sedation and most children needing supplementary sedation failed to complete their procedures successfully. It is important to note however, that half of the children were undergoing painful procedures as opposed to none of those with chloral which could have influenced the results. This is in accordance with the study by Wheeler et al. (2001) which found that 0.5 mg/kg midazolam is less effective when compared to chloral hydrate 75 mg/kg for children aged from 1 to 5 years [175]. However, our findings are in contrast with the results of a study by Kazak et al. (2010) which found that 0.25 mg/kg midazolam with presence of parents or 0.5 mg/kg midazolam without presence of parents provided a good sedation effect compared to the patients who were not given any sedative and only with presence of parents [375].

7.6. Limitations

This study is a pilot study which was designed to not interfere with or alter normal care provided by the nursing and medical staff to the patients. Therefore, control for possible confounding variables, such as if the patient's mouth was free of other conflicting tastes was not attempted, however, all participants were fasting as per the hospital protocol. An additional limitation to this study was that we cannot compare the opinion of the children and parents because of the very small participants' number and the differences of the age groups. Other study limitations include that only English- speaking families were included however there is a possibility that cultural differences may affect taste preferences as mentioned in the previous literature.

7.7. Conclusion

The results of this pilot study suggest that oral chloral hydrate has a relatively good sedation effect, but it was poorly accepted by the children. On the other hand, midazolam was shown to be more accepted by patients; however its effectiveness was low. Further studies directly comparing the palatability and effectiveness of the two drugs are required.

CHAPTER EIGHT

Use of Sedation in the Middle East Countries: A literature Review

8.1. Introduction

In the previous chapters, the effectiveness and safety of some of the most commonly used sedatives in paediatrics were discussed and evaluated systematically. In this chapter, the use of sedatives in children in the Middle East is evaluated further, as it is where I am from and where I will return to work.

The "Middle East" refers to the geographic region where Africa, Asia and Europe meet. It includes 17 countries which are; Bahrain, Cyprus, Egypt, Iran, Iraq, Israel, Jordan, Kuwait, Lebanon, Oman, Palestine, Qatar, Saudi Arabia, Syria, Turkey, United Arab Emirates, and Yemen. The population of these countries is approximately 300 million [376]. Children (younger than 15 years old) in these countries constitute 35% of the population compared to approximately 18% in developed countries [376]. Middle East countries are ranked economically into High Income Countries (HIC); Bahrain, Israel, Kuwait, Oman, Qatar, Saudi Arabia, and the United Arab Emirates (UAE), the Upper-Middle Income Countries (UMIC); Iran, Jordan and Lebanon and the Lower-Middle Income Countries (LMIC); Egypt, Palestine, Syria, Yemen and Iraq [377]. The health care systems in the Middle East countries differs between countries [378]. There have been very limited numbers of studies that have evaluated the patterns of sedative prescribing in the Middle East

8.2. Aim

This review aims to evaluate the use of sedative agents for procedural sedation (PS) outside the operating theatre in the Middle East, and to assess the use of practical PS guidelines in these countries.

8.3. Method

Literature searches were conducted using MEDLINE (1948–January 2015), EMBASE (1980– January 2015), International Pharmaceutical Abstracts (IPA) (1970 to January 2015), and PubMed database (until January 2015). The reference lists of the relevant studies were searched manually to identify further related papers.

An initial search for related terms was conducted in order to select the most specific and sensitive key words for the search strategy. These terms were used by previously published studies by Lourenço-Matharu et al. 2012 and Kastner et al. 2006 [166, 379]. The search terms were Children or infant or pe*diatric* or neonate or adolescence or adolescences or adolescent and Hypnotics or Sedatives or Anti-Anxiety Agents or Sedation or Conscious sedation or Preanesthetic medication or preanaesthetic medication or sedate or Anxiety or anxiety or anxious or fear$ or fright$ or stress$ or distress$ or phobi$ or uncooperative or un-cooperative or unco-operative and Middle East countries or Bahrain or Cyprus or Egypt or Iran or Iraq or Israel or Jordan or Kuwait or Lebanon or Oman or Palestine or Qatar or Saudi Arabia or Syria or Turkey or United Arab Emirates or Yemen.

All languages were included and the search was limited to data from humans. The inclusion criteria were original studies assessing or reporting the use of sedative agents in children and adolescents from birth up to 18 years, undergoing PS. Letters,

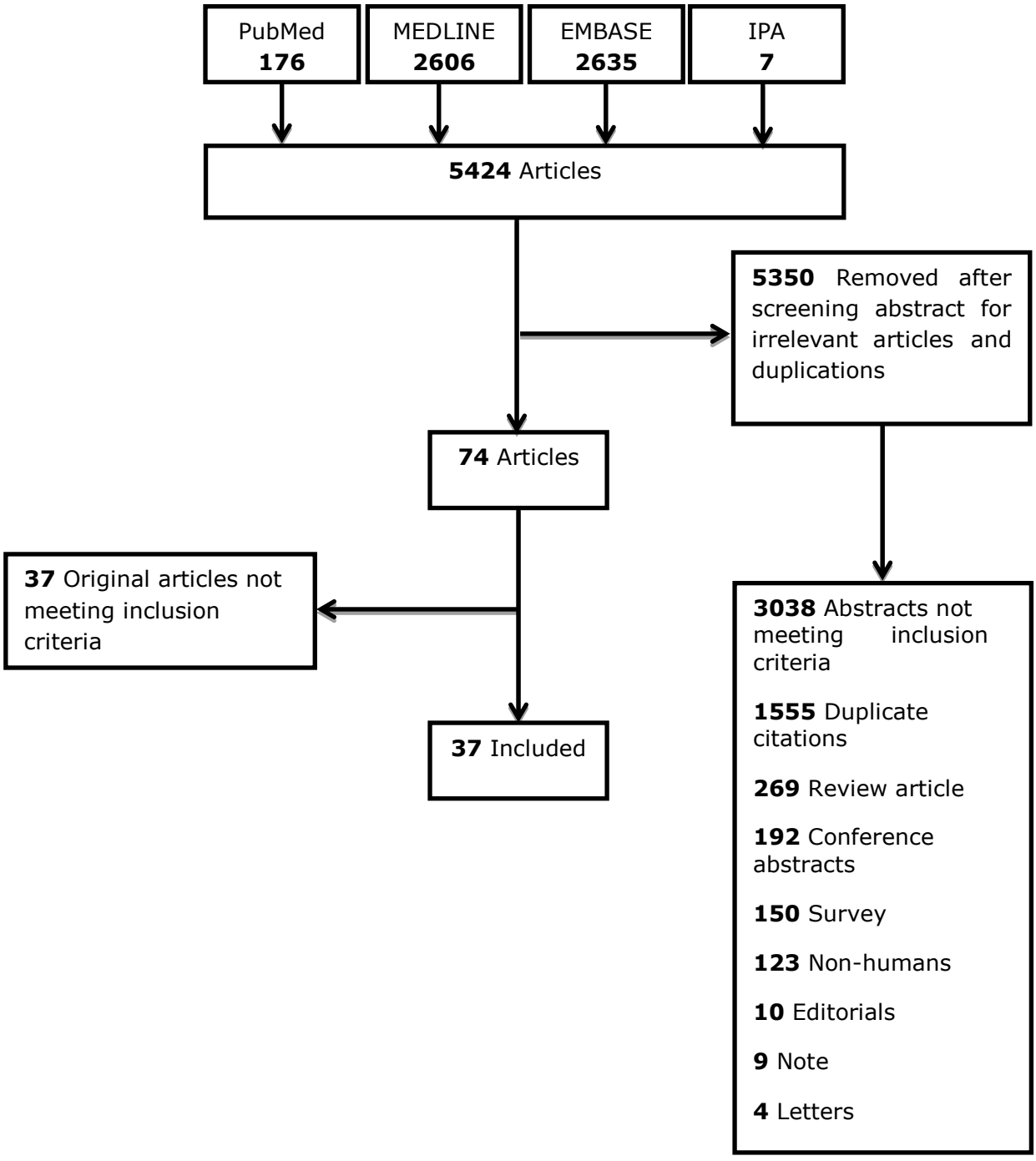
comments, editorials or review articles were excluded. The full articles of all related abstracts were read carefully according to the study inclusion criteria.

8.4. Results

8.4.1. Search results

Searching throughout the electronic databases yielded 5424 references. Limiting the search to humans and removing duplications gave 3746 articles. Reading the abstracts for potential related articles excluded 3672 articles, as they did not fulfil the review's inclusion criteria (Figure 8.1), leaving 74 articles. The full texts of these remaining articles were read carefully and 37 of them were considered to be not relevant. This left a total of 37 articles that fulfilled the inclusion criteria (Figure 8.1).

Figure 8. 1: Flow chart for search and review process



8.4.2. Countries with data

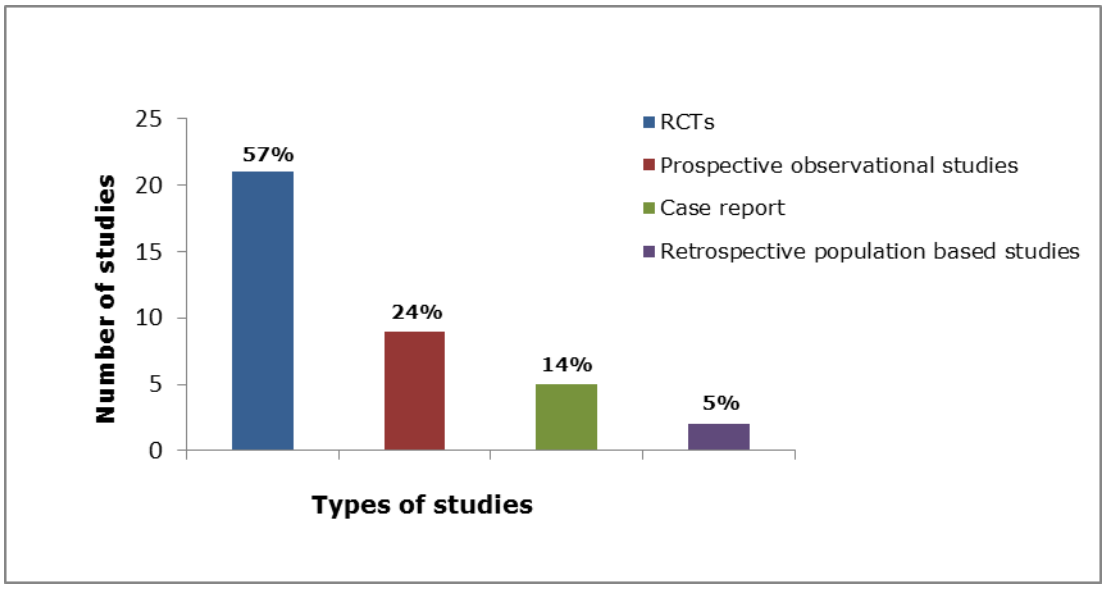
The search produced information for 7 of the 17 countries of the Middle East. The highest numbers of studies were conducted in Turkey followed by Iran, Israel and Saudi Arabia (Table 8.1). There were no publications available for the use of sedation in the following countries: Bahrain, Cyprus, Iraq, Lebanon, Oman, Palestine, Qatar, Syria, United Arab Emirates, and Yemen.

Table 8. 1: Number of studies for each country

Country	Number of studies
Turkey	16
Iran	8
Israel	4
Saudi Arabia	4
Jordan	3
Egypt	1
Kuwait	1
Total	37

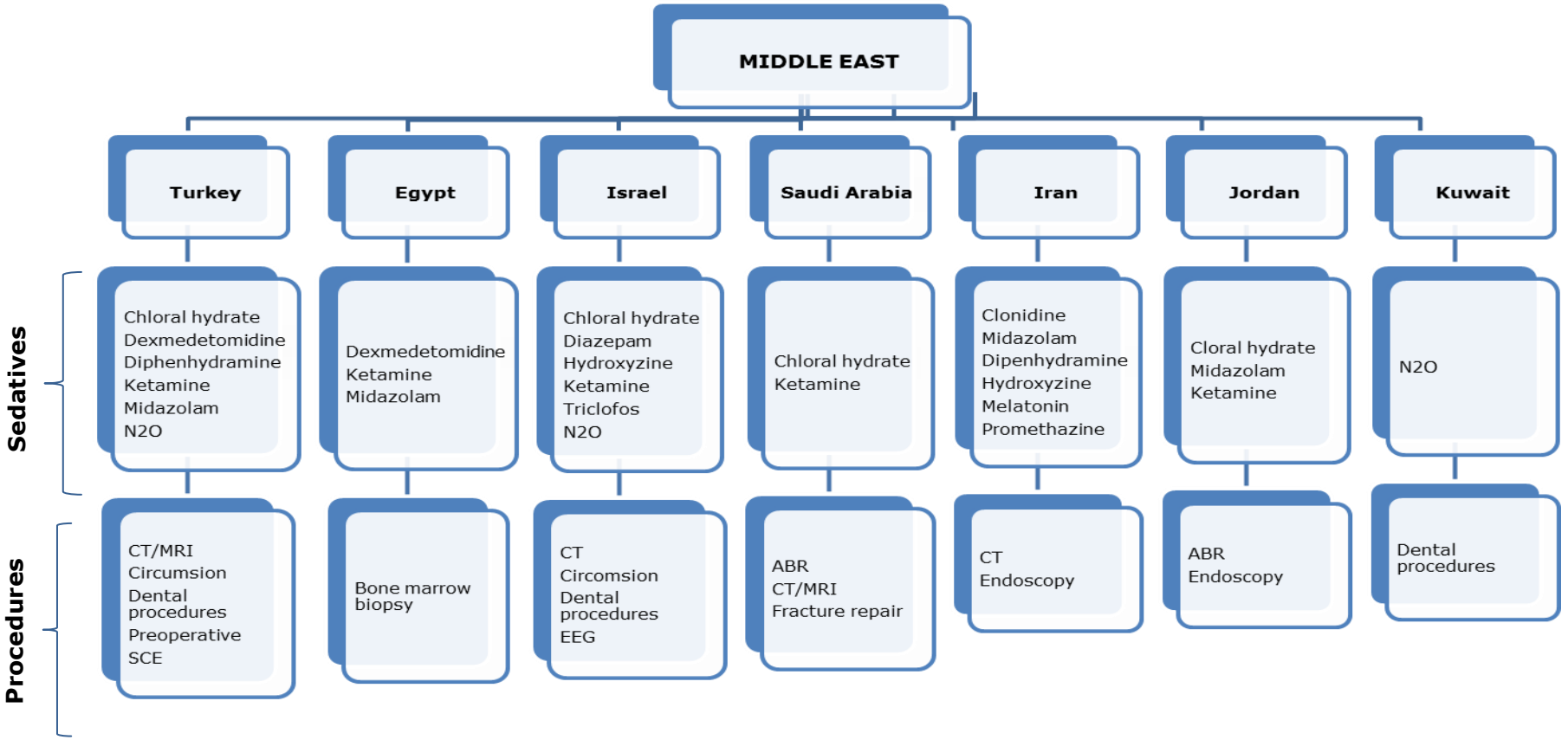
All 37 studies were published between 1979 and 2014. RCTs were most common (n=21, 57%), followed by prospective studies (n=9) (Figure 8.1). The total number of children was 3070, with ages that ranged from birth to 18 years.

Figure 8. 2: Types of included studies



Twelve different sedative agents were evaluated: chloral hydrate, dexmedetomidine, diphenhydramine, diazepam, clonidine, ketamine, melatonin, midazolam, nitrous oxide (N2O), promethazine, propofol, and triclofos. Painless procedures such as CT/MRI were most common (Figure 8.3). Ketamine was the most frequently evaluated, followed by Chloral hydrate and midazolam Figure (8.3).

Figure 8. 3: Flow chart for the use of sedative agents in the Middle East



- **Turkey**

16 studies were conducted in Turkey. They included 11 RCTS, 3 prospective observational studies and 2 case reports (Table 8.2, 8.3, 8.4).

Two RCTs were conducted in the same institution (a University teaching hospital)[348, 380]. Both studies evaluated the effectiveness of midazolam. The first study compared the effectiveness of oral midazolam with intranasal midazolam, in children aged from 6 months to 3 years[348]. They underwent an ECG and they found that both routes were 100% effective. The other study (Caliskan et. al, 2013) compared the effectiveness of intravenous paracetamol (15 mg/kg) and dipyrone (15 mg/kg) as analgesic agents, in 60 children scheduled for elective surgery, as premedication. All children were administered intravenous midazolam before surgery[380]. They found that (24, 40%) needed additional sedation (intravenous bolus of Propofol).

Two RCTs were conducted by Mirzak to evaluate the effectiveness of dexmedetomidine, ketamine and propofol as premedication[381, 382]. The first study conducted between September 2005 and April 2006 evaluated ketamine and propofol. Ketamine significantly reduced preoperative agitation compared to propofol (p=0.0001)[381]. Between February 2009 and August 2009 they assessed the effectiveness of dexmedetomidine versus placebo as premedication. They found that dexmedetomidine was significantly more effective in reducing agitation scores than placebo (P=0.01)[382].

Alp et al. (2002) compared the effectiveness of three sedative agents including midazolam, thiopental, and cocktail (meperidine, chlorpromazine and pheniramine) for CT/MRI procedures, in a prospective observational study [3]. They found that thiopental and the cocktail were more effective than midazolam for CT scan, while midazolam and the cocktail were more effective than thiopental for MRI. A prospective

observational study in the same hospital evaluated chloral hydrate effectiveness for taking a blood test[242]. The success rate was 100%.

Other studies were conducted in different hospitals within the country. Four RCTs evaluated oral midazolam effectiveness for CT/MRI, dental and MCUG procedures [271, 345, 383, 384]. Midazolam procedural success rate was variable, ranging from 54% to 100%. The effectiveness of rectal midazolam for CT/MRI procedures was evaluated in a prospective observational study [336]. All procedures were completed successfully.

Two studies evaluated ketamine safety and/or effectiveness for painful procedures (lumbar puncture and circumcision) [385, 386]. They were conducted between 2004 and 2007 and found that ketamine was 100% effective.

One study compared the effectiveness of dexmedetomidine with propofol in 60 children aged from 1 to 7 years, who underwent MRI[331]. The results demonstrated that procedural success was 100% in both groups.

Two case report studies reported the toxicity of chloral hydrate (Table 8.4)[225, 296]. Both cases described respiratory toxicity requiring intervention.

None of the studies conducted in Turkey mentioned the existence of sedation guidelines.

Table 8. 2: RCTs conducted in Turkey

Reference, country	Design/ Setting	Hospital name	Duration	Number of children	Age (Y)	Drugs/dose (mg/kg)	Procedure	Findings
Akil et al. 2005[271]	Single- blind RCT / University teaching hospital	Celal Bayar University hospital, Manisa	2002-2003,	53	0.6-15	Chloral hydrate / 25 PO midazolam / 0.6 PO	MCUG	Success rate was 100% for chloral and 94 % for midazolam group Onset of sedation ranged from 10-20 minutes for chloral and 10- 35 minutes for midazolam
Cengiz et al. 2006[345]	Double- blind RCT / University teaching hospital	Harran University, Sanliurfa	NA	96	1- 7	Midazolam / 0.5 mg/kg PO+ Placebo Midazolam / 0.5 mg/kg PO+ Diphenhydramine / 1.25 mg/kg PO	MRI	Success rate was 59% for midazolam+ placebo and 82% for midazolam+ Diphenhydramine Onset of sedation was ranged from 15- 30 minutes for M and 15- 43 minutes midazolam+ Diphenhydramine
Koroglu et al. 2005[331]	Single- blind RCT / University teaching hospital	Inonu University, Malatya	NA	60	1- 7	Dexmedetomidine / 1 Mcg/kg/hr. IVI or Propofol / 100 Mcg/kg/min IVI	MRI	Success rate was 100% for both groups Hypoxia (4 cases in Propofol group)
Yildirim S. et al. 2006[348]	Single- blind RCT / University teaching hospital	Baskent University, Ankara	March 2006- May 2006	80	0.6 -3	Midazolam / 0.4 PO Midazolam / 0.2 IN	ECG	Success rate was 100% for both groups

Po=orally, IN=intranasal, IVI=intravenous infusion

Table 8.2: RCTs conducted in Turkey

Reference	Design/ Setting	Hospital name	Duration	Number of children	Age (Y)	Drugs/dose (mg/kg)	Procedure	Findings
Dilli et al. 2008[385]	Single- blind RCT / Tertiary hospital	Ministry of Health tertiary hospital, Ankara	January 2004- December 2006	99	2-14	Ketamine /1 IV Ketamine+ midazolam/1 IV+ 0.1 IV	Lumbar puncture	Success rate was 100% for both groups Hypoxia (ketamine (0); ketamine& midazolam (3)) Dizziness (ketamine (5); ketamine & midazolam (10)) Vomiting (ketamine (10); ketamine & midazolam (5))
Sayin et al. 2008[386]	Single- blind RCT / University teaching hospital	Yeditepe University, Istanbul	January 2006- July 2007	100	NA*	5% ketamine / 10 PR 2.5% ketamine /10 PR	Circumcision	Success rate was 100% for both groups Mean sedation score was significantly higher in 5% K group (P = 0.02).
Baygin et al. 2010[383]	Double blind RCT / University teaching hospital	Gazi University, Ankara	NA	60	5–8	Midazolam / 0.7, PO Ketamine / 3 PO Midazolam / 0.25 PO+ 40% N2O+ 60% O2	Dental procedures	0.7 mg/kg midazolam was significantly more effective than other groups (54% for 0.7 midazolam group versus 33% for ketamine group, 13 for midazolam 0.25, and 7% for control group) (P< 0.05)
Demir et al. 2012[384]	Single- blind RCT / Tertiary hospital	Tatvan State Hospital, Bitlis	NA	100	2- 12	Midazolam / 0.5 PO Placebo	CT/MRI	Success rate was 100% for both groups Mean duration of sedation was 21 min for M and 26 min for placebo group

*Authors reported the weight only and it was 10-20kg

Table 8.2: RCTs conducted in Turkey

Reference	Design/ Setting	Hospital name	Duration	Number of children	Age	Drugs/dose (mg/kg)	Procedure	Findings
Caliskan et al. 2013[380]	Double blind RCT of analgesia / University teaching hospital	Baskent University, Ankara	NA	60	7- 15	Midazolam / 0.05 IV Paracetamol/Dipyrone IV	Preoperative	(24, 40%) needed additional sedation (propofol /0.5–1.0 mg/kg IV bolus)
Mizrak et al. 2013[382]	Double blind RCT / University teaching hospital	Gaziantep University, Gaziantep	December 2008- April 2009	60	5- 15	Dexmedetomidine / 0.5 IV Placebo	Preoperative	Sedation scores significantly higher with dexmedetomidine mean scores 3 versus 1 respectively (P=0.001). Dexmedetomidine significantly reduced the agitation scores (P < 0.01)
Mizrak et al. 2010[381]	Double blind RCT / University teaching hospital	Gaziantep University, Sahinbey	February 2009- August 2009	60	4-11	Ketamine/ 1 IV Propofol/ 3 IV	Preoperative	Agitation score was significantly lower in ketamine group (P = 0.0001). Vomiting (one case in K and 4 cases in Pro group.

Table 8. 3: Prospective observational studies conducted in Turkey

Reference	Setting	Hospital name	Duration	Number of children	Age group	Drugs (Mg/kg)	Procedure	Findings
Doganay et al. 2001[336]	Tertiary hospital	Anabilim hospital, Istanbul	NA	30	1- 18 years	Midazolam/ 0.35 PR	CT/MRI	Success rate was 100%
Alp et al. 2002[3]	University teaching hospital	Atatürk University, Erzurum	NA	70	2- 78 months	Midazolam/ 1 PR Thiopental/ 25-50 PR Cocktail/0.1 mL from (meperidine 11 mg/mL, chlorpromazine 2.8 mg/mL and pheniramine 2.8 mg/mL)	CT/MRI	Success rate of CT scan was 0% for M, 77% for T, and 24% for cocktail. Success rate of MRI was 36% for M, 9% for T, and 55% for cocktail
Ikbal et al.2004 [242]	University teaching hospital	Ataturk University, Erzurum	NA	18	31- 55 days	Chloral hydrate / 50 PO	Blood test	Success rate was 100%.

Po=orally, PR=Rectally, IV=intravenous

Table 8. 4: Case reports conducted in Turkey

Reference	Setting	Number of children	Age	Drugs	Procedure	AEs	Treatment
Kirimi et al. 2002[225]	University teaching hospital	1	28 days	Oral 250mg/kg chloral hydrate	CT	Respiratory distress, Excessive salivation, Respiratory depression, Severe hypoxia	IV fluid. O2 therapy
Cecen et al. 2009[296]	University teaching hospital	1	4 months	50mg/kg chloral hydrate rectally, then after 5 min another dose of 50mg/kg was given orally	Vaccination (agitation)	Tachycardia, dyspnea, cyanosis	Intubation, O2 therapy

- **Iran**

There were 8 studies (7 RCTs and one prospective observational study) conducted in Iran. These included 805 children aged from one month to 16 years (Table 8.5). Three of the 7 RCTs were conducted in the same hospital [387-389].

These three studies were conducted one after each other from January 2010 to August 2012 and all examined the effectiveness of sedation for EEG. The first compared chloral hydrate with promethazine in children aged from 1 to 10 years[388], the second melatonin and midazolam in children aged from 1 to 8 years[389], and the final study compared chloral hydrate/promethazine and chloral hydrate/hydroxyzine in children aged 1 to 7 years[387]. Initially, chloral hydrate was found to be more effective[388], in the next study melatonin was more effective than midazolam, but still less effective than chloral hydrate[389]. Finally the combination of chloral hydrate and promethazine was found to give the best results[387].

The other (5) studies were conducted in different hospitals to evaluate the effectiveness of various sedatives. Three studies evaluated the effectiveness of midazolam for GI endoscopy[390], CT[391] and for dental procedures[392]. The success rate of midazolam ranged from 59% to 100%.

The remaining two RCTs evaluated either the effectiveness of clonidine to reduce anxiety in patients undergoing adenotonsillectomy[393], or the effectiveness of chloral hydrate and melatonin for EEG procedure[176]. None of the studies mentioned the existence of a sedation guideline.

Table 8. 5: Studies conducted in Iran

Reference	Design/ Setting	Hospital name	Duration	Number of children	Age	Drugs/dose (mg/kg)	Procedure	Findings
Jahromi et al. 2009[393]	Double blind RCT/ Tertiary hospital	Rajaee Hospital, Qazvin	NA	120	3- 12	Paracetamol / 20 PO Clonidine / 4Mcg/kg PO	Preoperative	Both drugs reduced anxiety (mean anxiety scores 6.08 and 6.13 for clonidine and paracetamol respectively)
Ashrafi et al. 2010[176]	Single- blind RCT/ University children hospital	Tehran University hospital, Tehran	2007-2008	348	0.1- 5.4	Chloral hydrate / 50 PO Melatonin/ 2-6	EEG	Success rate was 100% for both groups Onset of sedation ranged from 10-150 min for CH and 5-210 min for Melatonin Duration of sedation was 15-240 min for both group
Rafeey et al. 2010 [390]	Single- blind RCT/ University children hospital	Tabriz University hospital, Tabriz	March 2007- March 2008	61	1-16	Midazolam / 0.5 PO Midazolam / 0.05–0.1 IV	GI endoscopy	Procedural success rate was 100% for both groups. Recovery time was longer with oral group compared to IV group (mean 55 min versus 42 min) respectively.
Fallah et al. 2013[388]	Single- blind RCT/ University teaching hospital	Shahid sadoughi hospital, Yazd	January 2010- February 2011	60	1-10	Chloral hydrate / 70 PO Promethazine / 1 PO	EEG	Chloral hydrate was more effective than promethazine (98% and 70% respectively (P = 0.02). Vomiting (6 cases, 20%) of chloral hydrate group Agitation (2 cases, 7%) of promethazine group. Onset of sedation was more rapid with chloral hydrate (mean 32 versus 52 min, P<0.001).

IV=intravenous, Po=orally

Table 8.5: Studies conducted in Iran

Reference	Design/ Setting	Hospital name	Duration	Number of children	Age	Drugs/dose (mg/kg)	Procedure	Findings
Fallah et al. 2014[389]	Single- blind RCT/ University teaching hospital	Shahid sadoughi hospital, Yazd	September 2011- March 2012	60	1-8	Melatonin/ 0.3 PO Midazolam/ 0.75 PO	EEG	Melatonin was more effective than Midazolam (73% and 37% respectively (P = 0.004).
Fallah et al. 2014[387]	Single- blind RCT/ University teaching hospital	Shahid sadoughi hospital, Yazd	April- August 2012	90	1–7	Chloral hydrate/ 40 PO Chloral hydrate /40 PO+ Promethazine/ 1 PO Chloral hydrate /40 PO+ hydroxyzine/ 2 PO	EEG	Chloral + promethazine was more effective than chloral hydrate and chloral hydrate + hydroxyzine groups (98% versus and 70% and 95% respectively (P = 0.02). Vomiting (5 cases, 17%) of chloral group, (7 cases, 2%) of chloral + promethazine, and (7 cases, 2%) of chloral hydrate + hydroxyzine Agitation (1 case, 3%) of chloral hydrate group. Hypotension (1 case, 3%) of chloral hydrate +hydroxyzine group.
Tavassoli-Hojjati et al. 2014[392]	Cross-over RCT / University teaching hospital	Shahed University hospital, Tehran	NA	18	2.5-6	Midazolam/0.3 buccal Midazolam/0.5 PO	Dental procedures	Success rate was 89% for oral midazolam and 83% for buccal midazolam group.
Mohammadshahi et al. 2014[391]	Prospective observational study/university teaching hospital	AJA University hospital, Tehran	NA	48	1- 7	Midazolam/ 0.5 PO+ diphenhydramine/ 1.25 PO Midazolam/0.5 PO	CT	Success rate was higher with midazolam + diphenhydramine compared to M alone (86% versus 59%) respectively.

Po=orally

- **Saudi Arabia**

Four studies were found (two prospective observational studies, one RCT and one retrospective study) (Table 8.6). Two studies were conducted in the same institution in May 1999- February 2002 and in July 2005- October 2006 for CT/MRI. The first study evaluated chloral hydrate effectiveness[196], the second compared chloral hydrate with midazolam in children aged from birth to 12 years[394]. Chloral hydrate was found to be more effective than midazolam.

The remaining two studies were conducted in different hospitals. Firstly a prospective observational study was conducted in a tertiary hospital to evaluate chloral hydrate in children undergoing brainstem auditory evoked potential procedures[395]. Procedural success rate was 100%.

A retrospective cohort study was conducted to evaluate the use of sedative agents in the paediatric emergency department of a university teaching hospital[396]. The most commonly prescribed sedative was Ketamine (IV), which was used for painful PS including; repair of bone fracture, abscess drainage and laceration repair. The authors documented the use of American college of emergency physicians' guideline (Table 8.6).

Table 8. 6: Studies conducted in Saudi Arabia

Reference	Design/ Setting	Hospital name	Duration	Number of children	Age	Drugs/dose (mg/kg)	Procedure	Findings
Hijazi et al. 2005 [196]	Prospective observational study/tertiary hospital	King Abdulaziz Medical City, Riyadh	May 1999-February 2002	148	0-12	Chloral hydrate / 100 PO	CT/MRI	Success rate was 89% Vomiting reported in 3 patient and hyperactivity in one patient
Hijazi et al. 2014 [394]	Double blind RCT / Tertiary hospital	King Abdulaziz Medical City, Riyadh	July 2005-October 2006	275	0-12	Midazolam/ 0.5 mg/kg PO Chloral hydrate/ 100 mg/kg PO	CT/MRI	Procedural success rate was 89% for chloral hydrate and 33% for midazolam
Al-Ayadhi 2008[395]	Prospective observational study/university teaching hospital	King Saud University hospital, Riyadh	September 2005- April 2006	61	0-10	chloral hydrate / 50 PO	BAEP*	Success rate was 100%

BAEP: Brainstem auditory evoked potential

Table 8.6: Studies conducted in Saudi Arabia

Reference	Design/ Setting	Hospital name	Duration	Number of children	Age (Y)	Drugs/dose (mg/kg)	Procedure	Findings
Salleeh et al. 2014[396]	Retrospective study/university teaching hospital	King Khalid University Hospital, Riyadh	December 2005- July 2008	179	0.4-13	Ketamine IV (mean 1.2) Ketamine IM (mean 3) Ketamine+ midazolam (mean 1.2 + 0.066) Ketamine+ propofol (mean + 1) Ketamine+ fentanyl (mean 2.5 Mcg/kg+ 1.8 Mcg/kg) Midazolam+ fentanyl (mean 0.3 Mcg/kg+ 1 Mcg/kg) Midazolam 0.1	Repair of bone fracture, repair of injury, abscess drainage, repair of laceration and removal of foreign body	The most common used sedative was ketamine IV in 90% of children with success rate of 100% Vomiting developed by 6 patients Hypoxia (SpO2 80%) developed by one patient* Emergence reaction developed by 2 patients** Seizure (jerky movement and shivering) developed by one patient***

* Patient was managed by using mask ventilation with 100% oxygen

** One patient required treatment using midazolam, the other was required no treatment

*** Patient was treated by 100% oxygen and IV midazolam

- **Jordan**

Three studies were found (one RCT, one prospective observational study, and one retrospective study) (Table 8.7). The first study was conducted to evaluate the effectiveness of midazolam and clonidine, in children who underwent tonsillectomy. Midazolam was found to be more effective than clonidine in reducing preoperative anxiety (75% versus 25%) respectively[397]. A study by Abdul-Baqi (1991) evaluated the effect of chloral hydrate on middle ear pressure in children during brainstem auditory evoked potential procedure[199]. Neither study mentioned they used sedation guideline.

Finally, a study by Miqdady et al. (2011) evaluated the use of midazolam and ketamine for endoscopy. It reported that it used an institutional sedation guideline[398].

Table 8. 7: Studies conducted in Jordan

Reference	Design/ Setting	Hospital name	Duration	Number of children	Age (Y)	Drugs/dose (mg/kg)	Procedure	Findings
Qteshat, 2011[397]	Double blind RCT / Tertiary hospital	King Hussein Medical City, Amman	September 2008- May 2009	54	6- 14	Midazolam/ 0.5 PO Clonidine/ 4 Mcg/kg PO	Preoperative	Midazolam produced rapid sedation effect than Clonidine (mean 42 minutes and 75 minutes respectively. Midazolam was more effective in reducing preoperative anxiety than Clonidine (75% versus 25%) respectively.
Abdul-Baqi K 1991[199]	Prospective observational study/university teaching hospital	Jordan University hospital, Amman	NA	34	0.9-7	Chloral hydrate / 40 PO	BAEP*	Middle ear pressure increased significantly in all patients ($p<0.05$)
Miqdady MS et al. 2011[398]	Retrospective study/university teaching hospital	King Abdullah University Hospital, Irbid	August 2002 - July 2008	301	1-18	Midazolam/ mean 0.16 IV+ Ketamine/ mean 1.06 IV	Endoscopic procedures	Sedation was effective in 79% Hypoxia (37, 12%) patients Respiratory distress (4, 1%) patients

* BAEP: Brainstem auditory evoked potential

- **Israel**

Four studies (one RCT[330] and three case reports[222, 315, 399]) evaluated the safety and/or effectiveness of different sedatives (Table 8.8 and 8.9). A RCT was conducted to evaluate the effectiveness of chloral hydrate and nitrous oxide for VCUG procedure, with both sedatives were found to be 100% effective. Two studies reported the toxicity of chloral hydrate and triclofos as sedative agents[222, 315]. One study described successful treatment with nitrous oxide[399].

Table 8. 8: Studies conducted in Israel

Reference	Design/ Setting	Hospital name	Duration	Number of children	Age (Y)	Drugs/dose (mg/kg)	Procedure	Findings
Keidan et al. 2005[330]	Single- blind RCT / Tertiary hospital	Tel-Aviv University hospital, Tel-Aviv	June 2003-February 2004	47	3- 15 years	Midazolam / 0.5 mg/kg PO N2O/ 50% inhaled	VCUG	Success rate was 100% for both groups Mean duration of sedation was 20 min for M and 23 min for N2O group

Table 8. 9: Case reports conducted in Israel

Reference	Setting	Number of children	Age (Y)	Drugs	Procedure	AEs	Treatment
Shahar et al. 1979[315]	Teaching hospital	1	0.2	Oral 1600- 1800 mg triclofos	Circumcision	Deep coma, Severe hypothermia, Hypotension, Lack of tendon reflexes	Intravenous fluids
Farber Abramow 1985[222]	Tertiary hospital	1	1.6	Oral 100 mg/kg chloral hydrate	CT	Sever dyspnea, Tachycardia, Tachypnea severe, Severs laryngeal edema, Respiratory acidosis	Hydrocortisone (IV), Racemic adrenalin (INH)
Moskovitz et al. 2005[399]	Teaching hospital	2	Case1: 4.7 Case2: 14	Case1: 3.7 mg/kg hydroxyzine and 50% N2O/ O2, 6 mg diazepam and 50% N2O/O2 Case2: 5 mg diazepam and 50% N2O/O2	Dental procedures	None	None

- **Other countries**

A study by Mostafa and Morsy (2013) in Egypt evaluated the effectiveness of midazolam and dexmedetomidine in 96 children, aged from 2 to 8 years, for bone marrow biopsy[400]. Nitrous oxide was used for dental procedures in a study conducted by Muhammad and colleagues (2011) in center-based clinics in Kuwait, and involved 118 children aged from 6 to 13 years [401]. None of the studies stated the use of a sedative guideline (Table 8.10).

Table 8. 10: Prospective observational studies continued

Reference	Country	Design/ Setting	Hospital name	Duration	Number of children	Age (Y)	Drugs	Procedure	Finding
Mostafa, Morsy 2013[400]	Egypt	Double blind RCT / Teaching hospital	Asyut University hospital, Asyut	NA	96	2- 8	Midazolam/ 0.2 mg/kg IN Dexmedetomidine/ 1 Mcg/kg IN ketamine / 5 mg/kg IN	Bone marrow biopsy	Dexmedetomidine produced faster effect compared to other groups sedatives ($p < 0.05$).
Muhammad et al. 2011[401]	Kuwait	Prospective observational study	Ministry of Health hospital, Salmiya	NA	118	6- 13	N2O	Dental procedures	99% of parents preferred the use of BMT versus 20% of parents who preferred N2O sedation.

BMT= behavioral management techniques, Po=orally, IN=intranasal

8.5. Discussion

This is the first review of studies that evaluated the use of sedation in the Middle East. Almost half the studies were from Turkey.

Most of the studies were RCTs (57%). Comparative studies can only give a potential snap shot of the research question, and do not allow comments on regional or national practice. Moreover, from the studies identified in this review, it was difficult to compare practices, because they were mostly single-centre studies that examined a single procedure. One study retrospectively examined sedative prescribing, and this was confined to painful procedures in the emergency department [396].

Few studies from the Middle East referenced the use of a sedation guideline. A national survey in the UK conducted in 2006 revealed that 80% of responding hospitals used a sedation guideline (ages of the patients were not specified) [402].

The current research consists of isolated studies, which did not follow each other sequentially. For example, Mizrak et al (2010) showed ketamine was better than propofol as a pre-medication[381]. The subsequent study compared dexmedetomidine to a placebo[382]. It would have been better to compare dexmedetomidine to ketamine. In contrast, Fallah et al. (2013) and (2014) in Iran examined sedation for EEG and showed that the combination of chloral hydrate and promethazine was more effective than chloral hydrate alone[387, 388].

Ketamine was the most commonly examined drug for painful procedures in five countries. It was given by various administration routes, IV and IM routes most commonly. The dose of ketamine varied widely. This may have reflected the divergent literature related to several procedures, and contributed to the reported variable efficacy of ketamine. Results showed that ketamine was effective and safe in most cases. This is in line with the study by Green et al. in the USA which evaluated the

safety and effectiveness of IM Ketamine mainly for laceration repair and fracture reduction, in 1022 children younger than 15 years[403]. The researchers found that ketamine was highly effective in 98% of the children and had a good safety profile. Ketamine was associated with a high incidence of adverse events, especially vomiting (17, 6%), but all cases were mild and improved without treatment. This review also reported four patients who were given ketamine and developed serious adverse events; three of them required medical intervention.

Midazolam and chloral hydrate were the second most studied sedatives across the Middle East. Chloral hydrate was used for painless procedures, while midazolam was used for both painless and painful procedures. The dosage varied according to the type of procedure and patient age.

Practice around chloral hydrate, midazolam and ketamine is similar in the Middle East and the UK. Chloral hydrate is used for painless imaging procedures for patients who weigh less than 15 kg. Midazolam is recommended for painless imaging procedures in children who weigh more than 15 kg and in children undergoing painful procedures [80]. Ketamine is used alone as a second-line option for painful procedures. As a second sedative, chloral hydrate was associated with adverse events. Vomiting was the most frequent adverse event (14, 6.7%). All cases were mild and self-limiting.

8.6. Conclusion

This review is the first study that aimed to evaluate the use of sedation in the Middle East. Although the studies originating from the Middle East were relatively few in number, there was a similarity between studies in the use of sedation for specific paediatric procedures. The use of guidelines or protocols for sedation was rare, which was reflected in inappropriate clinical sedation practice. The indications for the use of a sedative drug in the Middle East are quite similar to the UK. Vomiting was reported to have occurred frequently, mainly with chloral hydrate and ketamine.

CHAPTER NINE

A Survey of Procedural Sedation Practices in Children in the Kingdom of Saudi Arabia

9.1. Introduction

The Kingdom of Saudi Arabia (KSA) occupies about 850,000 square miles, which represents the largest area of the Arabian Peninsula [404]. The population of the country was placed by the last official census, in 2010, at 27.1 million [405]. The population younger than 30 years comprises 67%, and 37% are below 15 years of age[406]. The infant mortality rate for the year 2012 was 16.2 per 1000, which is 63% less than the regional rate (44 per 1000) and 56% less than the global rate (37 per 1000) [407].

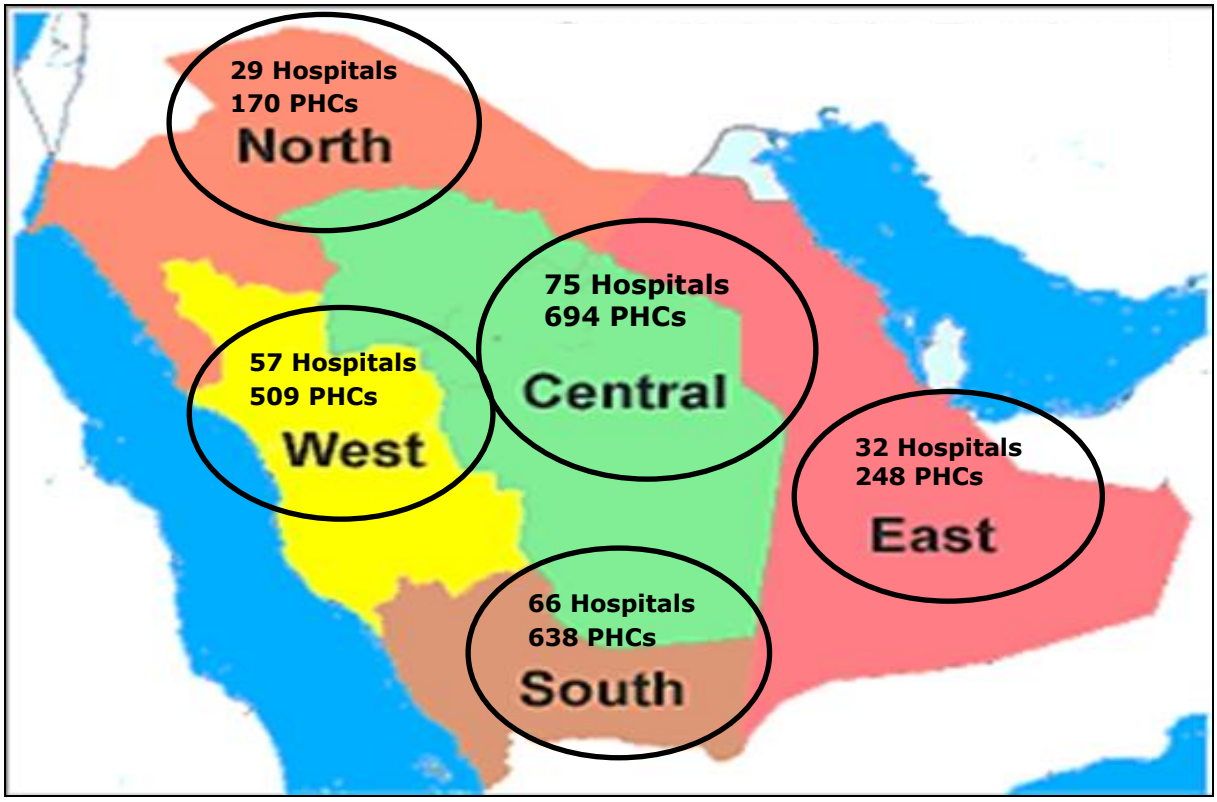
The KSA is one of the fastest growing and richest countries in the Middle East and is a dominant producer and exporter of oil, which comprises the major percentage of the country's incomes[408, 409]. National income per capita for Saudi individuals increased from US$8,140 in 2000 to US$24,726 in 2008 (a three-fold increase) [376, 410, 411] and this improvement is expected to positively affect its services, including heath care.

Health care services in the KSA have improved and increased dramatically over the past decade [412]. In 1925, the first public health section was established in the city of Mecca by royal decree [413]. It was responsible for providing free health care for residents and pilgrims by establishing hospitals and dispensary clinics [413]. In 1950, the Saudi Ministry of Health (MOH) was established by royal decree and this step represents the fundamental advance in the health care system [413].

The health care sector in the KSA is mainly managed by the government through the MOH and a number of government agencies that operate various hospitals and medical facilities for their employees. Additionally, the private sector runs many hospitals that provide medical services in the Kingdom [407]. The MOH provides universal health care coverage for the whole country [407]. There are a total of 415 hospitals (58,126 beds) including private hospitals [414]. The MOH operates 62% of the hospitals and 53% centers and clinics; other health care facilities are operated by various government agencies, including the Ministry of Education, the Ministry of Defense, the Ministry of the Interior, the National Guard Ministry and the Red Crescent Society. The total number of hospitals operated by the MOH is 259, with 35,828 beds (Figure 9.1) [400]

The main health care system in the KSA is managed by the MOH and its responsibilities include management, strategic and technical planning, formulation of health policies and supervising all delivery programs of health services, in addition to private sector health services. In conformity with the KSA constitution, all citizens and expatriates employed by the public division are provided free and full access to all health care services [414, 415]. According to a WHO report, the total government expenditure on the public health sector in Saudi Arabia during 2009 was 5% of total domestic product which is less than the USA (16%) and Japan (7%) [416]..

Figure 9. 1: Distribution of the MOH's hospitals and primary health care centres according to the regions of Saudi Arabia



PHC= Primary Health Care Centers

Currently, the MOH operates 2,259 primary care centers all over the country, each serving approximately 10,000 people [417]. The primary care centers are responsible for providing residents with various services, including educating the people regarding common health problems and ways to avoid and control them; providing adequate sources of safe water; increasing the food supply and ensuring suitable nutrition; providing comprehensive paediatric and maternal care; administering immunisation to children against various infectious diseases; controlling and preventing endemic diseases that develop locally; and giving immediate treatment for injuries and common diseases[418, 419]. In addition, primary care centres act as the gateway to secondary health care centres when a patient's condition requires special treatment.

The secondary health care services mainly are delivered at the regional level in approximately 395 general hospitals managed by the local directorates. The number of secondary care hospitals is increasing as a result of decentralisation in the delivery of health care services. The goal of this decentralisation is for each region of the country to have its own general hospital(s).

There are 56 tertiary hospitals covering most regions in Saudi Arabia, these include 20 hospitals for obstetrics and paediatric patients.

Government agencies usually provide health care services for their employees. They have their own budgets, administration management, medical policies and procedures. These agencies, for instance, include the Ministry of Education hospitals and the Saudi Red Crescent Authority. With regard to private sector providers, they offer around 20% of the total health care services to the general public in the kingdom [420]. They have specialised children's hospitals that provide health care for paediatric patients.

The MOH for Health Care Accreditation has been establishing hospital quality and safety appraisals since 1995[417]. The guidelines for administration of medications, including sedative agents, fall under the assessment of health care accreditation criteria. Hence, more hospitals will have achieved the procedural sedation (PS) guidelines as accreditation developments. However, the treatment and/or diagnostic procedure guidelines in most hospitals differ, and in some instances health care professionals tend to neglect them[417]. There is limited data regarding the use of sedation in the Middle East, especially in Saudi Arabia, as shown in the previous chapter (Chapter 8).

Saudi Arabia is one of the biggest countries in the Middle East region. Moreover, it is the country where I am from and where I will return to work. Therefore, it was

decided to examine practice further and to survey clinical practice patterns to evaluate how often sedative agents are used for treatment and/or diagnostic procedures. We consequently designed a web-based survey to evaluate practitioner's use of sedation in paediatric patients in the kingdom of Saudi Arabia.

9.2. Aim

Sedation in children and young people has become a standard tool in several diagnostic and therapeutic procedures. The aim of this chapter was to gain information on current practice and to evaluate the views of practitioners on; use of sedation, availability of guidelines, the drugs being used and the level of practice being undertaken.

9.3. Methods

No standardised questionnaire was found in the literature. One was therefore composed to include multiple-choice and open-ended questions, with the chance to expand answers to some given questions in free text. Following a moderate response to the sending of the initial survey, a shortened survey was resent focusing on the questions felt to be most relevant. The results were analysed as one group, including only questions common to both surveys. It consisted of two main sections including; demographic questions and general questions (Appendix C).

9.3.1. Demographic questions

The questions in this section were designed to obtain individual data from the respondents about their working area, and type of hospital.

9.3.2. General questions

This section was designed to collect data about the current sedation practices including; sedation guidelines, patients monitoring during PS, medical instructions during and after PS and the most commonly used sedative drug(s) including: route of administrations.

9.3.3. Study design and population

A web-based survey was sent throughout all hospitals that belong to the MOH of Saudi Arabia across the country. The study participants were paediatric doctors and nurses who were members of the Saudi Commission for Health Specialties. A questionnaire and cover letter describing the study were available through an internet link (Survey Monkey), this provider was used as it was readily recognisable by professionals. A response to the survey was requested through email. A second and, if needed, a third mailing message were sent to remind the non-responders.

9.3.4. Data analysis

Categorical data was described by frequencies. Chi-squared test was used for analysis of variables. Differences were considered to be statistically significant at $P < 0.05$.

9.4. Results

In total, 571 questionnaires were sent electronically. Questionnaires were completed by 93 (16.3%) respondents. The middle area of the country represented 44% of the total respondents. This is owing to it being the largest area and includes the capital city (Riyadh), which contains a large number of specialist and universities' hospitals (Figure 9.1). Approximately 60% of the respondents were working in a tertiary hospital (Table 9.1).

Table 9. 1: Demographic data of the respondents

Variable	Number of respondents
Area of work	
• Middle	41 (44%)
• South	16 (17%)
• West	13 (14%)
• East	12 (13%)
• North	11 (12%)
Type of hospital	
• Tertiary	56 (60%)
• Community	18 (19%)
• University	12 (13%)
• Ambulatory centre	7 (8%)

A sedation guideline was reported to be used by 59 (63%) of the respondents, of which 34 (58%) had an institutional sedation guideline, and 25 (42%) used the American Academy of Pediatrics and American Society of Anesthesiology guideline. 51 (63%) reported that they had a written procedural sedation (PS) informed consent form. Discharge criteria after (PS) were mentioned by 44 (54%) respondents, and a discharge instruction form were specified by 31 (38%) (Table 9.2).

Table 9. 2: Sedation practice

Variable	Number of respondents
Use of sedation guideline	
• Yes	59 (63%)
• No	34 (37%)
Discharge criteria	
• Yes	51 (55%)
• No	42 (45%)
Use of discharge instructions form	
• No	62 (67%)
• Yes	31 (33%)

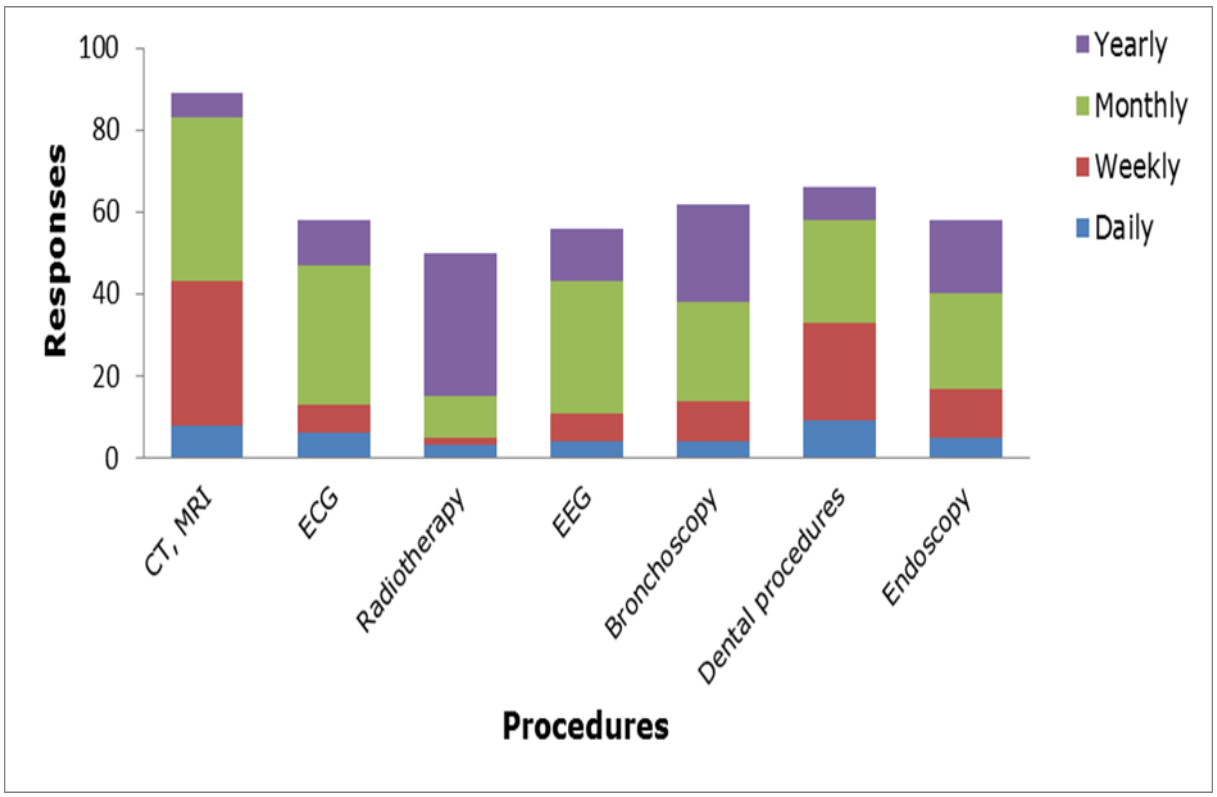
9.4.1. Monitoring during procedural sedation

Monitoring of patients during procedures took place frequently (91%), however 9% reported that they don't monitor patients during procedures. Approximately half of these did not feel that the monitoring of sedation is necessary, whilst others referred to either shortage of staff (22%) or shortage of equipment (22%).

9.4.2. Procedural sedation and the most common sedative used

Imaging procedures such as CT and MRI were the most common painless procedures for which sedation was used, while dental procedures and bronchoscopy were the most common painful procedures (Figure 9.2).

Figure 9. 2: Painless and painful procedures and how often sedation is being used



Overall all, chloral hydrate was the most frequently stated sedative agent (84, 93%) used by respondents, followed by midazolam (71, 76%), diazepam (56, 60%), and lorazepam (34, 40%) (Table 9.3).

Table 9. 3: Sedatives commonly used

Sedative	Number of respondents	% of respondents
Chloral hydrate	84	93
Midazolam	71	76
Diazepam	56	60
Lorazepam	37	37
Ketamine	34	40
Propofol	21	23
N2O inhalation	20	22
Thiopental	20	22
Etomidate	7	8

9.5. Discussion

This survey is the first study of the use of sedation in children in Saudi Arabia. The results of this survey showed that the sedation practice in Saudi Arabia is not ideal.

As shown in the chapters in my thesis, sedative agents have the potential to cause respiratory, CNS, or cardiovascular adverse events. The use of sedation guidelines can reduce or prevent the development of many of these adverse events [2]. Despite the advantages of using sedation guidelines, not all responding practitioners have them.

There are no national or standard guidelines for PS in hospitals in Saudi Arabia; therefore, physicians use institutional or international guidelines in each hospital, or provide PS to children without a guideline in some hospitals. In this survey, 63% of the respondents used a sedation guideline, 55% had criteria for patient's discharge after PS, however only 33% provided discharge instructions to the patients after PS. This is comparable with the results from an Australia and New Zealand survey that evaluated sedation practice in children [421]. They found that 58% of the general departments used sedation guidelines.

Many sedation guidelines recommend patient monitoring during PS in order to prevent the development of any potential adverse event [21, 422]. Fortunately, the results of this study demonstrated that 91% of the respondents monitored their patients during PS. These results show that there is an interest in the safety of sedation in children. The exact methods and equipment used for monitoring, and the recommendations for practice in the local guidelines, would be useful to explore further.

Chloral hydrate and midazolam were the most common sedatives respondents said they used for both painless procedures and painful procedures (93%, 76% respectively). This finding is in line with the NICE guideline recommendations for the use of these agents, which recommends them for painless diagnostic imaging

procedures [80]. The use of chloral hydrate for painful procedures is in contrast with the guideline in which the use of chloral hydrate is recommended for only painless procedures [80].

9.6. Limitation

It is important to mention the limitations of this survey. The data presented in this study has been composed from questionnaires completed by health care professionals and involves individual-reporting of behaviour instead of objective data. Furthermore, the response rate was relatively low which happens commonly with web surveys. However, the wide ranges of hospitals responding from different areas make it likely that the results of this study give a reasonable indication of practice.

9.7. Conclusion

The results of this survey suggest that there is room for improvement in the practice of PS for children in Saudi Arabia. Unified PS guidelines were rare in surveyed hospitals. Chloral hydrate and midazolam were the most frequently used sedative agents for both painless and painful procedures. Our study suggests that development and implementation of a national PS for paediatric patients are required as early as possible.

CHAPTER TEN

General conclusion

10.1. Introduction

For any medication used regularly in children it is important to consider the safety and clinical effectiveness. At the start of this thesis the clinical literature was searched for guidelines and the local hospital consulted for its policy on sedation. Consequently, I performed systematic reviews of the literature evaluating the sedatives that are most frequently used. Palatability has been shown to play a major role in drug treatment adherence [96]. This thesis adds new evidence about the palatability of two sedative medicines commonly used in children. This was achieved by evaluating published studies and by conducting a prospective study to assess their palatability clinically in a children's hospital. This thesis also adds new evidence about the use of sedation in the Middle East, particularly focusing on Saudi Arabia, since this area is particularly important for its author.

10.2. Summary of findings

10.2.1. Evaluation of the most commonly used sedatives

Three systematic reviews were conducted to evaluate the safety and effectiveness of chloral hydrate, its derivative (triclofos) and midazolam. Meta-analysis was not performed due to the heterogeneity of the studies.

Chloral hydrate's safety and effectiveness were evaluated via three types of procedures including painless, painful, and treatment procedures (Chapter 2). The

success rate for painless and painful procedural sedations was variable (50%–100%), higher for shorter imaging procedures such as CT imaging. The success rate for treatment procedures was higher, ranging from 86% to 100%. One in seven children undergoing painless procedures and one in six for painful procedures, receiving chloral hydrate, experienced an AE. Hypoxia was the most commonly reported AE, occurring in approximately one in nineteen children. It was usually mild. Moderate hypoxia (SpO2 <90%) was uncommon, occurring in less than 2% of cases and was reversible after using simple manoeuvres, such as supplemental oxygen therapy. No deaths were reported; however there were seventeen serious AEs, all requiring medical interventions and/or hospitalisation. Hypoxia was more common in infants under two years. Vomiting was the second most frequently reported AE occurring in approximately one in thirty children. The majority occurred during dental procedures. The incidence of AEs was higher during painful procedures (17.3%, 313AEs/1810 patients) than in painless procedures (13%, 1,951AEs/14439 patients).

The incidence of AEs was even higher in children who were given chloral hydrate for treatment of agitation (18.5%, 81AEs/438 patients) with hypoxia affecting one in six children; severe complications such as hypoxia and respiratory depressions were reported in 7 children.

The systematic review that evaluated triclofos safety and clinical effectiveness during procedural sedation (Chapter 3) also identified vomiting and hypoxia as the most commonly reported AEs, 10% (62/613) and 7.8% (48/613) respectively. All cases of hypoxia were mild and none required medical intervention. The incidence rate of reported AEs was dramatically higher for painful procedures (27.3%, 121/444)

compared to painless (7.7%, 13/169) procedures. The success rate was higher for painless procedural sedation (84-100%) compared to painful procedures (50–98%).

We noticed that paraldehyde is still used for sedation in children as a part of the local hospital sedation policy, but not the NICE guidance. Therefore it was felt to be important to conduct a systematic review to evaluate its effectiveness and safety in children. Just five studies were identified (Chapter 4) and only two of these evaluated paraldehyde safety in 29 children. Meta-analysis was not performed due to the heterogeneity of the studies. Vomiting was the most commonly reported AE, with an incidence rate of 25% (2 cases/8 patients). Three studies evaluated paraldehyde effectiveness, with a procedural success rate that ranged from 75% to 93.1%. The quality and number of studies were very limited.

Chapter 5 evaluated midazolam effectiveness and safety during imaging procedures. Procedural success rates ranged from 0% to 100%, with a median of 82%. Midazolam was incompletely effective for both MRI and CT (median success rate was 67% and 68.5%) respectively. The most common AE was hypoxia affecting one in 74 children. Most cases were mild. Most of the moderate cases were reversible after simple airway manoeuvres. Vomiting was the second most frequently reported AE, occurring in 1% of children.

In conclusion there is good evidence to support the use of chloral hydrate, as recommended in the NICE guidance. It has a moderate rate of adverse events and because of the risk of hypoxia, children should always be monitored closely and managed by an experienced practitioner who is able to perform airway manoeuvres and resuscitation if required[423]. Its use for procedures such as dental extractions should be limited by community dentists, this is supported by it not being

recommended in the current UK guidance[424]. Midazolam is primarily recommended for use as a sedative for imaging procedures, although it was found to have less than a two thirds success rate for MRI [80]. This is not sufficient to recommend its regular use in practice and many hospitals are now moving towards general anaesthetic[424]. The evidence for the use of paraldehyde in sedation is very limited and does not support its continued use without further studies.

10.2.2. Palatability of the two most commonly used sedatives

After taking into consideration the effectiveness and safety of the most commonly used sedatives, it known that factors such as taste, which may affect the ease of drug administration and therefore treatment adherence, should be taken into account. It was therefore decided to evaluate the palatability of the two most commonly used sedatives in children (chloral hydrate and midazolam) (Chapter 6 and Chapter 7).

Only 9 studies were identified in a systematic review (Chapter 6). The majority of the studies (8) evaluated midazolam's palatability, while only two studied chloral hydrate. There was a great variability in the tools used for assessment of palatability. Midazolam was acceptable to most children; however, chloral hydrate was found to have a poor palatability.

The results from the prospective observational study (Chapter 7) reinforced the results found in the systematic review, showing a poor acceptance of oral chloral hydrate as judged by the children, their parents and nursing staff. Midazolam, however, had a relatively good acceptance and parents were more likely to prefer midazolam. Despite this, chloral hydrate was associated with a high success rate (19/20), whereas the success rate with midazolam was lower (12/20), with sedation supplementation given to 5 patients in each group. This could be because half of the procedures using midazolam were painful compared to none of those with chloral

hydrate. This limited effectiveness is in line with the results previously shown in the systematic reviews.

10.2.3. Evaluating the use of sedation in Middle Eastern countries

The safety and effectiveness of sedative agents for procedural sedation of children have been well evaluated in Western countries. However, there have been very few clinical studies of their use in children in Middle East countries. I have focussed on this area as it is the region where I am from, and where I will return to work. A literature review and survey study (Chapter 8 and Chapter 9) were conducted and, to my knowledge, these studies are the first to look at the use of sedation in children in the Middle East.

The literature review (Chapter 8) showed that the number of studies that evaluated the prescribing patterns of sedative agents in paediatric patients was limited. More than half originated from one country (Turkey) and most studies were conducted at a single centre and assessed a single procedural sedation. Sedation guidelines and/ or protocols were used rarely, which may indicate the possibility of inappropriate use of sedative agents and a lack of coordinated practice in the region.

A survey study was therefore carried out to evaluate the use of sedation in the Kingdom of Saudi Arabia, and involved 81 health care professionals from throughout the country (Chapter 9). It demonstrated that the practice of administering sedation in Saudi Arabia is not ideal. The majority (90%) of respondents reported the use of monitoring during sedation. However only 61% of the respondents reported the use of sedation guidelines, 54% had discharge criteria and 36% reported the use of consent for sedation. Chloral hydrate and midazolam were most commonly reported to be used as sedative agents, for both painless and painful procedures.

10.3. Conclusions from this thesis

The results of this work have provided some recommendations for paediatric professionals and clinical practice in both the UK and worldwide.

- Chloral hydrate is appropriate for sedation for painless imaging procedures in young children.
- Midazolam was found to be more effective for procedures that require a sedative agent with anxiolytic and amnestic effects.
- Midazolam does not provide good sedation for longer procedures like MRI, with only a two thirds success rate overall in the literature.
- Chloral hydrate and midazolam both have a significant incidence of hypoxia, reinforcing the importance of monitoring children during sedation.
- The palatability of chloral hydrate is poor.
- Due to the very limited clinical studies evaluating the use of paraldehyde for sedation in children, its effectiveness and safety in this setting remain questionable. Its use in children should be avoided.
- Further work is needed to support the administration of sedation in Middle Eastern countries. Work both nationally and regionally should be undertaken to consider implementation of a unified procedural sedation guideline.
- Awareness of health care professionals about sedation guidelines in the Middle East region should be raised.

10.4. Lessons learned and future plans

During my PhD studies I have learned how to design a research project including creating a research question based on the existing bibliographic knowledge. Moreover, I have learned how to manage a research project through setting up and designing

the study protocols; collecting, archiving and interpreting results. Additionally I have learned how to conduct a systematic literature review and have improved during my studies and am now aware of how to use a good methodology, this is reflected in improvements in the quality of my midazolam systematic review compared to the chloral hydrate systematic review. In addition to the above, I have acquired some complementary skills and experiences which will be helpful for my future job such as oral presentations, organising meetings, managing my time and organising work.

10.5. Implications for future research and practice

- Although this thesis evaluated the most commonly used sedatives, further research studies are required to evaluate other sedatives that are still currently used in paediatric patients, such as ketamine.
- More clinical studies are needed to evaluate the effectiveness and safety of paraldehyde, for its continued use for the sedation of children.
- The rarity of reported severe AEs from clinical studies may possibly be due to improper documentation of safety data or the lack of large prospective studies. This underscores the importance of developing a reporting system that is easy to use and directly accessible to all health care professionals and patients.
- Palatability in children's medicines development is important and should continue to be assessed by conducting studies to inform the pharmaceutical companies about children' opinions, by paying attention to patients' feedback about adherence and compliance.
- Further evaluation of sedation guidelines in the Middle East is needed.
- The successful establishment of guidelines needs substantial planning, continuous education, and training (Taylor, 2003). Therefore, my suggestions on how to establish guidelines in Saudi Arabia include:

- A local PS quality and assurance monitoring group. This group, working as an authorised hospital committee, with various responsibilities, including local application of the recommendations in the PS guidelines, quality control, implementing and developing local protocols, and local training.
- A national PS support group. This group, comprised of experts in children's procedural sedation, will coordinate the establishment of the guidelines. This working group could have responsibility for conducting pilot-trials in particular settings and hospitals. Moreover, this group may assist in consultations.
- Training for PS. Currently, there are no national training credentials for PS in children in Saudi Arabia. However, designing a universal training program for the various types of procedural sedation is difficult. All health care professionals involved in paediatric sedation should have skills in airway management and resuscitation. Future training courses could educate health care professionals in the following fields: administration of sedation, monitoring patients before, during, and after procedural sedation, policy, and research.

In closing, the use of sedatives has increased globally; this has led to a rise in concerns about their safety and effectiveness, particularly in the paediatric population. The effectiveness of most frequently used sedatives was variable according to the type of procedural sedation. Palatability was seen to influence drug acceptance. The significant incidence of AEs (especially respiratory complications), highlights the importance of close patient monitoring. Some of the current practice identified for PS for children in the Middle East was not ideal. Thus, national PS guidelines must be developed and implemented.

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Appendix A: Ethical and trust (R&D) Approval

HSC Business Services Organisation

Office for Research Ethics Committees Northern Ireland (ORECNI)

Customer Care & Performance Directorate
Office Suite 3
Lisburn Square House
Haslem's Lane
Lisburn
Co. Antrim BT28 1TW
Tel:+44 (0) 28 9260 3107
www.orecni.hscni.net

HSC REC A

17 September 2014

Dr Helen Sammons
Associate Professor of Child Health
University of Nottingham
Uttoxeter Road
Derbyshire/ Derby
DE22 3DT

Dear Dr Sammons

Study title:	**A pilot study to assess the palatability of two commonly used sedative medicines in a children's hospital.**
REC reference:	**14/NI/1061**
Protocol number:	**14075**
IRAS project ID:	**158296**

Thank you for your letter of 17 September 2014. I can confirm the REC has received the documents listed below and that these comply with the approval conditions detailed in our letter dated 16 September 2014

Documents received

The documents received were as follows:

Document	*Version*	*Date*
Covering letter on headed paper [Dr H Sammons, Cover letter 3]		
Covering Email, Dr H Sammons		17 September 2014

Providing Support to Health and Social Care

Protocol, Clean copy	1.2	17 September 2014
Protocol, Tracked changes	1.2	17 September 2014
PIS, Age 6-10, Clean copy, Final	1.2	17 September 2014
PIS, Age 6-10, Tracked Changes, Final	1.2	17 September 2014

Approved documents

The final list of approved documentation for the study is therefore as follows:

Document	*Version*	*Date*
Covering letter on headed paper [Dr H Sammons, Cover letter 3]		
IRAS Checklist XML [Checklist_23072014]		23 July 2014
IRAS Checklist XML [Checklist_05092014]		05 September 2014
Letter from sponsor	1.0	14 July 2014
Letters of invitation to participant [Parent Invitation Letter V1.1 12.8.14 (tracked changes)]	1.1	12 August 2014
Letters of invitation to participant [Parent Invitation Letter V1.1 12.8.14 (updated clean version)]	1.1	12 August 2014
Other	v 1.0	09 July 2014
Other [Datacollection form 6-15 year old, Final V1.1 12.8.14 (tracked changes)]	1.1	12 January 2014
Other [REC Sub-Committee covering letter]		12 August 2014
Other [Protocol, Tracked changes, Final version]	1.2	17 September 2014
Other [Datacollection form 6-15 year old, Final V1.1 12.8.14 (updated clean version)]	1.1	12 August 2014
Other [Protocol, Clean copy, Final version]	1.2	17 September 2014
Other [Data collection form 0-5 year old, Final V1.1 12.8.14 (updated clean version)]	1.1	12 August 2014
Other [Data collection form 0-5 year old, Final V1.1 12.8.14 (tracked changes)]	1.1	12 August 2014
Other [Covering email, Dr H Sammons]		17 September 2014
Participant consent form [CONSENT FORM Parental, Final V1.1 12.8.14 (tracked changes)]	1.1	12 August 2014
Participant consent form	v 1.0	09 July 2014
Participant consent form [CONSENT FORM Parental, Final V1.1 12.8.14 (updated clean version)]	1.1	12 August 2014
Participant information sheet (PIS) [Age 6-10 years Final, Tracked Changes]	1.2	17 September 2014
Participant information sheet (PIS) [Parents information Sheet, Final V1.1.12.8.14. (updated clean version)]	1.1	12 August 2014
Participant information sheet (PIS) [Age 6-10 years Final,	1.2	17 September

Clean copy]		2014
Participant information sheet (PIS) [Parents information Sheet, Final V1.1.12.8.14. (tracked changes)]	1.1	12 August 2014
Participant information sheet (PIS)	v 1.0	09 July 2014
REC Application Form [REC_Form_23072014]		23 July 2014
Summary CV for Chief Investigator (CI)	1.0	09 July 2014
Summary CV for student	v 1.0	09 July 2014
Summary CV for supervisor (student research)	v 1.0	09 July 2014

You should ensure that the sponsor has a copy of the final documentation for the study. It is the sponsor's responsibility to ensure that the documentation is made available to R&D offices at all participating sites.

14/NI/1061	**Please quote this number on all correspondence**

Yours sincerely

Jan Daley

Miss Jan Daley
REC Manager

E-mail: RECA@hscni.net

Copy to: *Ms Angela Shone, University of Nottingham*
Dr Teresa Grieve, Royal Derby Hospital

DHFT Research & Development Dept. Issued 19 NOV 2014

Derby Hospitals NHS
NHS Foundation Trust

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Research and Development Office

TRUST APPROVAL LETTER

Dr Helen Sammons
Associate Professor of Child Health & Honorary Consultant Paediatrician
Royal Derby Hospital NHS Trust
University of Nottingham – Medical School
School of Graduate Entry Medicine and Health
Uttoxeter Road
Derby DE22 3DT

Dear Dr Helen Sammons

Re: A pilot study to assess the palatability of two commonly used sedative medicines in a children's hospital

R&D Reference: DHRD/2014/078

The agreed Recruitment Target for this Study is: 40

Further to the Research Ethics Committee approval for the above study, I am pleased to confirm Trust management approval for you to proceed in accordance with the agreed protocol, the Trust's financial procedures for research and development and the Research Governance Framework (which includes the Data Protection Act 1998 and the Health & Safety at Work Act 1974).

Please supply the following information at the appropriate time points to Dr Teresa Grieve, Assistant Director of R&D via (dhft.randdadmin@nhs.net):

- The date of your first patient recruited to the study
- A report every six months if the study duration is greater than six months
- Notification of any SUSARS, amendments, urgent safety measures or if the trial is abandoned.
- Notification of end of the study and an end of study report.
- Details of any publications arising from this research project.

Please note that approval for this study is dependent on full compliance with all of the above conditions.

The 70 day Target Date for Recruiting the First Patient is 7th January 2015

The Government's Plan for Growth (March 2011) announced the transformation of incentives at local level for efficiency in initiation and delivery of research. As a result the NIHR have introduced research performance benchmarks: ***studies must recruit to time and target, and first patient must be recruited onto the study within 70 days of submission of local application.*** Trusts will be fined, otherwise penalised and funding withheld if these metrics

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are not met. Please ensure you work towards recruiting the first patient by the above date, and inform us if you envisage any problems as we will endeavour to help you meet this target.

I would like to take this opportunity to wish you every success with this study.

Yours sincerely

Teresa M. Levine

P.P.

Dr Fran Game FRCP
Director of Research & Development

Short Study Title: A pilot study to assess the palatability of two commonly used sedative medicines in a children's hospital

R&D Ref: DHRD/2014/078

In accordance with your application and subsequent R&D approval dated 10th November 2014 the following documentation was reviewed and may therefore be used on the above study with Trust approval.

List of reviewed Documents:

Document	Version	Date
IRAS R&D Form 158296/686885/14/197		
Letter from sponsor	1.0	14 July 2014
Letters of invitation to participant Parent Invitation Letter V1.1 12.8.14	1.1	12 August 2014
Data collection form 6-15 year old, Final V1.1 12.8.14	1.1	12 August 2014
Protocol, Final version	1.2	17 September 2014
Data collection form 0-5 year old, Final V1.1 12.8.14	1.1	12 August 2014
Covering email, Dr H Sammons		17 September 2014
Participant consent form CONSENT FORM Parental, Final V1.1 12.8.14	1.1	12 August 2014
Participant information sheet (PIS) Parents information Sheet, Final V1.1.12.8.14.	1.1	12 August 2014
Participant information sheet (PIS) Age 6-10 years Final	1.2	17 September 2014
NHS REC Approval letter		17 September 2014
Summary CV for Chief Investigator (CI)	1.0	09 July 2014
Summary CV for student	v 1.0	09 July 2014
Summary CV for supervisor (student research)	v 1.0	09 July 2014

Appendix B: Participant information sheet

The University of Nottingham

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A STUDY TO ASSESS THE TASTE OF TWO SLEEPY MEDICINES IN A CHILDREN'S HOSPITAL

Children (6-10 years) Information Sheet

(Final version 1.2: 17.9.14)

We would like to ask for your help with our study. Please read this leaflet with your mum and dad. Please ask us if you have questions.

Why are we doing this research?

This is to try to make medicines for children better.

Why have I been asked to take part?

You have been asked to take part because you will take a medicine to make you sleepy in hospital.

Do I have to take part?

No, it is up to you. If you do take part you can keep this paper and you (if you want) and your parent will sign a form. If you then don't want to carry on, just let your parents and us know. It's ok to do this.

What will happen to me if I take part?

If you and your parents are happy to take part then you will be asked a few easy questions. This is about if the medicine you have taken tastes nice. This will take just a few minutes.

What are the possible good things if I take part?

The study will not help you but might help us use better tasting medicines.

What happens when the project stops?

We will look at all the answers given to us. We plan to write a paper in a medical magazine about what everyone thought.

What if there is a problem or something goes wrong?

We want only to ask you some questions, so we don't think anything will go wrong. If you have a question, please tell your parents who can speak to us.

Will my taking part in this study be kept private?

We will write down your medicines, your age, whether you are a boy or girl and what you say. We won't keep your name or address.

Who is organising and paying for the project?

This study is being organised by the University of Nottingham.

Who has reviewed the study?

A Committee, the hospital and a Professor of Children's medicines.

Thank you for reading this – please ask any questions if you need to.

The University of Nottingham

Derby Hospitals NHS
NHS Foundation Trust

A STUDY TO ASSESS THE PALATABILITY OF TWO COMMONLY USED SEDATIVE MEDICINES IN A CHILDREN'S HOSPITAL

Children (11 to 15) Information Sheet

(Final version 1.0: 8.7.14)

- Would you like help with our research project?

We are asking if you could participate in a research project. Before you decide about joining in, it is important to understand why the research is being done and what it will involve for you. Please read this leaflet carefully. Talk to us if you want more information. Take time to decide whether or not you wish to take part.

What is the purpose of the study?

As you may know the taste of a medicine and how it looks and smells is important to make sure you are willing to take it. There has been very little work in this country asking young people themselves how they would like their medicines to taste and look. Therefore this project will ask what you think of the taste of certain medicines you will be given whilst in hospital to make you feel sleepy and this will try to help people who make medicines for children to make better ones in the future.

Why have I been chosen to take part?

You have been asked to take part because you will be taking some medicine we are interested in looking at. They are ones that make you feel sleepy if you are having a scan or having a medical procedure.

Do I have to take part?

It is up to you whether or not to take part. If you do decide to take part you will be given this information sheet to keep and you and your parent will be asked to sign a form. We will need your parents agreement as well. If you decide to talk to us you are free to stop at any

time and without giving a reason. If you want to stop, or not to talk to us at all, that is fine and will not affect how you are looked after in hospital.

What will happen to me if I take part?

We will ask you what you thought of the medicine you have just taken and ask you to score it on a scale. This will take around 10 minutes depending on how much you want to say to us. We will also record how long it takes you to take the medicine, if you have any problems and if it works.

What are the possible benefits of taking part?

We cannot promise the study will be of help to you, but we hope that the information we get will encourage people who make medicines to take children' opinions into consideration and involve them more when making new medicines for children.

What happens when the project stops?

We will analyse our results, and will write a paper to publish it in a medical journal to tell other people about our results.

What if something goes wrong?

We only want to ask you a few questions. Therefore, we are not expecting anything to go wrong with our study. You will be having the medicines even if you do not take part in our study.

Will my taking part in this study be kept private?

Your information will be kept private. We will only record your age, sex and what you say about the medicine.

What will happen to the results of the project?

Once we have analysed our results we will write papers to publish them in a journals read by children's doctors, nurses and pharmacists. No one will know that you have taken part. You will not be identified in any report/publication.

Who is organizing and funding the research?

The University of Nottingham.

Who has reviewed the study?

Before any study project goes ahead it has to be looked at by a Research Ethics Committee which will ensure that the project is fair. Your project has been checked by the Derbyshire Research Ethics Committee and the Research and Development Unit of the hospital.

Contact for Further Information:

If you would like further information please contact Dr Helen Sammons, Associate Professor in Child Health, Division of Medical Sciences & Graduate Entry Medicine, School of Medicine, University of Nottingham, Royal Derby Hospital Centre, Uttoxeter Road, Derby, DE22 3DT. Tel: 01332 724691 or

Mrs Badriyah Alotaibi, Postgraduate Student, University of Nottingham, Academic Division of Child Health, Clinical Sciences Building, School of Medicine, Royal Derby Hospital Centre, Uttoxeter Road, Derby, Derby DE22 3DT. Tel. 01332 724840

The University of Nottingham

Derby Hospitals NHS
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A STUDY TO ASSESS THE PALATABILITY OF TWO COMMONLY USED SEDATIVE MEDICINES IN A CHILDREN'S HOSPITAL

Parents Information Sheet (Final version 1.1: 12.8.14)

We would like to invite your child to take part in our research study. Before you decide we would like you to understand why the research is being done and what it would involve for you. One of our team will go through the information sheet with you and answer any questions you have. Talk to others about the study if you wish. Ask us if there is anything that is not clear.

What is the purpose of this study?

The taste of a medicine and how it looks and smells is important to make sure children are willing to take it. In the UK there has been very little research that has asked for children's opinions on the taste of medicines they have to take. This study will look at children views on the taste of medicines they are given to make them feel sleepy (to sedate them) when they need to have a scan or a procedure. Parents and nurses views will also be asked and we will look at whether the medicines work well.

Why has my child been invited?

Your child is being invited to take part because he or she has been prescribed one of the medications that we are interested in whilst in hospital – chloral hydrate or midazolam. We are inviting 40 participants like your child to take part

Does my child have to take part?

It is up to you and your child to whether or not to take part. If you do decide to take part you will be given this information sheet to keep and be asked to sign a consent form. If you decide to take part you are still free to withdraw at any time and without giving a reason. This would not affect your legal rights.

What will happen if we take part?

If you decide to take part, we will ask your child what they thought of the medicines they are given to take. This will take approximately 10 minutes depending on how much your child wants to say to us. We will either write down what the child tells us or ask your child to fill a faces scale in themselves. If they are too young we will ask you to fill it in for them. We will also record how long it takes your children to take their medicine, any problems they have in taking it, whether it works well for them and any comments you or the nurses have.

Expenses and payments

Participants will not be paid to participate in the study.

What are the possible disadvantages and risks of taking part?

There are no risks associated with taking part in this project; we will just ask you and your child some questions about the medicine(s) they have just taken. This will be a medicine they would have been given even if they were not taking part in our study.

What are the possible benefits of taking part?

We cannot promise the study will help your child, but the information we get from this study may help manufacturers know more about what children would prefer medicines to be like. It is hoped this will encourage them to take children' opinions into consideration and involve them more when making new medicines for children.

What happens when the study stops?

We will analyse our results and we will write a paper to publish it in a medical journals to inform other people about our results.

What if there is a problem?

If you have a concern about any aspect of this study, you should ask to speak to the researchers who will do their best to answer your questions. The researchers contact details are given at the end of this information sheet. If you remain unhappy and wish to complain formally, you can do this by contacting the Patient Advice and Liaison Service (PALS) (Phone the PALS team on Free phone: 0800 783 7691 or Office: 01332 785156)

Will my child's taking part in this study be kept confidential?

We will follow ethical and legal practice and all information about your child will be handled in confidence.

If your child joins the study, some parts of their medical records and the data collected for the study will be looked at by authorised persons from the University of Nottingham who are organising the research. They may also be looked at by authorised people to check that the study is being carried out correctly. All will have a duty of confidentiality to your child as a research participant and we will do our best to meet this duty.

All information which is collected about your child during the course of the research will be kept strictly confidential, stored in a secure and locked office, and on a password protected database. Any information about your child which leaves the hospital will have your name and address removed (anonymised) and a unique code will be used so that you cannot be recognised from it. All research data will be kept securely for 7 years. After this time your child's data will be disposed of securely. During this time all precautions will be taken by all

those involved to maintain your confidentiality, only members of the research team will have access to your personal data.

What will happen if I don't want to carry on with the study?

Your participation is voluntary and you are free to withdraw at any time, without giving any reason, and without your clinical care being affected. If you withdraw then the information collected so far can be erased if that is your wish or this information may still be used in the project analysis.

Involvement of the General Practitioner/Family doctor (GP)

No need for your GP to be notified.

What will happen to the results of the research study?

Once we have analysed our results we will publish them in a journal read by children's doctors, nurses and pharmacists. It is hoped this will encourage manufacturers of children's medicine to listen to children and involve them more when making new medicines for children. Your child will not be identified in any report/publication.

If you would like to know about the results of our study please contact Dr Helen Sammons (details below). This is because we will not routinely keep your contact details.

Who is organising and funding this study?

This study is being organised and funded by the University of Nottingham.

Who has reviewed the study?

All research in the NHS is looked at by independent group of people, called a Research Ethics Committee, to protect your interests. This study has been reviewed and given favourable opinion by the Research Ethics Committee and the Research and Development Unit of the hospital.

Contact for further information:

If you would like further information please contact:

Dr Helen Sammons, Associate Professor in Child Health, Division of Medical Sciences & Graduate Entry Medicine, School of Medicine, University of Nottingham, Royal Derby Hospital Centre, Uttoxeter Road, Derby, DE22 3DT. Tel: 01332 724691 or helen.sammons@nottingham.ac.uk

Mrs Badriyah Alotaibi, Postgraduate Student, University of Nottingham, Academic Division of Child Health, Clinical Sciences Building, School of Medicine, Royal Derby Hospital Centre, Uttoxeter Road, Derby, Derby DE22 3DT. Tel. 01332 724840

THANK YOU FOR HELPING US WITH THIS PROJECT

The University of Nottingham
UNITED KINGDOM · CHINA · MALAYSIA

Derby Hospitals NHS
NHS Foundation Trust

CONSENT FORM FOR PARENTS
(Final version 1.1: 12.8.14)

Title of Study: A STUDY TO ASSESS THE PALATABILITY OF TWO COMMONLY USED SEDATIVE MEDICINES IN A CHILDREN'S HOSPITAL

REC ref: ***(to be added after approval given)***

Name of Researchers: Dr. Helen Sammons, Associate Professor and Honorary Consultant in Child Health; Badriyah Alotaibi, PhD Student

Name of Participant (Parent):

Name of Participant (Child):

Please initial box

1. I confirm that I have read and understand the information sheet version number 1.1 dated 12.8.14 for the above study and have had the opportunity to ask questions. ☐
2. I understand that my child's participation is voluntary and that they are free to withdraw at any time, without giving any reason, and without their care being affected. I understand that should they withdraw then the information collected so far can be erased if that is our wish or this information may still be used in the project analysis. ☐
3. I understand that relevant sections of my child's medical notes and data collected in the study may be looked at by authorised individuals from the University of Nottingham, the research group and regulatory authorities where it is relevant to our taking part in this study. I give permission for these individuals to have access to these records and to collect, store, analyse and publish information obtained from my child's participation in this study. I understand that my child's personal details will be kept confidential. ☐
4. I understand that medication names from my child's treatment chart will be noted by the researcher. I give permission for these individuals to have access to my child's treatment chart and to use my child's anonymous comments in written reports. ☐
5. I agree for my child (named above) to take part in the above study. ☐

_____	_____	_____
Name of Parent	Date	Signature
_____	_____	_____
Name of Person taking consent	Date	Signature

(OPTIONAL) Section for children to give assent

I agree to take part in this study

_____	_____	_____
Name of Child (for assent)	Date	Signature

3 copies: 1 for participant, 1 for the project notes and 1 for the medical notes if applicable

The University of Nottingham

Derby Hospitals NHS
NHS Foundation Trust

DATA COLLECTION FORM

A STUDY TO ASSESS THE PALATABILITY OF TWO COMMONLY USED SEDATIVE MEDICINES IN A CHILDREN'S HOSPITAL

(Final version 1.1: 12.8.14)

Participant number ☐

Date of Completion ____/____/____ (Day/month/year)

RESEARCHER TO FILL IN THE 1ST PAGE BY ASKING CLINICAL CARE TEAM (NURSE AND/OR MEDICAL PRACTITIONER)

- Age at entry into study: _____ years _____months
- Sex: _____ male _____female
- Procedure type:----------

1. Which sedative agent was administered in this child/adolescent today? (answered by nurse)

   Chloral hydrate 500mg/5ml oral solution ☐

   Midazolam 5mg/ml Solution for Injection/Infusion Hypnovel (Roche) ☐

2. Initial dose given (mg/kg)? (answered by nurse)

   ----

3. Total dose given (mg/kg)? (answered by nurse)

   ----

4. How many times has this drug been given to this patient before for sedation? (answered by nurse)

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NURSE AND/OR MEDICAL PRACTITIONER TO FILL IN THIS PAGE

Participant number ☐

5. Total time taken from the nurse picking up the syringe to approach the child & administration of all of the medication? (answered by nurse or researcher)

---

6. Any manipulation of the medication by nursing staff or other strategies to aid administration? (answered by nurse or researcher)

_____ Yes _____No

6.1. If yes (specify)----------

7. What is the nurses' opinion about the acceptance of given medicine by the child? (answered by nurse or researcher)
   1. Totally refused
   2. Refuses to accept, but forced
   3. Dislike, but accepts
   4. The child liked the medicine (if yes specify)----------

   ---

8. What was the sedation outcome after completion of the procedure? (answered by the health care professional)

8.1 Rating Scale for Sleep Score (answered by the health care professional)

1. Fully awake, alert
2. Drowsy, disoriented
3. Asleep

8.2 Rating Scale for Movement (answered by the health care professional)

1. Violent movement that interrupts treatment
2. Continuous movement that makes treatment difficult
3. Controllable movement that does not interfere with treatment
4. No movement

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NURSE AND/OR MEDICAL PRACTITIONER TO FILL IN THIS PAGE

Participant number ☐

8.3 Rating Scale for Crying (answered by the health care professional)

1. Hysterical crying that interrupts treatment
2. Continuous, persistent crying that makes treatment difficult
3. Intermittent, mild crying that does not interfere with treatment
4. No crying

8.4 Rating Scale for Overall Behaviour (answered by the health care professional)

1. Aborted- No treatment
2. Poor- Treatment interrupted, only partial treatment completed
3. Fair- Treatment interrupted but eventually all completed
4. Good- Difficult, but all treatment performed
5. Very Good- Some limited crying or movement
6. Excellent- No crying or movement

9. Any other comments? (answered by the health care professional)

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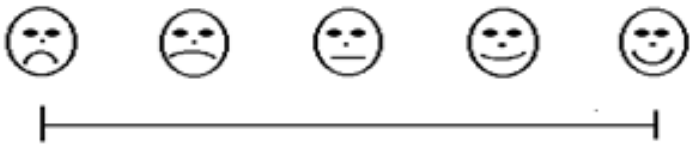
NHS Foundation Trust

CHILD OR PARENTS TO FILL IN THIS PAGE

Participant number ☐

10. Please **mark on the line** below what you thought about the taste of the drug that you have just taken: (answered by child or parents)



11. What did it taste like? (answered by child or parents)

---

12. Would you take it again? (answered by child or parents)

---

13. How palatable (including easy to swallow) do you feel the study medication is? (answered by parents)

1. Really good
2. Good
3. Not sure
4. Bad
5. Really bad

14. Have you any other comments about the medicine you/your child have just taken? (answered by parents)

THANK YOU VERY MUCH FOR YOUR HELP

The University of Nottingham

Derby Hospitals NHS
NHS Foundation Trust

DATA COLLECTION FORM

A STUDY TO ASSESS THE PALATABILITY OF TWO COMMONLY USED SEDATIVE MEDICINES IN A CHILDREN'S HOSPITAL

(Final version 1.1: 12.8.14)

Participant number ☐

Date of Completion ____/____/____

RESEARCHER TO FILL IN THE 1ST PAGE BY ASKING CLINICAL CARE TEAM (NURSE AND/OR MEDICAL PRACTITIONER)

- Age at entry into study: ____ years ____ months
- Sex: ____ male ____ female
- Procedure type:----------

1. Which sedative agent was administered in this child/adolescent today? (answered by nurse)

   Chloral hydrate 500mg/5ml oral solution ☐

   Midazolam 5mg/ml Solution for Injection/Infusion Hypnovel (Roche) ☐

2. Initial dose given (mg/kg)? (answered by nurse)

   ----

3. Total dose given (mg/kg)? (answered by nurse)

   ----

4. How many times has this drug been given to this patient before for sedation? (answered by nurse)

The University of Nottingham

Derby Hospitals NHS
NHS Foundation Trust

NURSE AND/OR MEDICAL PRACTITIONER TO FILL IN THIS PAGE

Participant number ☐

5. Total time taken from the nurse picking up the syringe to approach the child & administration of all of the medication? (answered by nurse or researcher)

---

6. Any manipulation of the medication by nursing staff or other strategies to aid administration? (answered by nurse or researcher)

____ Yes ____No

6.1. If yes (specify)----------

7. What is the nurses' opinion about the acceptance of given medicine by the child? (answered by nurse or researcher)

    1. Totally refused
    2. Refuses to accept, but forced
    3. Dislike, but accepts
    4. The child liked the medicine (if yes specify)----------

    ---

8. What was the sedation outcome after completion of the procedure? (answered by the health care professional)

8.1 Rating Scale for Sleep Score (answered by the health care professional)

1. Fully awake, alert
2. Drowsy, disoriented
3. Asleep

8.2 Rating Scale for Movement (answered by the health care professional)

1. Violent movement that interrupts treatment
2. Continuous movement that makes treatment difficult
3. Controllable movement that does not interfere with treatment
4. No movement

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NURSE AND/OR MEDICAL PRACTITIONER TO FILL IN THIS PAGE

Participant number ☐

8.3 Rating Scale for Crying (answered by the health care professional)

1. Hysterical crying that interrupts treatment
2. Continuous, persistent crying that makes treatment difficult
3. Intermittent, mild crying that does not interfere with treatment
4. No crying

8.4 Rating Scale for Overall Behaviour (answered by the health care professional)

1. Aborted- No treatment
2. Poor- Treatment interrupted, only partial treatment completed
3. Fair- Treatment interrupted but eventually all completed
4. Good- Difficult, but all treatment performed
5. Very Good- Some limited crying or movement
6. Excellent- No crying or movement

9. Any other comments? (answered by the health care professional)

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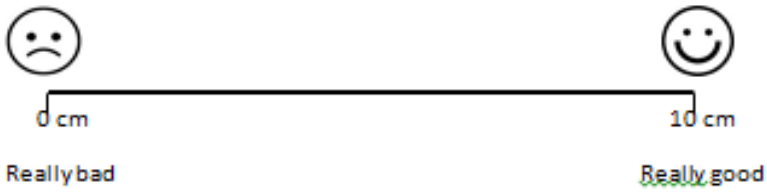
CHILD OR YOUNG ADULT TO FILL IN THIS PAGE

Participant number ☐

10. Please **mark on the line** below what you thought about the taste of the drug that you have just taken: (answered by child or young adult)



11. What did it taste like? (answered by child or young adult)

---

12. Would you take it again? (answered by child or young adult)

---

13. How palatable (including easy to swallow) do you feel the study medication is? (answered by child or young adult)

1. Really good
2. Good
3. Not sure
4. Bad
5. Really bad

14. Have you any other comments about the medicine you/your child have just taken? (answered by child or parents)

THANK YOU VERY MUCH FOR YOUR HELP

Appendix C: Questionnaire for healthcare proffesional in Saudi Arabia

A Survey of Procedural Sedation Practices in Children in the kingdom of Saudi Arabia

* 1. **In which area of the Kingdom do you work?**

- ○ Middle
- ○ North
- ○ South
- ○ East
- ○ West

* 2. **Type of your hospital**

- ○ Community
- ○ University
- ○ Ambulatory centre
- ○ Tertiary
- ○ Other (please specify)

3. Do you sedate children for any painless or painful procedures and if so how often?

	Daily	Weekly	Monthly	Yearly
Imaging procedures (CT, MRI and etc...)	☐	☐	☐	☐
Electrocardiogram (ECG)	☐	☐	☐	☐
Electroencephalography (EEG)	☐	☐	☐	☐
Radiotherapy-sleep	☐	☐	☐	☐
Bronchoscopy	☐	☐	☐	☐
Dental procedures	☐	☐	☐	☐
Endoscopy	☐	☐	☐	☐

Other (please specify the procedures that sedation is used for))

1

* 4. **Which sedative agent(s) do you use ?**

	PO	PR	IM	IV	IN
Chloral hydrate (if you pick this answer go to 13)	☐	☐	☐	☐	☐
Diazepam	☐	☐	☐	☐	☐
Etomidate	☐	☐	☐	☐	☐
Ketamine	☐	☐	☐	☐	☐
Lorazepam	☐	☐	☐	☐	☐
Midazolam	☐	☐	☐	☐	☐
N2O inhalation	☐	☐	☐	☐	☐
Propofol	☐	☐	☐	☐	☐
Thiopental	☐	☐	☐	☐	☐

Other (please specify the drug(s) and the route of administration(s) as above)

* 5. **Do you follow a sedation guideline?**

- ○ YES
- ○ NO

If Yes, please specify the guideline

* 6. **Dose monitoring of paediatric patients during PS take place?**

- ○ NO .... answer question (7)
- ○ YES

* 7. **If you selected "NO", what is your reason?**

- ○ Don't feel the necessity
- ○ Shortage of medical staff
- ○ Shortage of equipment
- ○ Other (please specify)

2

* 8. Are there criteria for discharge of patients after PS?

- YES
- NO

9. If yes, what are they?

* 10. Do you give instructions to patients at discharge?

- YES
- NO

11. If yes, what are they?

12. If you would like a copy of the results of this survey after publication, please indicate below

- YES
- NO

Contact Email

3

Appendix D: Publications and prizes

International Journal of Paediatric Dentistry

Submission Confirmation

Print

Thank you for your submission

Submitted to
International Journal of Paediatric Dentistry

Manuscript ID
IJPD-04-16-5471

Title
Safety of Chloral Hydrate for Dental Procedural Sedation in Children: A Systematic Review of the Literature

Authors
Al otaibi, Baddriyah
Choonara, Imti
Sammons, Helen

Date Submitted
09-Apr-2016

Author Dashboard

International Journal of Paediatric Dentistry - manuscript proof

INTERNATIONAL JOURNAL OF
PAEDIATRIC DENTISTRY

Safety of Chloral Hydrate for Dental Procedural Sedation in Children: A Systematic Review of the Literature

Journal:	*International Journal of Paediatric Dentistry*
Manuscript ID	Draft
Manuscript Type:	Original Article
Keywords:	chloral hydrate, children or infant or peadiatric or neonate or adolescence or adolescences or adolescent, sedation

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