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CONVULSIVE STATUS EPILEPTICUS IN CHILDREN

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DEDICATION

This thesis is especially dedicated to children suffering with epilepsy.

ABSTRACT

Convulsive status epilepticus (CSE) is an emergency condition associated with mortality and morbidity. It is commonly treated with antiepileptic drugs (AEDs), but these may cause serious adverse events and even death in children. Research on their effectiveness for CSE, and related adverse events in children remains limited. The primary aim of this research was thus to evaluate the effectiveness and safety of AEDs in treating acute tonic-clonic seizure including convulsive status epilepticus (CSE). Two systematic reviews and meta-analyses were conducted to address these aims. The first evaluated the effectiveness of AEDs in children with acute tonic-clonic seizures including (CSE). The second evaluated the safety of AEDs in this population.

The systematic review of AED effectiveness identified 20 studies published between 1946 and April 2015. It showed that buccal midazolam was more effective than rectal diazepam for treating acute tonic-clonic seizures including CSE in children, and was associated with a lower recurrence rate. Lorazepam and diazepam were equally effective in terminating seizures, but for lorazepam, intravenous administration was more effective than the buccal, sublingual or intranasal routes. Intravenous valproate appeared to be more effective than intravenous phenytoin and phenobarbital; however, the difference was not significant.

The systematic review of AED safety for children with acute tonic-clonic seizures identified 25 studies, published between 1946 and April 2015. These studies were predominantly randomised controlled trials and of these 19 studies reported more than one adverse event, while 6 reported none. A total of 203 adverse events were

documented, most commonly respiratory depression (101 children), mainly after treatment with diazepam (46 children). The rates of respiratory depression with buccal midazolam and rectal diazepam were similar (3.0% and 3.3%, respectively). Compared to intravenous diazepam, intravenous lorazepam was associated with less respiratory depression. No child suffered respiratory depression associated with intravenous valproate treatment, compared to one child with intravenous phenobarbital. When looking at all adverse events, intravenous valproate was significantly safer than intravenous phenobarbital. Respiratory depression was not noted in children who received intravenous levetiracetam; however, all levetiracetam studies identified in this review were cohort and non-comparative.

In conclusion, in the treatment of acute tonic-clonic seizures (including CSE), buccal was the best administration route for children admitted to the emergency department. Intravenous lorazepam treatment was associated with less respiratory depression than intravenous diazepam. Where IV access was practicable, intravenous lorazepam was the drug of choice. More randomised control trials are needed to evaluate the effectiveness and safety of AEDs as a second-line treatment.

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TO ALL OF THOSE GOES MY MOST SINCERE GRATITUDE

LIST OF ABBREVIATIONS

AE(s)	Adverse event(s)
AED(s)	Antiepileptic drug(s)
APLS	Advanced Paediatric Life Support recommendation
BUC	Buccal
CI	Confidence Interval
CLZ	Clonazepam
CNS	Central Nervous System
CSE	Convulsive status epilepticus
DZP	Diazepam
ILAE	International League Against Epilepsy
IM	Intramuscular
IO	Intraosseous
IPA	International Pharmaceutical Abstracts
IQR	Interquartile range
IV	Intravenous
Kg	Kilogram
LVT	Levetiracetam
LZP	Lorazepam
NCI	National Cancer Institute in the US (NCI)
NICE	National Institute for Clinical Excellence
PB	Phenobarbital
PHT	Phenytoin
P-value	Probability
RCTs	Randomised controlled trials
RR	Relative risk
SE	Status epilepticus
SIGN	Scottish Intercollegiate Guidelines Network
SPSS	Statistical Package for Social Science
STROBE	Strengthening the Reporting of Observational Studies
VAP	Valproate

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CHAPTER 1: INTRODUCTION

1. Background

Status epilepticus (SE), and specifically convulsive status epilepticus (CSE) is a neurological emergency associated with a low, but definite mortality and significant morbidity; this applies to both adult and paediatric (<18 years) populations[1].

The earliest description of CSE was found in a series of medical texts known as Skikku ("all diseases") on Babylonian clay tablets from the period between 1067 and 1046 B.C. [2]. In the fourth century BC, Hippocrates described a severe condition associated with prolonged seizures and concluded that death may occur from these seizures [3]. At the beginning of the 19th century, systematic studies of epileptic seizures were started on hospitalised patients and led to the description of many types of seizures including CSE, which was known at that time as grand mal status or "etat de mal" [3]. The expression "status epilepticus" was first used in Bazire's translation of Trousseau's lectures in clinical medicine in 1868 and these lectures made it clear that CSE is a series of attacks rather than a single seizure with a different form [4].

1.1 Definition

There are two broad categories of SE: convulsive status epilepticus (CSE) and non-convulsive status epilepticus (non-CSE). The identification of non-CSE from behavioural signs is difficult and electroencephalography (EEG) is often a crucial diagnostic tool [5]. Therefore, this thesis will focus discussion on CSE.

Most authors distinguish CSE from other types of seizure based on the duration of the attack. The International League Against Epilepsy (ILAE) standard definition is a single seizure or series of seizures lasting for 30 minutes or longer with unconsciousness

between seizures [6]. They suggest that the incidence of brain injury rises markedly after a 30-minute period and is almost certain after 60 minutes of continued CSE. This definition has been used widely for epidemiological and pathophysiological purposes [7, 8].

There are four phases of status epilepticus. They are classified on the basis of duration as follows[9-12]:

1- Early phase or premonitory status: in which the convulsion continues for more than 5 minutes. At this stage the first line treatments (benzodiazepines) are used to control the seizure either prior to arrival at hospital, by the patient's parents or paramedics, and at hospital in the emergency department.
2- Established status epilepticus: in which the seizure activity continues for more than 10 and up to 30 minutes with loss of consciousness between seizures. In this stage second line treatments such as intravenous phenytoin, phenobarbital or levetiracetam are used to try and terminate it. This phase of status epilepticus may be termed benzodiazepine-resistant status epilepticus.
3- Refractory status epilepticus: in which the seizure activity (convulsion) lasts for more than 30 minutes or has failed at least one dose of benzodiazepine and a dose of second-line intravenous AED, or both.
4- Super-refractory status epilepticus: in which the seizure activity lasts for more than 24 hrs and the patient will have been treated with intravenous anaesthetics such as thiopental, pentobarbital or propofol.

1.2 Classification

The first classification of CSE was established in 1962 in Marseille [13]. The classification was based on the type of seizure: partial, generalised or unclassified. However, this classification was not useful in routine clinical practice. Moreover, it was unhelpful in failing to include the aetiology. Correspondingly, it was unhelpful in determining the treatment and outcome of CSE.

In 1994, Shorvon introduced a new classification based on several factors: seizure type, age group, pathophysiological mechanisms and clinical features including EEG. This classification was more appropriate in clinical practice because it provided valuable information about prognosis and aetiology [14]. Shorvon further divided SE into four age-related categories: the neonatal period, infancy and childhood, childhood and adulthood.

Mastrangelo and Celato in their 2012 review [15] categorised SE into CSE and non-CSE (Table 1.2).

Table 1. 1: Status epilepticus classification

Convulsive SE	Non-convulsive SE

• Focal
  ▪ Focal motor
  ▪ Focal motor with secondary generalization
  ▪ Epilepsia partialis continua
• Generalized
  ▪ Myoclonic
  ▪ Clonic
  ▪ Tonic
• Tonic-clonic
	• Absences (typical/atypical)
	• Focal status epilepticus with sensory symptoms
	• Autonomic or focal status epilepticus with affective symptoms
	• Focal status epilepticus with autonomic symptoms (Panayiotopoulos
	• syndrome)
	• Complex-partial status epilepticus
	• Continuous spike and wave during slow sleep

This table is adapted from Mastrangelo and Celato [15]

Non-CSE is not considered a medical emergency since patients do not lose consciousness and usually return to normal within minutes of its resolution (either spontaneously or in response to treatment). In CSE, however, early treatment is essential to avoid irreversible brain injury through both metabolic decompensation and respiratory depression which further exacerbates the cerebral metabolic injury through anoxia, and subsequently, profound hypotension [16].

1.3 Aetiology

The formal aetiology of status epilepticus has been classified by the International League Against Epilepsy [17] into five divisions: acute symptomatic, remote symptomatic, idiopathic epilepsy-related, cryptogenic epilepsy-related and unclassified.

In 2006, the North London Convulsive Status Epilepticus in Childhood Surveillance Study (NLSTEPSS) classified the aetiology into 7 groups: prolonged febrile seizure, acute symptomatic, remote symptomatic, remote with acute causes, idiopathic epilepsy related, cryptogenic epilepsy related and unclassified (Table 1.3) [18].

Table 1. 2: Aetiology of status epilepticus

Aetiology	Definition	Causes
Prolonged febrile seizure	CSE that occurred in normal children who had no history of central nervous system (CNS) infection and aged between 6 months and 5 years with a temperature at least 38.0C	Febrile seizure
Acute symptomatic	CSE that occurred in otherwise healthy children who had neurological insult within the past week	Meningitis Viral CNS infection Head injury Hypoxia
Remote symptomatic	CSE reported in children who had a pre-existing CNS abnormality for more than 1 week	Tuberous sclerosis Encephalopathy
Remote with acute causes	CSE that occurred in children within a week from febrile illness or acute neurological insult and associated with a history of previous neurological abnormalities	Cerebral palsy Hydrocephalus
Idiopathic epilepsy related	CSE that occurred in children who had a history of idiopathic epilepsy with no symptomatic causes for the seizure	Idiopathic epilepsy
Cryptogenic epilepsy related	CSE that occurred in children who had a history of cryptogenic epilepsy with no symptomatic causes for the seizure	Cryptogenic epilepsy
Unclassified	All other SE	--------

This table is adapted from Chine et al [18]

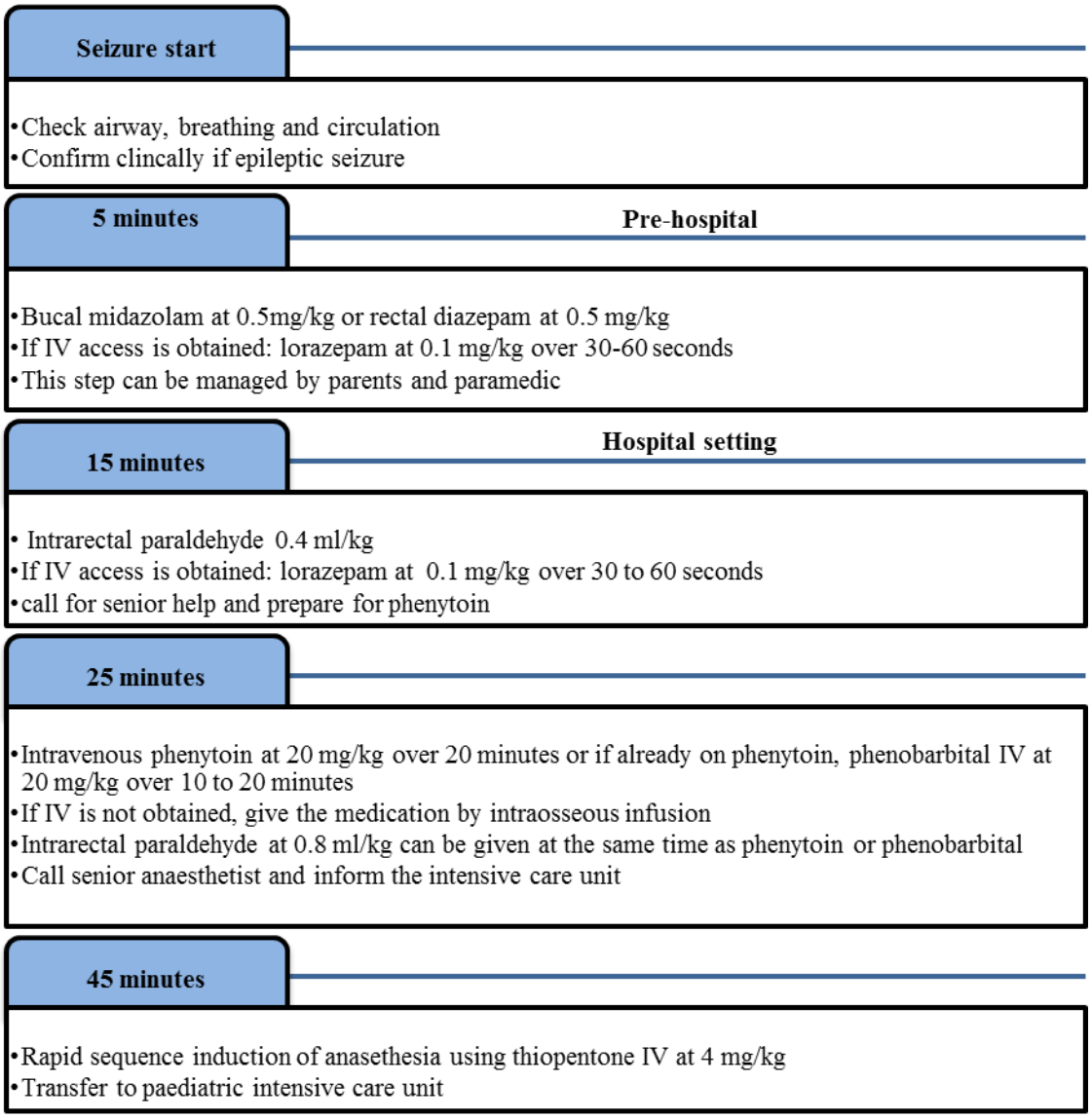
1.4 Epidemiology

The incidence of CSE in children ranges from 10 to 38 in 100,000 per year [18-20]. The higher incidence is reported in children aged less than 4 years [21] and is most common in children aged less than one year. The risk decreases in the teenage years[22]. Children with a history of pre-existing epilepsy constitute the highest proportion of SE patients (10-20%) [23, 24]. Febrile SE was most commonly documented in children less than 2 years old while cryptogenic and symptomatic SE were more frequently documented in older children [25]. In the NLSTEPSS study, prolonged febrile SE was the cause of first episodes of CSE in 32% of children; idiopathic epilepsy-related SE was identified in 10% of paediatric cases and cryptogenic epilepsy in 2% [18].

1.5 Treatment

Current treatment protocols for CSE are designed to terminate the seizure and maintain vital functions [26] as rapidly and as safely as possible. International organisations and institutions follow different guidelines and algorithms based on local experience and the availability of anti-epileptic drugs (AEDs) [27-36], but all recommend starting treatment early to avoid brain injury [26]. Traditionally and almost universally, treatment is instituted if the episode of CSE has not stopped after 5 minutes; the rationale for this is that over 90% of convulsive seizures will stop spontaneously after 3-4 minutes and if the seizure has not stopped after 4-5 minutes, it is highly unlikely to then stop spontaneously. In addition, the longer the duration of the presenting convulsive seizure, the more difficult it will be to terminate with AEDs. In the UK, the Status Epilepticus Working Group recommended a CSE protocol for children based on a comprehensive literature review and consequent consensus among its expert group [32]. The experts included Consultants in General Paediatrics, Paediatric Accident and Emergency Medicine, Paediatric Pharmacology and Paediatric Neurology. This guideline was adopted by the National Institute for Health and Care Excellence (NICE, 2004) [37], the Scottish Intercollegiate Guidelines Network (SIGN, 2005) [34] and is used in the Advanced Pediatric Life Support (APLS) course [38] (Figure 1.4). In 2012, the revised Epilepsy Guideline published by NICE indicated that rectal paraldehyde should no longer be considered as a definite, but only as an optional treatment in the management algorithm, depending on the policy of each local Emergency Department or Emergency Room [33]. In part this change reflected the concern that paraldehyde might have contributed to the incidence of respiratory depression observed in the NLSTEPSS Study [18].

Figure 1. 1: Drug management protocol for CSE in the UK



This diagram is adopted from Appleton et al [32]

All international guidelines recommend intravenous (IV) short-acting benzodiazepine as a bolus and then a second dose if the seizure is not terminated. In the UK[33] , Canada [39] and US [35] intravenous lorazepam is the preferred treatment for CSE if IV access is already available or obtained immediately on arrival in the Emergency Department / Room. In France, clonazepam is the preferred first treatment if IV access is obtained [40]. Phenytoin and phenobarbital (long-acting AEDs) are the second-line treatments used in the UK. Howevr, phenobarbital may be associated with a higher risk of

hypotension and respiratory depression than phenytoin [32]. Early studies suggested that IV phenobarbital had comparable anticonvulsant activity to IV phenytoin; however, an increased incidence of respiratory depression has been reported, particularly when phenobarbital was administered in combination with a benzodiazepine [41-45]. Fosphenytoin is the preferred second-line AED in the US [35], Canada [39] and France [40]. There are two significant advantages in using fosphenytoin over phenytoin: first, it can be given intramuscularly and second, it can be infused slightly more rapidly than phenytoin[46]. However, one randomised study reported that fosphenytoin and phenytoin showed a similar frequency of adverse side-effects[47]. Fosphenytoin is usually prescribed as 'phenytoin-equivalents' and this may result in dose-miscalculation and consequent dosing-errors. Finally, fosphenytoin is considerably more expensive than phenytoin (at least four to five times more expensive in the UK) and is not considered to be cost-effective when compared with phenytoin.[47, 48]. For these reasons, fosphenytoin is not currently prescribed in the UK. It is possible that other AEDs, and specifically levetiracetam or sodium valproate may replace phenytoin in the future [49]. However, sodium valproate may be associated with serious adverse events, particularly hepatotoxicity and pancreatitis[50]. Several studies have recommended levetiracetam instead of sodium valproate or phenytoin as a second-line treatment following the failure of benzodiazepines [51-55].

A current study entitled **E**mergen**C**y Treatment with **L**evet**I**racetam or **P**henytoin in **S**tatus **E**pilepticus ('EcLiPSE') in children – an open-label randomised controlled trial has been approved by the North West - Liverpool Central Research Ethics Committee in the UK. This is an NIHR HTA-funded study which will be conducted in approximately 25-30 Accident and Emergency Departments (Emergency Rooms) throughout the UK.

Children aged between 6 months and <18 years with focal or generalised CSE which has failed to respond to first-line treatment (typically, one or two doses of a benzodiazepine) [56]. The children will be randomly selected for treatment with either intravenous levetiracetam (40 mg/kg administered over 5 minutes) or intravenous phenytoin (20mg/kg infused) administered over 20 minutes. The aim of the study is to evaluate whether levetiracetam is more effective than phenytoin as a second-line emergency antiepileptic drug, and to compare their adverse side effects. The study is ongoing and the results are expected to be published in late 2019.

1.6 The Research Aims

Children with CSE are at high risk of mortality and also morbidity. As this is a medical emergency, the management of CSE must be rapid, effective and safe. Consequently, there is a risk that the treatment of CSE may be associated with iatrogenic complications, including potentially serious adverse side-effects. Despite the fact that much research has been carried out to assess the effectiveness and safety in adult patients, less research has been done to evaluate this in infants, children and young people.

This research was designed to assess the effectiveness and safety of 1st and 2nd line treatment of acute tonic clonic status epilepticus in children. This was achieved through two systematic reviews and meta-analyses namely:

1. A systematic review of the effectiveness of 1st and 2nd line treatment of acute tonic clonic status epilepticus in children. The effectiveness of the following AEDs were evaluated; benzodiazepines, paraldehyde, phenytoin, phenobarbital, sodium valproate and levetiracetam **(Chapter 3)**.

2. A systematic review of the safety of AEDs in children who received benzodiazepines, paraldehyde, phenytoin, phenobarbital, sodium valproate and levetiracetam, in the treatment of acute tonic clonic status epilepticus **(Chapter 4)**

CHAPTER 2: METHODS

2.1 Introduction

For this thesis I have conducted two systematic reviews in the paediatric population; the effectiveness of AEDs for convulsive status epilepticus (CSE) **(chapter 3)** and the safety of AEDs for convulsive status epilepticus (CSE) **(chapter 4)**.

Systematic reviews are the gold standard for evaluating valuable scientific evidence in health care, they play a major role in helping practitioners develop guidelines and improve health care [57]. The key points of systematic reviews are that they include a clear objective and eligible criteria and have a rigorous methodology that attempts to identify all relevant studies of high quality to answer the question posed [58].

2.2 Objectives

a) To compare the effectiveness of AEDs for convulsive status epilepticus (CSE) **(chapter 3)**

b) To compare the safety of AEDs for convulsive status epilepticus (CSE) **(chapter 4).**

The primary and secondary objectives are outlined in the respective chapters.

2.3 Search strategy and eligibility criteria

Six electronic databases were searched in these studies, namely the ; US National Library of Medicine's bibliographic database (MEDLINE), Excerpta Medica Database (EMBASE), International Pharmaceutical Abstract (IPA), Cumulative Index to Nursing and Allied Health Literature (CINHAL), Cochrane database, and PubMed. All scientific papers involving children aged up to 18 years were included.

MEDLINE, EMBASE and IPA were searched separately and then combined to remove duplications. While Cochrane, CINHAL and Pubmed were not combined with previous databases, both were searched and reviewed manually to remove duplications and identify relevant articles. The search strategy included all languages. Foreign language publications were translated to English (were translated where possible) and then the applicable data were extracted for analysis.

The types of studies, the types of participants, the types of interventions and the types of outcome measures were the main four criteria identified for selecting the scientific papers that included and analysed in these systematic reviews.

The following subsections will describe in detail the search strategy and eligibility criteria for each systematic review.

2.3.1 The effectiveness of AEDs for convulsive status epilepticus (chapter 4)

2.3.1.1 Databases and search terms

A literature search was conducted electronically on MEDLINE (1946-April 2015), EMBASE (1974-April 2015), Cochrane database (until April 2015) and Pubmed database (until April 2015). The search terms were selected based on their sensitivity and specificity according to the previous systematic reviews available [59]. The search terms used are shown table 2.1.

Table 2. 1: Search strategy for Ovid database (EMBASE AND MEDLINE)

	Subject	Result	Search type
1	epilep$.tw.	241072	Advance
2	seizure$.tw.	213878	Advance
3	convulsion$.tw.	35265	Advance
4	exp Epilepsy/	317612	Advance
5	exp Seizures/	153216	Advance
6	1 or 2 or 3 or 4or 5	467656	Advance
7	exp Epilepsy, Tonic-Clonic/	7715	Advance
8	tonic clonic.tw.	11598	Advance
9	status epilepticus.tw.	20675	Advance
10	exp Status Epilepticus/	21427	Advance
11	1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10	467731	Advance
12	limit 25 to human	341377	Advance
13	(pediatr$ or paediatr$).tw.	562824	Advance
14	child$.tw.	2273156	Advance
15	exp child/ or exp child, preschool/ or exp infant/	4239990	Advance
16	13 or 14 or 15	4922336	Advance
17	12 and 16	8869	Advance
18	emergency.tw.	383850	Advance
19	17 and 18	267	Advance
20	benzodiazepines.mp. [mp=ti, ab, ot, nm, hw, kf, px, rx, ui, sh, tn, dm, mf, dv, kw]	49227	Advance
21	paraldehyde.mp. [mp=ti, ab, ot, nm, hw, kf, px, rx, ui, sh, tn, dm, mf, dv, kw]	1907	Advance
22	phenytoin.mp. [mp=ti, ab, ot, nm, hw, kf, px, rx, ui, sh, tn, dm, mf, dv, kw]	74297	Advance
23	phenobarbital.mp. [mp=ti, ab, ot, nm, hw, kf, px, rx, ui, sh, tn, dm, mf, dv, kw]	83492	Advance
24	levetiracetam.mp. [mp=ti, ab, ot, nm, hw, kf, px, rx, ui, sh, tn, dm, mf, dv, kw]	6139	Advance
25	sodium valproate.mp. [mp=ti, ab, ot, nm, hw, kf, px, rx, ui, sh, tn, dm, mf, dv, kw]	5985	Advance
26	valproic acid.mp. [mp=ti, ab, ot, nm, hw, kf, px, rx, ui, sh, tn, dm, mf, dv, kw]	62631	Advance
27	20 or 21 or 22 or 23 or 24 or 25 or 26	227607	Advance
28	19 and 27	620	Advance
29	remove duplicates from 28	490	Advance

2.3.1.2 Inclusion and Exclusion criteria

The inclusion criteria were:

1) Randomised controlled studies (blinded or unblinded) or non-randomised controlled studies (prospective hospital based studies and retrospective population based studies).
2) Studies that evaluated the efficacy of the following antiepileptic drugs; benzodiazepines, phenytoin, phenobarbital, phenytoin, sodium valproate, paraldehyde and levetiracetam irrespective of route of administration.
3) Children aged ≤18 years admitted to hospital or emergency department with acute tonic-clonic convulsion.

We excluded case reports from the effectiveness analysis because it was impossible to determine the response rate from individual cases. Also, we excluded reviews, comments, letters, correspondence and short surveys, adult studies (aged over 18 years) and studies where the number of children or the data for children were not separately described.

2.3.1.3 Outcome measures

- The termination of acute tonic clonic seizures following treatment.
- The seizure recurrence rate from the termination of convulsion.
- Time to seizure control after drug administration.
- The need for additional dose(s).
- Additional antiepileptic drugs.

2.3.1.4 Data extraction

All analysed articles were read carefully and the following types of data were extracted:

- Year of publication
- Study region
- Study period
- Age of children
- Number of children receiving AEDs
- Route of administration
- Doses of AEDs
- Successful seizure control rate
- Time to seizure control after administration the medications
- Seizure recurrence rate
- Number of children who needed of second dose and/or additional AEDs

2.3.1.5 Quality assessments

The quality of RCTs (for meta-analysis) was assessed for risk of bias. Randomised controlled trials were assessed using the Cochrane risk of bias checklist [58]. For RCTs to be considered as having a low risk of bias, the rating should be $\geqslant$ 4 out of 7 marks. The qualities of prospective observational and retrospective population based studies were assessed using a STROBE checklist [60]. Any study with a minimum score of 50% was considered a good quality study. Two independent assessors (KA and research nurse JA) blinded to each other's scores assessed each paper, and a further paediatric clinical pharmacologist (Dr Sammons) independently resolved any disputes between the independent blinded reviewers.

2.3.1.6 Statistical analysis

A descriptive analysis for the number and age of children receiving each medication, the number of children who successfully controlled their seizure, time to seizure control after antiepileptic administration, the seizure recurrence rate and the need for a second dose and/or additional antiepileptic drugs to terminate the convulsion was conducted using SPSS version 12 statistical software. This measured the median, ranges and Interquartile range (IQR). The meta-analysis was performed using RevMan software version 5.3 and forest plots used to compare the effectiveness data between the AEDs. The relative ratio (RR) of effectiveness was calculated and 95% CI was determined. The heterogeneity (I^2) was assessed between studies by using Chi-squared (X^2) test when p-value were less than 0.05[58]. A random effect model was used for pooled data if heterogeneity (I^2) exists ($\geq$ 50%). However, a fixed effect model was used for pooled data if heterogeneity (I^2) did not exist (< 50%). The differences between treatments was considered significant at $p<0.05$.

2.3.2 The toxicity of AEDs for convulsive status epilepticus (CSE) (chapter 5)

2.3.2.1 Databases and search terms

We used the same databases and search terms described previously for the effectiveness systematic review (section 2.3.1.1, table 2.1.)

2.3.2.2 Inclusion and Exclusion criteria

The inclusion criteria were the same as for effectiveness of AEDs for CSE. However, case reports and retrospective population based studies were also included to provide a complete picture of all AEs documented in the literature.

The exclusion criteria were reviews, comments, letters, correspondence and short surveys, adult studies (aged over 18 years) and studies where the number of children or the data for children were not described separately.

2.3.2.3 Outcome measures

- The incidence of adverse effects.
- The incidence of admission to the ICU.
- Death due to the adverse effects.

2.3.2.4 Data extractions

All analysed articles were read carefully and the following types of data were extracted:

- Year of publication
- Study region
- Study period
- Age of children

- Number of children receiving AEDs
- Route of administration
- AEDs doses
- Number of children experiencing adverse events
- Adverse events classification (Adverse events were classified according to the recommendation of the National Cancer Institute in the US (NCI) [61]
- ICU admissions and death cases related to adverse effects

2.3.2.5 Quality assessments

We used the same quality assessments tools for RCTs, prospective observational and retrospective population based studies described in the previous chapter (section 2.3.2.5)

2.3.2.6 Statistical analysis

A descriptive analysis for the number and age of children receiving each medication, the reported numbers of adverse events, ICU admissions and deaths due to adverse events of the AEDs was conducted by using SPSS version 12 statistical software to measure the median, ranges and Interquartile range (IQR). The risk per 100 children was calculated from RCTs and cohort studies (both hospital and population) by dividing the number of children with adverse events by the total number of children receiving diazepam or midazolam or lorazepam or phenobarbital or phenytoin or levetiracetam or sodium valproate or paraldehyde (after combining all AEs from these study types).

For statistical analysis, a meta-analysis was performed using RevMan software version 5.3 and forest plots used to compare the safety data between diazepam, midazolam,

lorazepam, phenobarbital, phenytoin, levetiracetam, sodium valproate and paraldehyde. Relative risk of the safety was calculated and 95% CI were determined. The heterogeneity (I^2) was assessed between studies by using a Chi-squared (X^2) test when p-value were less than 0.05[58]. A random effect model was used for pooled data if heterogeneity (I^2) existed ($\geq$ 50%). However, a fixed effect model was used for pooled data when heterogeneity (I^2) did not exist (< 50%). The differences between treatments was considered significant at $p<0.05$. Also, a Fisher's exact test was used to compare the respiratory depression between the two most common AEDs. Values of $p<0.05$ were considered significant.

CHAPTER 3: SYSTEMATIC REVIEW ONE

3.1 Introduction

Status epilepticus is an emergency condition, with associated mortality and morbidity, and requires prompt and effective treatment. The definition for generalised convulsive tonic-clonic status epilepticus is seizures lasting for 30 minutes or more associated with loss of consciousness [62, 63]. However, effective management of acute tonic-clonic seizures should be given to all patients whose seizures have lasted ≥ 5 minutes and certainly those who attend emergency department, regardless of the duration of convulsion, to prevent progression to refractory or super refractory status epilepticus [59].

Benzodiazepines such as midazolam, lorazepam and diazepam are the first-line treatment for children with acute tonic-clonic seizures [38]. When benzodiazepines fail to stop convulsions, after a second dose, an alternative anticonvulsant should be given such as rectal paraldehyde, intravenous or intraosseous phenytoin, or intravenous or intraosseous phenobarbital. Other agents have also been explored; an open-label study showed that sodium valproate was more effective than phenytoin and phenobarbital for second-line treatment [64]. In 2012, an observational study showed that levetiracetam seemed to be effective and safe in the treatment of CSE [51].

The primary aim of this review was to evaluate the effectiveness of the following antiepileptic drugs: benzodiazepines, paraldehyde, phenobarbital, phenytoin, sodium

valproate, and levetiracetam, irrespective of the administration routes, for the treatment of acute tonic-clonic seizures including convulsive status epilepticus in children.

3.2 Methods

The methodology adopted in this review was described in chapter 2.

3.3 Results

1,851 articles were evaluated based on the specified inclusion and exclusion criteria (Figure 3.1 and Table 3.1). Twenty studies were identified and analysed. In addition, 8 studies identified by the search were published in Turkish and Japanese, it was not possible to translate them for further assessment for inclusion. (Figure 3.1 and Table 3.1).

Figure 3. 1: Flow chart for the systematic review

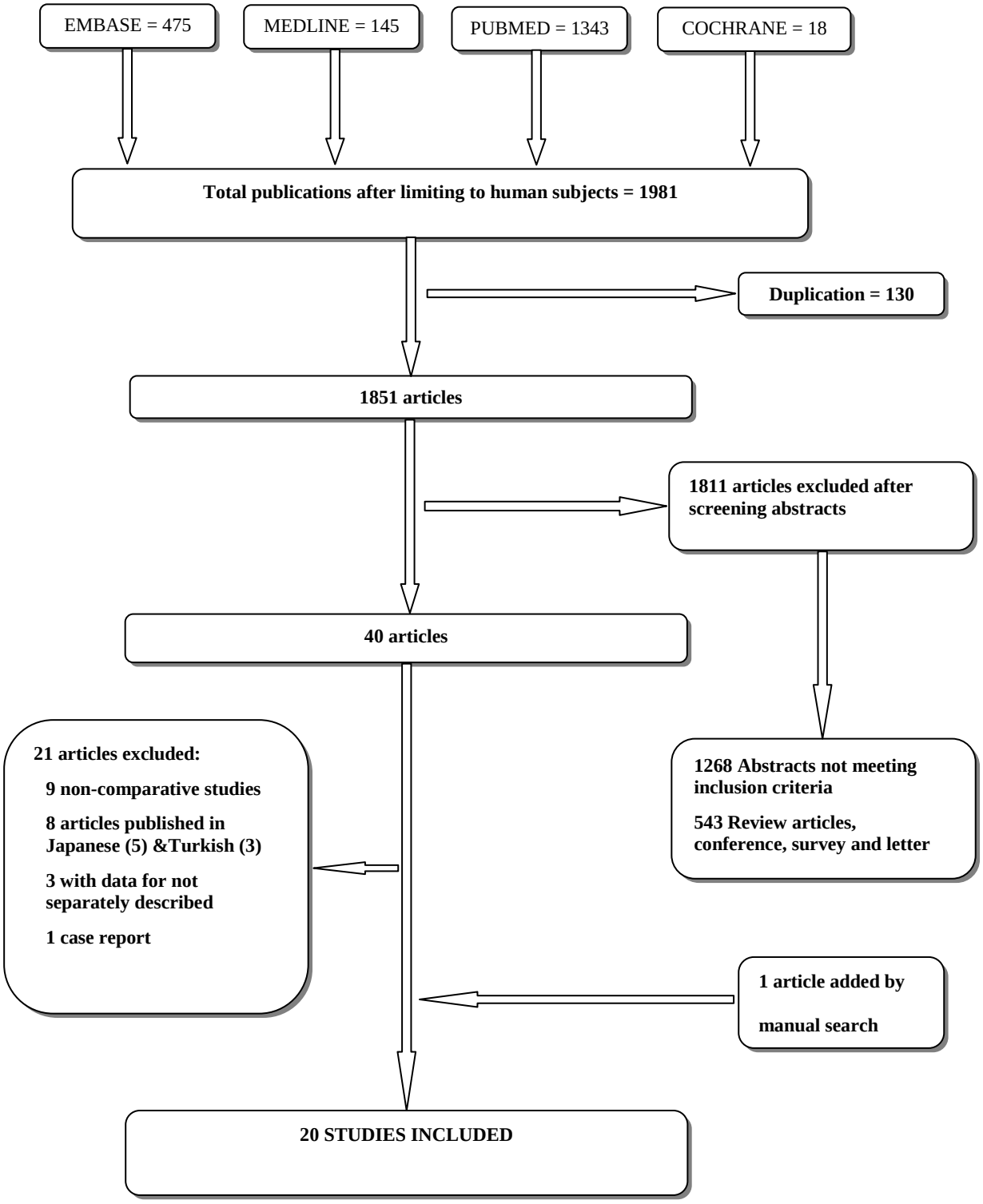


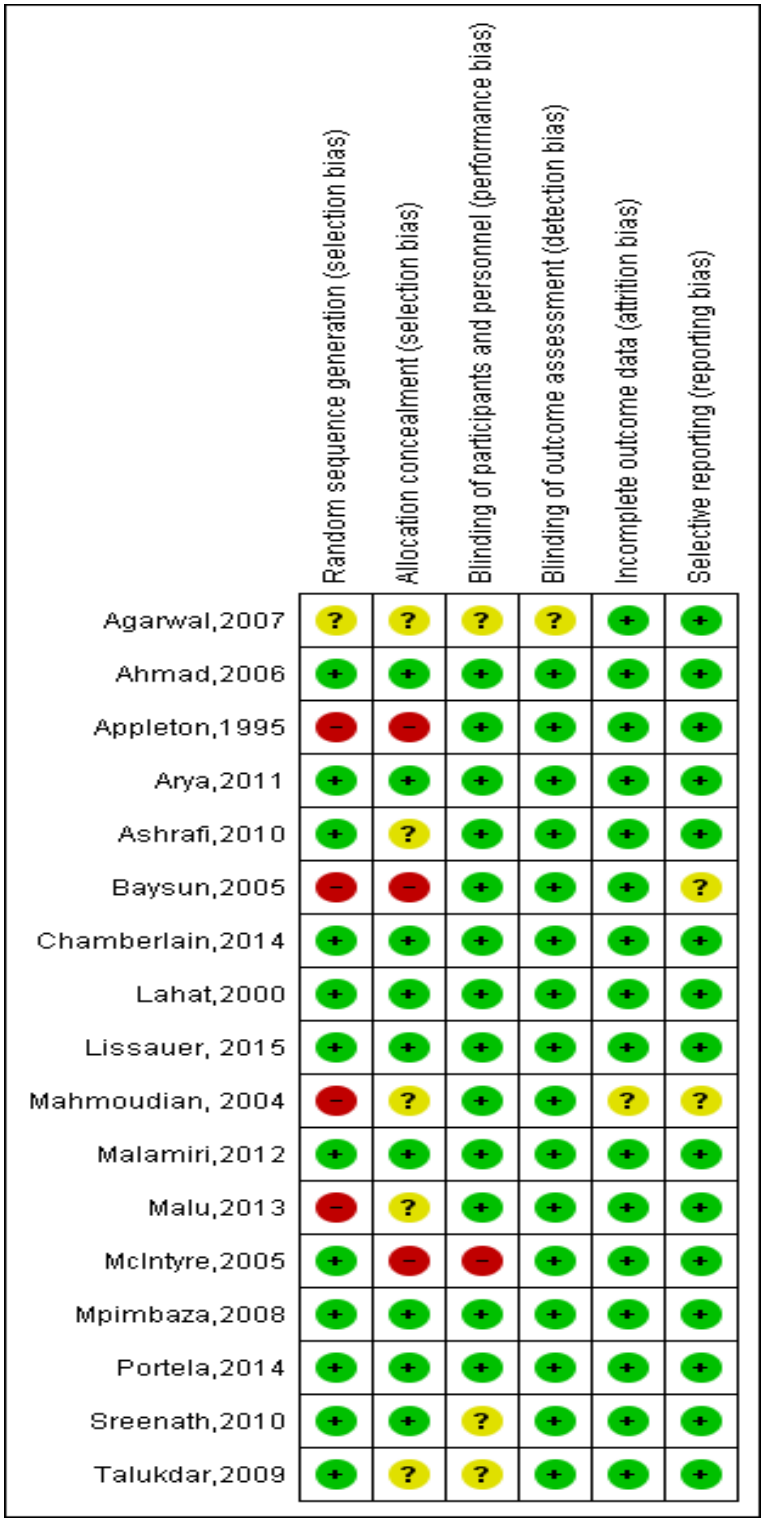
Table 3. 1: Reasons for exclusion from the systematic review

Reason	Total
Irrelevant article	1268
Review, conference, survey	543
Non-comparative studies	9
Studies in Turkish and Japanese	8
Studies reporting the efficacy without mentioning the number of children, or the data for children not described separately.	3
Case report	1
Total	**1832**

3.3.1. Quality assessment

The 20 studies that remained after screening were assessed; 17 RCTs with the Cochrane risk of bias tool [58] and three observational studies (comparative non-randomised studies) with the STROBE tool [60]. Eight RCTs were rated low-risk for all criteria [65-72]. The method of randomisation was inadequately described in 4 studies [73-76], and was unclear in one study [77]. In 3 RCTs, the risk of bias in the allocation concealment was high [73, 76, 78]. One RCT was rated high-risk in blinding of participants and personnel [78] (Figure 3.2). None of these RCTs were excluded from the systematic review. None of the observational studies (comparative non-randomised studies) were excluded as all studies were of sufficiently good quality.

Figure 3. 2 Risk of bias summary



3.3.2. The study descriptions

Twenty studies were included; 17 were randomised controlled trials [65-81] and 3 were comparative non-randomised studies [82-84]. These studies involved more than 3,000 children aged from birth to 18 years. Most of the children were treated with lorazepam (1503, 47%) and diazepam (1041, 32%) (Table 3.2).

Table 3. 2: Antiepileptic drugs used in 20 studies

Anti-epileptic drug used	No. of studies (N =20)*	No. of children (N = 3178)*
Lorazepam	8	1503
Diazepam	15	1041
Midazolam	8	416
Diazepam + phenytoin	1	88
Paraldehyde	1	80
Sodium valproate	2	52
Phenobarbital	2	41
Phenytoin	2	26
Phenobarbital + phenytoin	1	7
Other benzodiazepine not specified	1	7

*** Some children and studies accounted more than once.**

3.3.2.1 Randomised controlled studies

17 randomised controlled trials published between 1995 and 2015 were analysed, including 11 open-label studies [66, 69, 71-74, 76-79, 81], 4 single-blind studies [65, 68, 75, 80], and 2 double-blind studies [67, 70]. Of these 17 studies; 15 were 2-armed clinical trials, one was 3 arms [71] and the remaining study had 4 arms [76]. 8 studies compared midazolam and diazepam (Table 3.3).

Table 3. 3: Randomised controlled studies characteristics

Study characteristics	No. of studies (N = 17)	No. of children (N = 3047)
Type of blinding		
Open label	11	1796
Single blinded	4	918
Double blinded	2	333
Antiepileptic drugs compared		
A. Midazolam vs. diazepam	8	914
B. Lorazepam vs. diazepam	3	795
C. Lorazepam vs. paraldehyde	1	160
D. Lorazepam vs. diazepam + phenytoin	1	178
E. Intravenous lorazepam vs. intranasal lorazepam	1	141
F. Intravenous lorazepam vs. intranasal & buccal LZP	1	761
G. Sodium valproate vs. phenytoin	1	38
H. Sodium valproate vs. phenobarbital	1	60

Sixteen of the 17 randomised control trials included were conducted solely in the paediatric population. In the single mixed-population study, the rate of successful seizure control was described separately for the children [77]. The successful seizure-control rate was documented in all 17 RCTs studies. Twelve studies also documented the seizure recurrence rate (Table 3.4).

Table 3. 4 : Outcomes

Study characteristics	No. of studies (N = 17)*
Successful seizure control	17
Time to seizure control	16
Second dose or additional antiepileptic drugs	14
Seizure recurrence rate	12

*** Some studies accounted more than once.**

The definition of acute tonic-clonic seizures including convulsive status epilepticus varied among studies; nine [65, 67, 70-72, 75, 77, 79, 81] used a definition of at least 5 minutes of continuous seizure, while one study [66] used a definition of at least 10 minutes. Seven studies did not specify the definition [68, 69, 73, 74, 76, 78, 80].

The definition of effectiveness of the intervention also varied between studies. The time to seizure control was the sole measure for determining successful treatment in 11 studies; in 8 of these treatment was considered effective if the seizure was controlled within 10 minutes of drug infusion [66, 69-75]. In 2 studies, the criteria was 5 minutes [68, 80], and one study used an 8-minute definition [76]. The other 6 studies used some combination of a time frame along with recurrence rate and incidence of respiratory depression and hypotension. In 3 of these studies, the treatment was considered successful if the seizure was controlled within 30 minutes, without recurrence within 1 hour, and without respiratory depression [65, 78, 79]. In one study, the criteria were described as control of seizure within 20 minutes, no recurrence within 1 hour and no incidence respiratory depression or hypotension [67]. Another study defined effectiveness as seizure control within 20 minutes and no recurrence within 12 hours

[77]. In the remaining study, the criteria were defined as control within 10 minutes and no recurrence within 30 minutes [81].

The measurement of seizure recurrence also varied among studies. In 6 studies, it was measured for one hour [65, 66, 69, 70, 78, 79], in 5 for 24 hours [67, 71, 72, 75, 76] and in one study for 18 hours [81]. The remaining 5 studies did not define recurrence [68, 73, 74, 77, 80].

A. Midazolam versus diazepam

Eight studies compared the effectiveness of midazolam and diazepam. They involved more than 900 children (466 treated with midazolam) aged between birth and 14 years. Five were open-label [66, 73, 74, 78, 79] and 3 were single-blind [65, 68, 80]. The effectiveness of buccal midazolam was compared with rectal diazepam in 4 studies [65, 73, 78, 79] and with intravenous diazepam in one study [80]. Of the remaining 3 studies, 2 compared the effectiveness of intranasal midazolam with intravenous diazepam [66, 74], and the third compared the effectiveness of intramuscular midazolam with intravenous diazepam [68].

A.1. Buccal midazolam versus rectal diazepam

The following 4 studies compared buccal midazolam to rectal diazepam in more than 600 children aged between birth and 15 years. Three were open-label [73, 78, 79] and one was single-blinded [65].

McIntyre et al. (2005) conducted a 3-year, multicentre, randomised, controlled, open-label study in children who attended an emergency department with active convulsions in the UK [78]. The study medications were selected in weekly blocks at 4 hospitals.

Children were excluded if they presented with partial seizures or non-convulsive status epilepticus. A total of 219 episodes in 177 children were evaluated. The treatment was considered successful if the seizures were controlled within 10 minutes of the initial dose, with no recurrence within one hour and no respiratory depression. A local protocol was applied if the seizure lasted more than 10 minutes after the initial dose. Results were reported separately for the initial episode and the total episodes.

Baysun et al. (2005) performed a prospective, single-centre study in Turkey involving 43 children aged between 2 months and 12 years with acute tonic-clonic seizures [73]. Randomisation was achieved by alternating the study medications daily. Treatment was recorded as successful if the seizure terminated within 10 minutes of the initial dose. If seizures were still active after 10 minutes, crossover treatment was applied: diazepam for the midazolam group and midazolam for the diazepam group.

Mpimbaza et al. (2008) assessed buccal midazolam against rectal diazepam in 330 children, aged between 3 months and 12 years, who attended an emergency department with prolonged seizures [65]. This was an 8-month, single-blind, single-centre study in Uganda. Randomisation was performed by an independent staff member who used computer-generated treatment codes and opaque envelopes. Treatment was deemed successful if the seizures stopped within 10 minutes after the initial dose, without recurrence for one hour. If the seizure remained active for more than one hour, intravenous diazepam was given. This study also assessed respiratory depression. Children were excluded if they had received intravenous phenobarbital or intravenous diazepam within 24 hours prior to admission.

Ashrafi et al. (2010) conducted a one-year, open-label, randomised study in 2 paediatric referral hospitals in Iran on 98 children aged less than 12 years who attended the emergency room with acute convulsive seizures lasting for more than 5 minutes [79]. Half the children were selected to receive buccal midazolam via a random number table. The treatment was considered successful if the seizures were controlled within 5 minutes of the initial dose, with no respiratory depression or recurrence of seizure for one hour. If the seizure remained active or recurred within one hour after the initial dose, intravenous diazepam was given.

Overall, the seizure terminated in 231 of 329 children (70%) who received buccal midazolam and in 175 of 319 children (55%) who received rectal diazepam. Seizure termination was higher with buccal midazolam in 3 of the studies (Table 3.5). Diazepam was more effective in one small study in Turkey, however this was not statistically significant ($p = 0.57$) [73]. The pooled risk ratio of the outcomes of these 4 studies showed that the effectiveness of buccal midazolam in seizure termination was superior to that of rectal diazepam (RR: 1.29; 95% CI: 1.15 to 1.44; $p < 0.04$).

Seizure termination occurred 3 to 10 minutes after treatment with buccal midazolam, and 3 to 15 minutes after rectal diazepam.

No children in either group needed additional doses of the same drugs. However, 3 of the studies showed that 88 of 280 children (31%) who received buccal midazolam required additional antiepileptic drugs (AEDs) to terminate their seizures compared to 121 of 270 children (45%) who received rectal diazepam [65, 73, 78]; the difference was significant (RR: 0.7; 95% CI: 0.57 to 0.87; $p = 0.001$).

The seizure recurrence rate was reported in 2 of the studies [65, 78]. Seizures recurred in 17 of 257 children (7%) who received buccal midazolam and in 32 of 250 children (13%) who received rectal diazepam; the difference was significant (RR: 0.51; 95% CI: 0.29 to 0.9; p = 0.02) (Table 3.5).

In summary, buccal midazolam is superior to rectal diazepam for the treatment of acute seizures in children. It is more effective and associated with a lower recurrence rate of seizures (Table 3.5 and Figure 3.3).

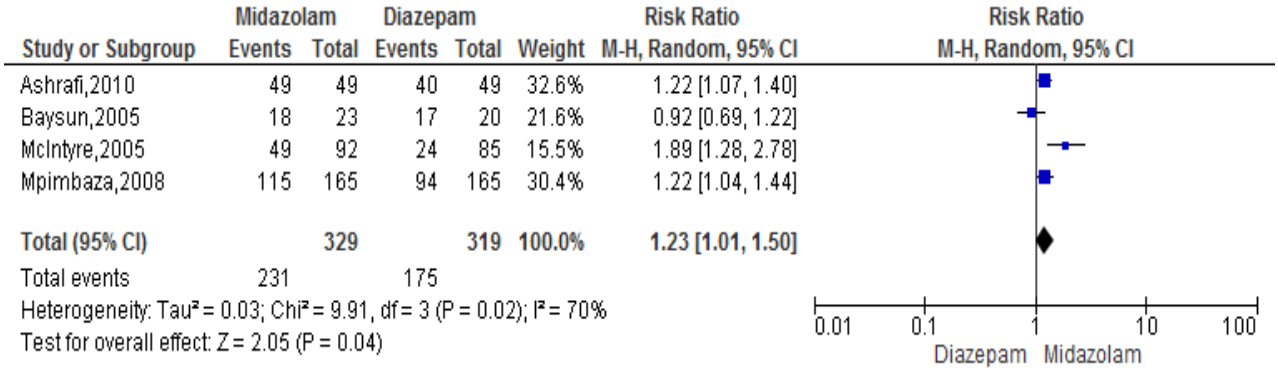
Table 3. 5: Buccal midazolam versus rectal diazepam

Reference, country	**Study design**	**Age (Y)**	**No. of children**	**AEDs**	**Dose (mg/kg)**	**Seizure control (No. of children) RR (95% CI) *P-value***		**Time to seizure control (No. of children)**		**Additional AEDs (No. of children) RR (95% CI) *P-value***		**Recurrence rate* (No. of children) RR (95% CI) *P-value***	
						MDZ	**DZP**	**MDZ**	**DZP**	**MDZ**	**DZP**	**MDZ**	**DZP**
McIntyre et al., 2005, UK [78]	Open label RCT	0.7-15	92 85	MDZ DZP	0.5 BUC 0.5 PR	49 1.89 (1.3-2.8) **p = 0.001**	24	Median 8 min	Median 15 min	33 0.65 (0.46-0.91) **p = 0.01**	47	7 0.54 (0.2-1.3) p = 0.17	12
Baysun et al., 2005, Turkey [73]	Open label RCT	0.2-12	23 20	MDZ DZP	0.25 BUC 0.3-0.5 PR	18 0.92 (0.7-1.2) p = 0.57	17	3 min (12) 3-5 min (3) 5-10 min (3)	3min (10) 3-5 min (4) 5-10 min (3)	5 0.45 (0.4-5.3) p = 0.58	3	***Data was not available***	
Mpimbaza et al. 2008, Uganda [65]	Single blind RCT	0.3- 12	165 165	MDZ DZP	0.5 BUC 0.5 PR	115 1.22 (1-1.4) **p = 0.02**	94	Median 4.7 min min	Median 4.3	50 0.7 (0.53-0.9) **p = 0.02**	71	10 0.5 (0.24-1) p = 0.06	20
Ashrafi et al., 2010, Iran [79]	Open label RCT	0-12	49 49	MDZ DZP	0.3-0.5 BUC 0.5 PR	49 1.22 (1.1-1.4) **p = 0.004**	40	Median 4 min	Median 5 min	***Data was not available***		0	0
Total	4	0-15	329 319	MDZ DZP	0.25-0.5 BUC 0.3-0.5 PR	231 1.23 (1.01 - 1.5) **p < *0.04***	175	3-10 min	3-15 min	88 0.7 (0.5-0.8) **p = *0.001***	121	17 0.51(0.29-0.9) **p = 0.02**	32

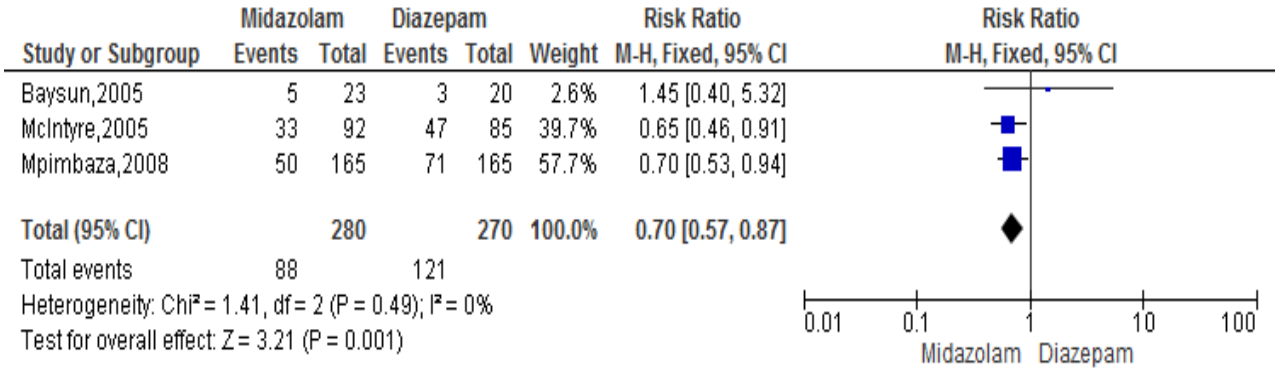
MDZ: Midazolam, DZP: Diazepam
*** Within one hour**
**** Median**

Figure 3. 3: The effectiveness of buccal midazolam versus rectal diazepam

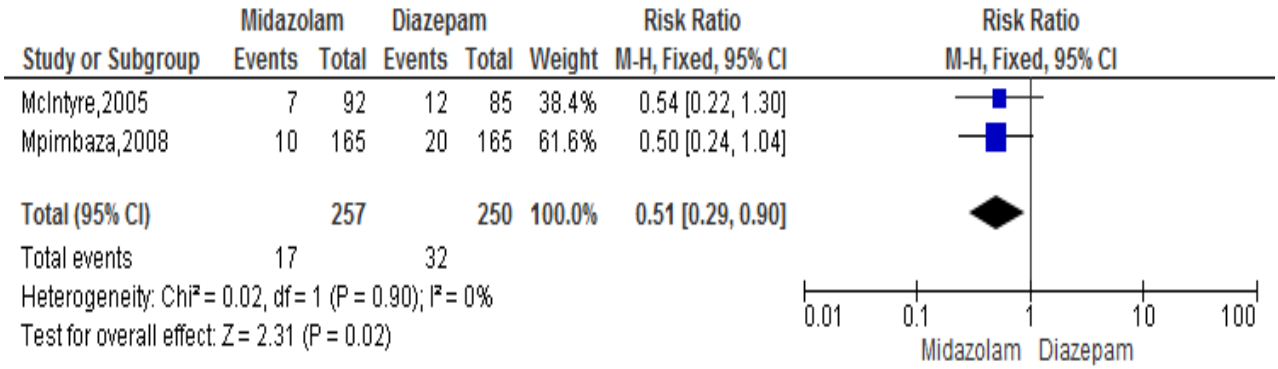
1. **Successful seizure control**



2. **Additional AEDs**



3. **Seizure recurrence**



A.2. Intranasal midazolam versus intravenous diazepam

There were 2 single-centre open-label studies that involved 114 children, aged between 0.2 to 15 years [66, 74].

Lahat et al. (2000) performed a 12-month, single-centre, open-label, randomised study in Israel to compare intranasal midazolam with intravenous diazepam for treating febrile seizures [66]. It involved 44 children aged between 6 months and 5 years. Twenty-one children with 26 episodes were given intranasal midazolam, while 23 children with 26 episodes were given intravenous diazepam. Patients were excluded if they had received AEDs or had an intravenous line established by paramedics prior to being admitted to the emergency room. Randomisation was performed by a hospital pharmacist (who was not involved in the study) via a number table and opaque, sealed envelopes. Treatment was considered effective if the seizures were controlled within 5 minutes, or successful but delayed if the seizures stopped between 5 and 10 minutes. For treatment failure (continued seizure more than 10 minutes after study medication was administered) the local treatment protocol was used.

Four years later, Mahmoudian et al. (2004) assessed intranasal midazolam against intravenous diazepam in 70 children aged between 2 months and 15 years, who attended an emergency department with convulsive status epilepticus (CSE) [74]. This was a 14-month, single-centre, open-label, randomised study conducted in Iran. Patients were excluded if they had received prior emergency AEDs. Randomisation was allocated based on an odd-and-even number table (children with odd numbers received intravenous diazepam, and children with even numbers received intranasal lorazepam).

Treatment was considered successful if the seizure stopped within 10 minutes of initial study medication. For treatment failure (continued seizure after 10 minutes), intravenous diazepam was prescribed for the midazolam group and phenobarbital for the diazepam group.

The seizure ended in 58 children (95%) who received the intranasal midazolam and in 59 children (97%) who received intravenous diazepam; the difference was not significant (RR: 0.98; 95% CI: 0.91 to 1.06; p = 0.67). The rate of seizure termination was the same in the Iranian study [74]. There was a non-statistically significant difference in seizure termination in the other study [66], with diazepam having the higher termination rate (Table 3.6).

Seizure termination occurred 2.5 to 3 minutes after treatment with intranasal midazolam and 2.5 to 2.6 minutes after intravenous diazepam.

The administration of additional antiepileptic drugs to terminate the seizures was reported only in the Lahat study. Three of 21 children (14%) who received intranasal midazolam needed additional antiepileptic drugs compared to 2 of 23 children (9%) who received intravenous diazepam; the difference was not significant (RR: 1.64; 95% CI: 0.3 to 8.9; p = 0.56)[66].

Neither study in this section recorded whether additional doses were required.

The seizure recurrence rate was also only reported in the Lahat study; it was 5% (one child) for intranasal midazolam and 4% (one child) for intravenous diazepam [66]; the difference was not significant (RR; 1.1; 95% CI: 0.07 to 16.4; p = 0.95) (Table 4.6).

In conclusion, from these two small studies we can conclude that intranasal midazolam and intravenous diazepam were equally effective (Table 3.6 and Figure 3.4).

Table 3. 6: Intranasal midazolam vs. intravenous diazepam

Reference, country	**Study design**	**Age (Y)**	**No. of children**	**AEDs**	**Dose (mg/kg)**	**Seizure control (No. of children)** **RR (95% CI)** ***P-value*** **MDZ** **DZP**	**Time to seizure control** **RR (95% CI)** ***P-value*** **MDZ** **DZP**	**Additional AEDs (No. of children)** **RR (95% CI)** ***P-value*** **MDZ** **DZP**	**Recurrence rate*** **(No. of children)** **RR (95% CI)** ***P-value*** **MDZ** **DZP**
Lahat et al., 2000, Israel [66]	Open label RCT	0.6-12	21 (26 episodes) 23 (26 episodes)	MDZ DZP	0.2 (IN) 0.3 (IV)	23 24 0.96 (0.8-1.1) *p = 0.64*	Mean 3.1 min Mean 2.5 min	3 2 1.64 (0.3-8.8) *p = 0.56*	1 1 1.1 (0.07-16.4) *p = 0.95*
Mahmoudian and Zadeh, Mohammadi, 2004, Iran [74]	Open label RCT	0.2-15	35 35	MDZ DZP	0.2 (IN) 0.2 (IV)	35 35 1 (0.9-1) *p = 1*	Mean 2.5 min Mean 2.6 min	***Data was not available***	***Data was not available***
Total	2	0.2-15	56 (61 episodes) 58 (61 episodes)	MDZ DZP	0.2 (IN) 0.2-0.3 (IV)	58 59 0.98 (0.91-1) *p = 0.67*	2.5-3.1 min 2.5-2.6 min	3 2 1.64 (0.3-8.8) *p = 0.56*	1 1 1.1 (0.07-16.4) *p = 0.95*

MDZ: Midazolam, DZP: Diazepam

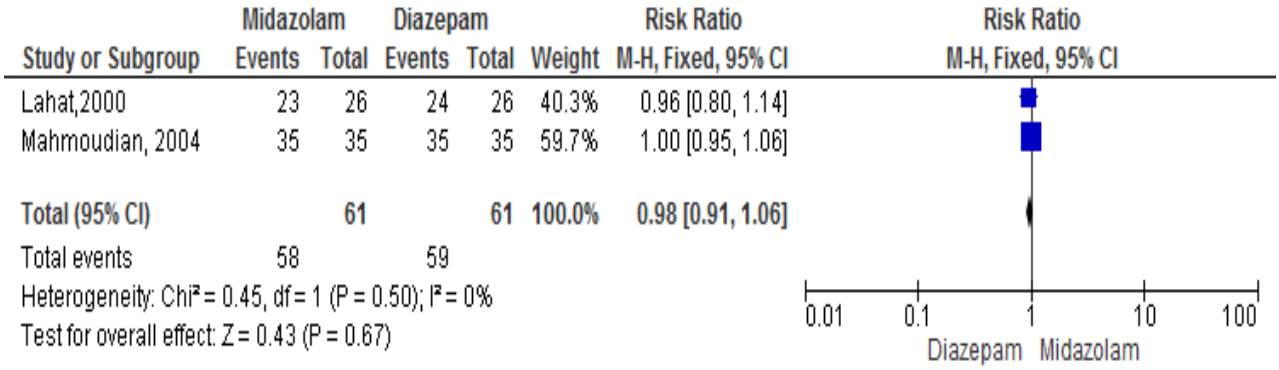
Data for whether additional dose(s) were administered was not reported

*** The seizure rate was measured within one hour.**

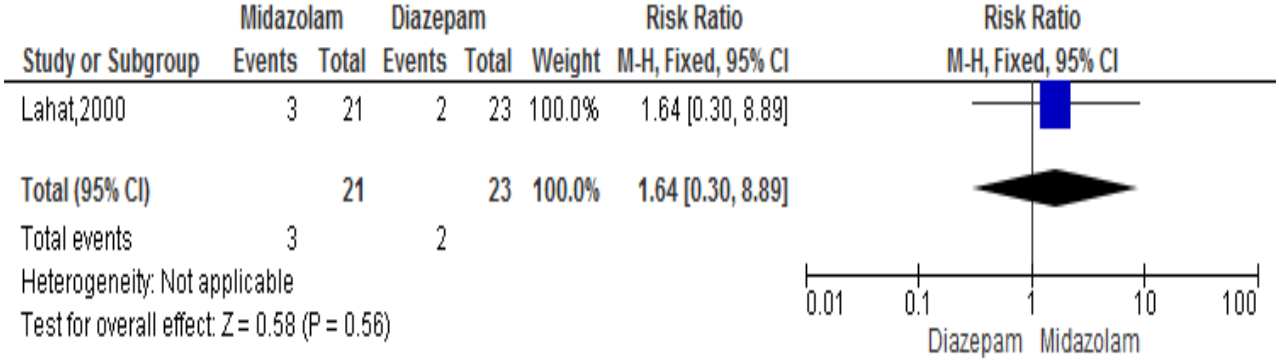
**** Median.**

Figure 3.4: The effectiveness of intranasal midazolam vs. intravenous diazepam

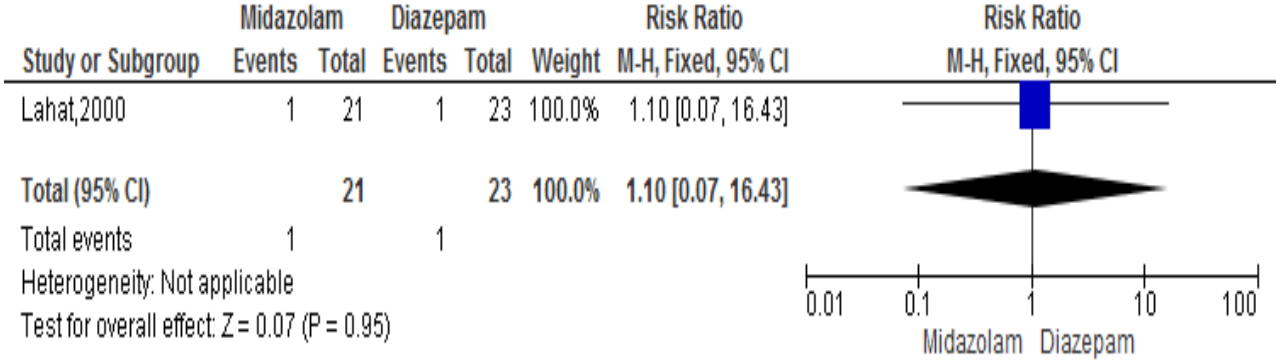
1. **Successful seizure control**



2. **Additional AEDs**



3. **Seizure recurrence**



A.3. Buccal midazolam versus intravenous diazepam

One study compared the efficacy of buccal midazolam against intravenous diazepam in children who attended the emergency room with convulsions, irrespective of duration. This randomised, single-blind, single-centre study in India was conducted by Talukdar et al. (2009) and involved 120 children aged less than 12 years of which 60 were treated with buccal midazolam [80]. Successful seizure remediation was defined as the ending of seizures within 5 minutes of the initial dose of study medications. When the seizures lasted longer than that, the local protocol was applied. Children were excluded if they had the following seizure types: myoclonic, atonic, or absence. Selection of the study medication was performed with a random number table. Cardiorespiratory compromise was evaluated at 5 and 10 minutes after administration of the study medications. This study documented the treatment success and time to seizure control rather than seizure recurrence rate.

The seizure stopped in 51 of 60 children (85%) who received buccal midazolam, and in 56 of 60 children (90%) who received intravenous diazepam; the difference was not significant (RR: 0.9; 95% CI: 0.8 to 1.03; p = 0.15) (Table 3.7).

Nor was there a significant difference in the time to seizure termination, with a mean of 1.7 minutes for buccal midazolam and of 1.1 minutes for intravenous diazepam.

Whether additional dose(s) were administered was not recorded. However, 9 children (15%) in the buccal midazolam group needed additional AEDs to terminate their seizures compared to 2 children (3%) in the intravenous diazepam group; the difference

was of borderline statistical significance (RR: 4.5; 95% CI: 1.01 to 19.96; p = 0.05) (Table 3.7).

The recurrence rates were not reported.

In conclusion, although the number of children whose seizure ended with buccal midazolam was lower than the intravenous diazepam group, the difference was not significant (Table 3.7 and appendix A). There was, however, a borderline statistical difference in the use of additional AEDs, favouring intravenous diazepam.

Table 3. 7: Buccal midazolam versus intravenous diazepam in one study

Reference, country	Study design	Age (Y)	No. of children	AEDs	Dose (mg/kg)	Seizure control (No. of children) RR (95% CI) *P-value* MDZ DZP	Time to seizure control MDZ DZP	Additional AEDs (No. of children) RR (95% CI) *P-value* MDZ DZP
Talukdar et al, 2009, India, [80]	Singl blind RCT	< 12	60 60	MDZ DZP	0.2 BUC 0.3 IV	51 56 0.91 (0.8-1.03) *p = 0.15*	Mean 1.7 min Mean 1.1 min	9 2 4.5 (1.01-19.96) *p = 0.05*

MDZ: Midazolam, DZP: Diazepam

Data for whether additional dose(s) were administered and recurrence rate were not reported

A.4. Intramuscular midazolam versus intravenous diazepam

One study in Brazil compared intramuscular (IM) midazolam and intravenous (IV) diazepam in 32 children who attended the emergency department with seizures, irrespective of type and duration [68]. Children were excluded if they had (IV) access prior to hospital admission, or a history of hepatic, renal or coagulopathic disorders. Children aged between 2 months and 14 years were randomly assigned (IM) midazolam or (IV) diazepam. Randomisation was performed by preparing blocks of 10 medications, 5 of which were (IM) midazolam and 5 (IV) diazepam. The study was blinded to participants only. Treatment was considered to have failed if the seizures did not terminate within 5 minutes, or if patients required a second dose of study medication or additional AEDs. This study documented the treatment success and failure rates, but not the recurrence rate.

The number of children who stopped seizing was the same in both groups (14 children, 88%) (RR: 1; 95% CI: 0.77 to 1.3; p = 1).

Seizure termination occurred within 4 minutes after treatment with intramuscular midazolam, and within 3 minutes after intravenous diazepam (Table 3.8).

One child (6%) in each group required additional dose(s) of the study medication to control their seizures (RR: 1; 95% CI: 0.07 to 14.6; p=1).

Two of 16 children (13%) with intramuscular midazolam required an additional AED to end their presenting seizure compared to one child (6%) who received intravenous diazepam (Table 4.8); the difference was not significant (RR: 2; 95% CI: 0.2 to 19.9; p = 0.5). The recurrence rate was not reported.

To summarise, this study showed equal effectiveness of intramuscular midazolam compared to intravenous diazepam (Table 3.8 and appendix A).

Table 3. 8: Intramuscular midazolam versus intravenous diazepam

Reference, country	Study design	Age (Y)	No. of children	AEDs	Dose (mg/kg)	Seizure control (No. of children) RR (95% CI) *P-value* MDZ DZP	Time to seizure control MDZ DZP	Second dose(s) (No. of children) RR (95% CI) *P-value* MDZ DZP	Additional AEDs (No. of children) RR (95% CI) *P-value* MDZ DZP
Portela et al, 2014, Brazial [68]	Singl blind RCT	0.2-14	16 16	MDZ DZP	0.2 IM (Max 15 mg) 0.3 at 5mg/min IV (Max 10 mg)	14 14 1 (0.77-1.3) *p = 1*	4 min 3 min	1 1 1 (0.07-14.64) *p = 1*	9 2 2 (0.2-19.91) *p = 0.55*

MDZ: Midazolam, DZP: Diazepam

Data for recurrence rate was not reported

A.5. Summary of midazolam versus diazepam

Four studies compared the effectiveness of buccal midazolam and rectal diazepam for treating acute tonic clonic seizure in children. Of these, three studies involving 605 children (306 treated with buccal midazolam and 299 treated with rectal diazepam) showed that the effectiveness of buccal midazolam in seizure termination was superior to that of rectal diazepam (RR:1.89 & p = 0.001[78], RR: 1.22 & p = 0.02 [65] and RR: 1.22 & p = 0.004 [79], respectively) (Table 4.5). These 3 studies provided the majority of the patients and were responsible for most of the significant differences in this systematic review. The fourth study showed no significant difference (p = 0.57)[73]. The overall pooled risk of ratio showed that the effectiveness of buccal midazolam in seizure termination was superior to that of rectal diazepam (RR: 1.29 & p < 0.04).

In contrast, there were no significant differences in seizure termination between midazolam (intranasal, buccal or intramuscular) and diazepam (intravenous) (Table 3.6, 3.7 and 3.8).

Additional doses were only documented in one study [68] involving 16 children; there were no differences among the groups.

The use of additional antiepileptic drugs (AEDs) to terminate seizures was documented in 6 studies [65, 66, 68, 73, 78, 80]. Two studies showed that the requirement of additional antiepileptic drugs was lower with buccal midazolam (median = 33%) than with rectal diazepam (median = 49%).

The seizure recurrence rate was documented in 3 studies [65, 66, 78]. The 2 studies comparing buccal midazolam with rectal diazepam reported a lower likelihood of seizure recurrence with buccal midazolam

In conclusion, buccal midazolam was more effective than rectal diazepam. Studies involving other routes of administration of the 2 drugs showed no difference between the 2 drugs.

B. Lorazepam versus diazepam

There were 3 studies that compared the effectiveness of lorazepam and diazepam, involving more than 700 children; one was open label [76], one a single-blinded study and one was double-blinded [70, 75].

B.1. Intravenous lorazepam vs. intravenous diazepam

Two studies recruited a total of 334 children; one was open-label, while the second was double-blinded.

Appleton et al. (1995) conducted a 12-month, single-centre, randomised, open-label study comparing lorazepam vs. diazepam in the UK. Children received one of the two drugs either intravenously or rectally [76]. The study recruited 102 children aged between one month and 16 years who attended the emergency department with an acute tonic-clonic convulsion. Sixteen children received the wrong medication and were therefore excluded. Sixty-one children received intravenous treatment (27 lorazepam and 34 diazepam). Randomisation was achieved by alternating the study medication daily. Treatment was considered effective if the presenting seizures terminated within 8 minutes of the initial dose. If the seizures were still active after 8 minutes, a second dose

of the study medication was given by the same route. The local protocol was applied if the second dose was not effective.

Efficacy and safety was assessed by the following measures: the time from drug administration to end of seizure, the incidence of respiratory depression, and the numbers of doses, children that required additional AEDs, and children with recurrent seizures in the first 24 hours.

In the second study, Chamberlain et al. (2014) assessed the efficacy of intravenous lorazepam against intravenous diazepam in 273 children, aged from 3 months through 17 years. One hundred and forty patients were given diazepam and 133 lorazepam [70]. This was a 4-year, double-blind, randomised clinical trial conducted in the USA at 11 paediatric hospitals. Status epilepticus was defined as 3 or more seizures within the hour prior to emergency admission and still ongoing at the emergency room, or 2 or more seizures with loss of consciousness and still ongoing at the emergency room, or single current seizures lasting at least 5 minutes. Patients were excluded from the study if they were pregnant, attended with cardiovascular complications including hypotension or cardiac dysrhythmia, required surgical interventions or general anaesthesia, were contraindicated for benzodiazepines, had used benzodiazepines within 7 days prior to hospital admission, or had received prehospital AEDs.

Randomisation was allocated within 3 age groups: 3 months - 2 years, 3 - 12 years, and 13 - 17 years. A unique dispensing system distributed the medications in opaque syringes with cards attached that described how to use the treatment at the patient's bedside.

If the seizures were controlled within 10 minutes of the initial dose, without recurrence for 30 minutes, the treatment was deemed successful. If the seizures remained active after 12 minutes from the benzodiazepine dose, phenytoin IV (15-20 mg/kg) or phenobarbital were used. If the seizure continued for more than 20 minutes from initial dose, the study became open-label, and AEDs were given according to the practitioner's decision.

The secondary outcomes included the number of children who required a second dose or additional AEDs in both treatment groups, and the number of children whose seizures were controlled for 1 and 4 hours after administration of the study medications. The primary safety outcome was respiratory depression within 10 minutes of the initial dose of the study medications; the secondary outcomes were incidences of aspiration pneumonia, sedation, or agitation, and time to recover consciousness.

In the two studies, the seizure terminated in 116 of 160 children (73%) who received intravenous lorazepam and in 123 of 174 children (71%) who received intravenous diazepam. There was no difference between intravenous lorazepam and intravenous diazepam in achieving seizure termination (RR: 1.02, 95% CI: 0.89 to 1.17; p = 0.73) (Table 3.9).

Seizure termination occurred 2 seconds to 2 minutes after treatment with lorazepam, and 2 seconds to 2.5 minutes after diazepam.

Fifty-two of the 160 children (33%) given intravenous lorazepam required additional doses to terminate their seizure compared to 54 of the 174 children (31%) on intravenous diazepam. One study favoured lorazepam and the other diazepam. The

pooled risk ratio showed that the requirement of additional doses was similar (RR: 1.05; 95% CI: 0.76 to 1.44; p = 0.77) (Table 3.9).

Both studies showed that the requirement for additional antiepileptic drugs was slightly lower with intravenous lorazepam (22 children, 14%) than with intravenous diazepam (26 children, 15%); the difference was not significant (RR: 0.91, 95% CI: 0.54 to 1.55; p = 0.73) (Table 3.9).

The seizure recurrence rates were lower for intravenous lorazepam (16 children, 10%) than for intravenous diazepam (23 children, 13%); however, the differences were not significant (RR: 0.79, 95% CI: 0.44 to 1.43; p = 0.44) (Table 3.9).

To summarise, the two studies showed that intravenous lorazepam and intravenous diazepam were equally effective for treating acute tonic clonic seizures (Table 3.9 and Figure 3.5).

A prospective comparative non-randomised study conducted by Wassmer et al. (2002) compared intravenous lorazepam and intravenous diazepam in the UK and also reported a similar result [84]. This study involved 48 children aged 5 months to 11 years with convulsive status epilepticus. A definition of convulsive status epilepticus was not given. Thirty-one children received intravenous lorazepam and 17 intravenous diazepam. The seizure was terminated in 20 children (65%) who received intravenous lorazepam and in 11 (65%) receiving intravenous diazepam within 15 minutes.

Table 3. 9: Intravenous Lorazepam vs. Intravenous diazepam

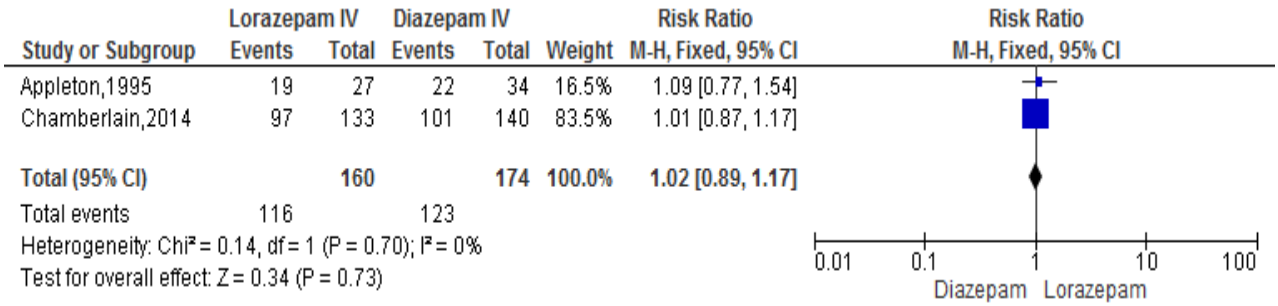
Reference, country	**Study design**	**Age (Y)**	**No. of children**	**AEDs**	**Dose (mg/kg)**	**Seizure control (No. of children)** RR (95% CI) *P-value* **LZP** **DZP**	**Time to seizure control** **LZP** **DZP**	**Additional dose(s) (No. of children)** RR (95% CI) *P-value* **LZP** **DZP**	**Additional AEDs (No. of children)** RR (95% CI) *P-value* **LZP** **DZP**	**Recurrence rate*** **(No. of children)** RR (95% CI) *P-value* **LZP** **DZP**
Appleton et al., 1995, UK [76]	Open label Quasi-RCTs	0.1-16	27 34	LZP DZP	0.05-0.1 (IV) 0.3-0.4 (IV)	19 22 1.09 (0.77-1.54) *p = 0.64*	20-60 sec. 20-60 sec.	8 12 0.84 (0.4-1.76) *p = 0.64*	1 5 0.25 (0.03-2.03) *p = 0.2*	6 12 0.63 (0.27-1.46) *p = 0.28*
Chamberlain et al.., 2014, USA [70]	Double blind RCT	0.3- < 18	133 140	LZP DZP	0.1 (IV), Max. 4 mg 0.2 (IV), Max. 8 mg	97 101 1.01 (0.87-1.17) *p = 0.88*	2 min 2.5 min	44 42 1.1 (0.78-1.56) *p = 0.58*	21 21 1.05 (0.6-1.84) *p = 0.86*	10 11 0.96 (0.42-2.18) *p = 0.92*
Total	2	0.3- < 18	160 174	LZP DZP	0.05-0.1 (IV) Max 4 mg 0.2-0.4 (IV) Max. 8 mg	116 123 1.02 (0.89-1.17) *p = 0.73*	0.2 - 2 min 0.2 – 2.5 min	52 54 1.05 (0.76-1.44) *p = 0.77*	22 26 0.91 (0.54 – 1.55) *p = 0.73*	16 23 0.79 (0.44-1.43) *p = 0.44*

LZP: Lorazepam, DZP: Diazepam

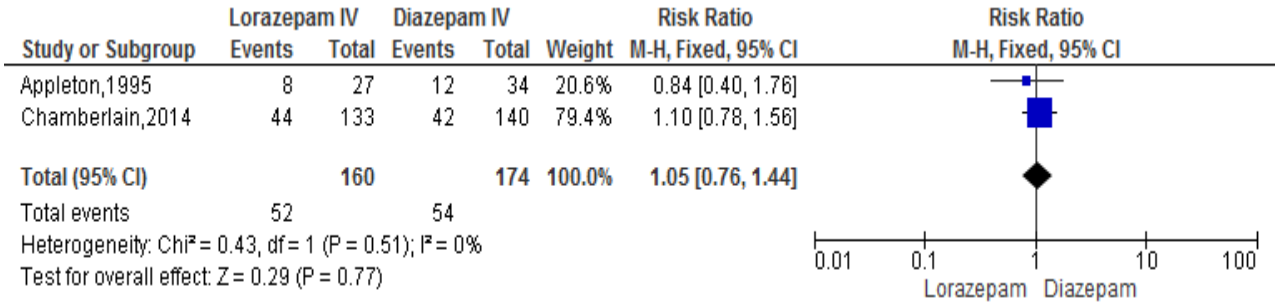
*** The first study documented the rate within 24 hours while the second study within one hr.**

Figure 3. 5: The effectiveness of intravenous lorazepam vs. intravenous diazepam

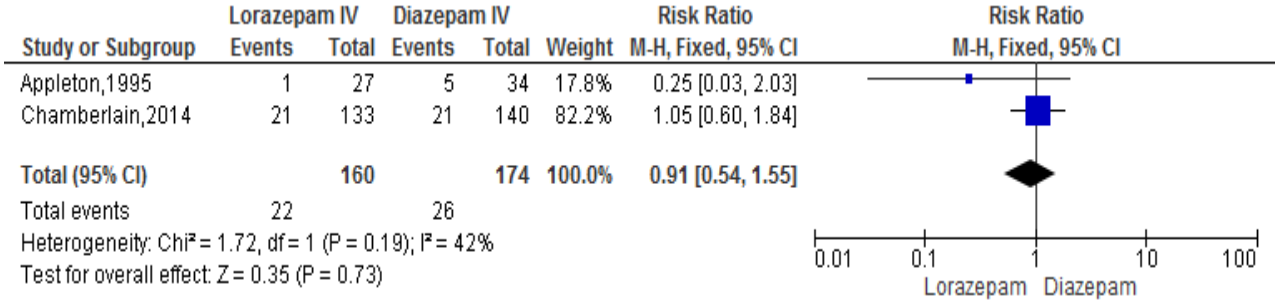
1. **Successful seizure control**



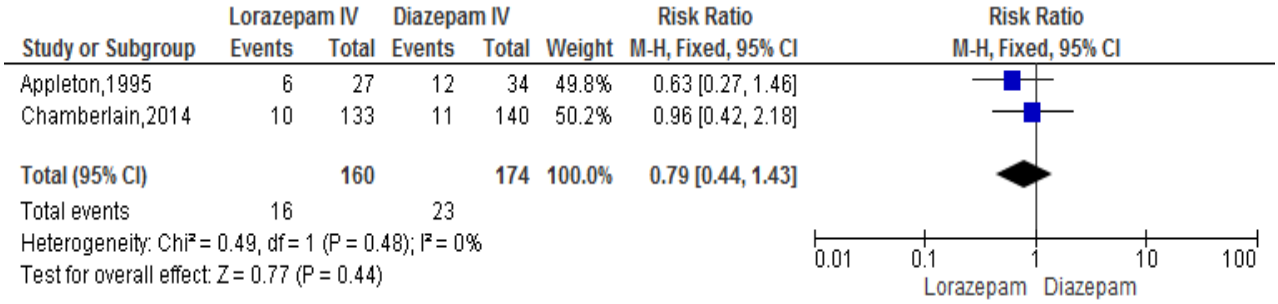
2. **Additional dose(s)**



3. **Additional AEDs**



4. **Seizure recurrence**



B.2.Rectal lorazepam vs. rectal diazepam

The study by Appleton et al. (1995) described above in the previous section (section I) also compared rectal lorazepam and rectal diazepam in 25 children [76]. Six children received lorazepam and 19 received diazepam.

Seizure termination occurred in all 6 children who received rectal lorazepam, compared to only 6 of 19 (32%) children who received rectal diazepam (Table 4.10). Lorazepam was more effective than diazepam in achieving seizure termination (RR: 2.8; 95% CI: 1.5 to 5.5; p = 0.002) (Table 3.10)

Thirteen children (68%) who received rectal diazepam required additional dose(s) (RR: 0.1; 95% CI: 0.01-1.56, p = 0.1) and 12 children (63%) in the same group required different AEDs (RR: 0.2; 95% CI: 0.01-1.69, p = 0.1) to terminate their seizures (Table 3.10).

In the lorazepam group, none of the six children in the study experienced a further seizure within 24 hours of drug administration, compared to 7 children in the diazepam group; the difference was not significant (RR: 0.2; 95% CI: 0.01 to 2.9; p = 0.2) (Table 3.10)

In summary, in this small study rectal lorazepam was seen to be more effective than rectal diazepam for initial seizure control and was associated with no recurrent seizures within 24 hrs (Table 3.10 and appendix A).

Table 3. 10: Lorazepam (PR) versus diazepam (PR) in one study

Reference, country	Study design	Age (Y)	No. of children	AEDs	Dose (mg/kg)	Seizure control (No. of children) RR (95% CI) *P-value*		Time to seizure control		Additional dose(s) (No. of children) RR (95% CI) *P-value*		Additional AEDs (No. of children) RR (95% CI) *P-value*		Recurrence rate* (No. of children) RR (95% CI) *P-value*	
						LZP	**DZP**	**LZP**	**DZP**	**LZP**	**DZP**	**LZP**	**DZP**	**LZP**	**DZP**
Appleton et al., 1995, UK [76]	Open label Quasi-RCT	0.1-16	6 19	LZP DZP	0.05-0.1 (PR) 0.3-0.4 (PR)	6 2.8 (1.5-5.5) *p = 0.002*	6	20-60 seconds	20-60 seconds	0 0.1 (0.01-1.56) *p = 0.1*	13	0 0.1 (0.01-1.69) *p = 0.1*	12	0 0.2 (0.01-2.9) *p = 0.2*	7

LZP: Lorazepam, DZP: Diazepam

*** Within 24 hours.**

B.3. Sublingual lorazepam vs. rectal diazepam

The efficacy of sublingual lorazepam was studied against rectal diazepam by Malu et al. (2013) [75]. This was an 18-month, randomised, controlled single-blind study of children admitted to the emergency room with seizures lasting more than 5 minutes. This study was conducted in sub-Saharan Africa at 9 different hospitals and involved 436 children aged from 5 months to 10 years. Treatment was considered effective if the presenting seizures terminated within 10 minutes of the initial dose. If the seizures were still active after 10 minutes, a second dose of the study medication was given by the same route. If this was not effective, intravenous phenobarbital was administered (15 mg/kg).

Randomisation was allocated based on an alternate-days basis (i.e., on even days of the month, children received rectal diazepam, and on odd days they received sublingual lorazepam). At the emergency room, blood pressure and oxygen levels were monitored for the first 20 minutes of admission. Monitoring was extended to 40 minutes for patients who needed a second dose, and supplemental oxygen was provided if oxygen saturation fell below 93%. Children were excluded if they had been administered AEDs prior to hospital attendance, had seizures lasting less than 5 minutes, or ejected the diazepam within 10 minutes.

The seizure ended in 131 of 234 children (56%) who received sublingual lorazepam and in 160 of 202 children (79%) who received rectal diazepam (Table 4.11). This result significantly favoured rectal diazepam for seizure termination (RR: 0.71; 95% CI: 0.62 to 0.81; $p < 0.00001$) (Table 3.11).

Seizure termination occurred within 9 minutes after treatment with sublingual lorazepam, and within 6 minutes after rectal diazepam.

Sixty-three of the 234 children (27%) treated with sublingual lorazepam required additional dose(s) to terminate their seizures compared to 24 of the 202 children (12%) on rectal diazepam; the differences was significant (RR: 2.3, 95% CI: 1.5 to 3.5; p = 0.0002) (Table 3.11)

Data related to additional AEDs was not available.

Eighty-five of the 234 children (36%) treated with sublingual lorazepam experienced a further seizure after drug administration compared to 80 of the 202 children (40%) given rectal diazepam; the difference was not significant (RR: 0.92, 95% CI: 0.72 to 1.17; p = 0.48) (Table 3.11).

To conclude, sublingual lorazepam was inferior to rectal diazepam for the treatment of acute seizures in children. It was less effective and more likely to require an additional dose(s) (Table 3.11 and appendix A).

Table 3. 11: Lorazepam sublingual versus rectal diazepam in one study

Reference, country	**Study design**	**Age (Y)**	**No. of children**	**AEDs**	**Dose (mg/kg)**	**Seizure control (No. of children)** RR (95% CI) *P-value*		**Time to seizure control**		**Additional dose(s) (No. of children)** RR (95% CI) *P-value*		**Recurrence rate*** **(No. of children)** RR (95% CI) *P-value*	
						LZP	**DZP**	**LZP**	**DZP**	**LZP**	**DZP**	**LZP**	**DZP**
Malu et al., 2013, sub-Saharan Africa [75]	single-blind RCT	0.5-10	234 202	LZP DZP	0.1 (sublingual) 0.3-0.4 (PR) ≤60 seconds	131 0.71 (0.62-0.81) *p < 0.00001*	160	9 min	6 min	63 2.27 (1.5-3.5) *p = 0.0002*	24	85 0.92 (0.72-1.17) *p = 0.48*	80

LZP: Lorazepam, DZP: Diazepam

Data for whether additional AEDs were administered was not reported

*** Within 24 hours.**

B.4. Summary of lorazepam vs. diazepam

The results suggest that IV lorazepam and IV diazepam are equally effective in terminating seizures (RR: 1.02 & p = 0.73) and there were no differences between the groups in term of additional doses (RR: 1.05 & p = 0.77), additional AEDs (RR: 0.91 & p = 0.73) and seizure recurrence (RR: 0.79 & p =0.44) (Table 3.9).

With regard the rectal route, there was one study involving a small number of children which makes it difficult to conclude anything in relation to effectiveness [76].

Sublingual lorazepam appears to be inferior to rectal diazepam for the treatment of acute seizures in children (RR: 0.71 & p < 0.00001) and this may due to its poor absorption. A pharmacokinetic study conducted by Anderson et.al (2012) showed that lorazepam was slowly absorbed following buccal administration [85]. Sublingual absorption is likely to be similar to buccal absorption. Peak absorption following buccal administration was at 180 minutes, suggesting that this may not be the best route for treating acute seizures [85].

In summary, intravenous lorazepam is the best route of administration for this drug. Intravenous lorazepam and diazepam appear to be equally effective

C. Lorazepam versus paraldehyde

Shafique et al. (2006) compared intranasal lorazepam (100 µg/kg) and intramuscular paraldehyde (0.2 ml/kg) in a 12-month, single-centre, randomised, open-label study conducted in sub-Saharan Africa [72]. It was carried out in 160 children aged 2 months to 12 years who attended the paediatric emergency department with generalized convulsions continuing for at least 5 minutes.

Children were excluded if they received antiepileptic drugs within 1 hour before attending, had seizures due to hypoglycaemia which were stopped with its correction, had signs of hepatic or hypertensive encephalopathy, or suffered organophosphate poisoning. Randomisation was assigned by computer, and treatment was allocated in unmarked sealed envelopes.

The primary outcome was whether the seizures stopped within 10 minutes of treatment. The secondary outcomes were time to seizure cessation, incidence of hypotension or hypoxia, and the seizure recurrence rate within 24 hours. The local protocol was applied for children whose seizures lasted more than 10 minutes.

Intranasal lorazepam was more effective than intramuscular paraldehyde in terminating seizures (60 children (75%) terminated their seizure vs. 49 children (61%)). However, this difference was not statistically significant (RR: 1.22; 95% CI: 0.9 to 1.52; p = 0.07) (Table 3.12 and appendix A).

There was no difference between medications in the time to achieve seizure termination, 7.5 minutes (median) for intranasal lorazepam and 8 minutes (median) for intramuscular paraldehyde.

Significantly fewer children receiving intranasal lorazepam (8 children, 10%) required an additional dose(s) and different antiepileptic drugs to terminate their seizures than with intramuscular paraldehyde (21 children, 26%) (RR: 0.38; 95% CI: 0.18 to 0.88; p = 0.01) (Table 3.12 and appendix A).

The seizure recurrence rate was 10% (8 children) for intranasal lorazepam compared to 14% (11 children) for intramuscular paraldehyde; the difference was not significant (RR: 0.73; 95% CI: 0.31 to 1.71; p = 0.47) (Table 3.12 and appendix A).

In summary, children receiving intranasal lorazepam as opposed to intramuscular paraldehyde were significantly less likely to require additional dose(s) or an alternative antiepileptic drug. It appeared to be more effective, but this difference was not statistically significant

Table 3. 12: Lorazepam (intranasal) vs. paraldehyde (intramuscular) in one study

Reference, country	Study design	Age (Y)	No. of children	AEDs	Dose	Seizure control (No. of children) RR (95% CI) *P-value*		Time to seizure control		Additional dose(s) and AEDs* (No. of children) RR (95% CI) *P-value*		Recurrence rate** (No. of children) RR (95% CI) *P-value*	
						LZP	**Paraldehyde**	**LZP**	**Paraldehyde**	**LZP**	**Paraldehyde**	**LZP**	**Paraldehyde**
Shafique et al., 2006, sub-Saharan Africa [72]	Open label RCT	0.2-12	80 80	LZP Paraldehyde	100 µg/kg (IN) 0.2 ml/kg (IM)	60 1.22 (0.9-1.52) *P = 0.07*	49	Median 7.5 min	Median 8 min	(8) 0.38 (0.18-0.88) *p = 0.01*	(21)	8 0.73 (0.31-1.17) *p = 0.47*	11

LZP: Lorazepam

*** The data for the requirement of additional dose(s) and AEDs was combined in this study.**

**** Within 24 hours.**

D. Intravenous lorazepam vs. intravenous diazepam plus phenytoin

A 2010 study compared intravenous lorazepam with an intravenous combination of diazepam and phenytoin in a tertiary hospital in India [81]. The study was randomised and open-label. Phenytoin was given 15 to 30 minutes after diazepam administration, even if seizures had not recurred. The study included178 children aged between 1 and 12 years with convulsive status epilepticus lasting for at least 5 minutes. If IV access could not be obtained, the same dose of lorazepam and diazepam was given rectally.

Children were excluded if they received antiepileptic drugs within the past 4 weeks or had headache, injury, jaundice, diarrhoea, renal failure or a history of poisoning.

Randomisation was assigned by a computer, and treatment was allocated in sealed envelopes.

If the seizures were controlled within 10 minutes of the initial seizure, without recurrence for 18 hours, the treatment was deemed successful.

The primary outcome was seizure cessation within 10 minutes of the first intervention, without recurrence of seizures during the next 18 hours. If the seizures did not stop immediately after the initial dose, a second dose of the same medication was used during the first 10 minutes from the initial seizure. If the seizure was still active after the second dose (after 10 minutes from the initial seizures), the following medications were used: phenytoin (18 mg/kg, IV), phenobarbital (20 mg/kg, IV) and midazolam (1–5 µg/kg/min, IV).

The secondary outcomes included time to stop seizure after the first dose, number of doses required to stop the initial seizures, number of seizures during 18 hours after the initial dose, incidence of respiratory depression, number of children who crossed over to another treatment regimen and number of cases transferred to the ICU. The study period was not documented.

The authors described both medicines to be effective in all patients (RR: 1; 95% CI: 0.98 to 1.02; p = 1), However, their definition of being effective included the use of a second dose of the anticonvulsant. Six (7%) of 90 children on intravenous lorazepam required an additional dose to terminate their initial seizure, compared with 14 of 88 children (16%) on intravenous diazepam and phenytoin (i.e. the effectiveness of lorazepam was 93% compared to 84% for diazepam with phenytoin). The difference was not statistically significant (RR: 1.1; 95% CI: 0.17 to 1.04; p = 0.06) (Table 3.13 and appendix A). All of the doses were received during the first 10 minutes of the emergency admission.

No children in either group required an additional antiepileptic drug or had a further seizure within 18 hrs after drug administration and this result was due to the longer action of duration of lorazepam and the use of the long-acting AED (phenytoin) along with diazepam (Table 3.13). Intravenous diazepam has a short duration of action, and seizure recurrence may occur within 2 hours after diazepam administration [86]. Moreover, the recommended concentration of diazepam to terminate a seizure is 200 μg/L, but this concentration decreases in less than 50 minutes after the dose is given, which explains the rapid recurrence of seizure [87]. Therefore, seizures may recur with

diazepam if patients are not given a loading dose of long-acting AEDs, such as phenytoin [81]. By contrast, intravenous lorazepam has a long action of duration, which helps avoid seizure recurrence within 18 hours after seizure termination [81].

In summary, intravenous lorazepam appeared to be more effective than the intravenous combination of diazepam and phenytoin in the treatment of acute seizures. The difference was of borderline statistical significant (RR: 1.1; 95% CI: 1 to 1.23; p = 0.05).

Table 3. 13: Intravenous lorazepam vs. intravenous diazepam plus phenytoin in one study

Reference, country	Study design	Age (Y)	No. of children	AEDs	Dose (mg/kg)	Seizure control (No. of children) RR (95% CI) *P-value*		Time to seizure control		Additional dose(s)* (No. of children) RR (95% CI) *P-value*	
						LZP	DZP+PHT	LZP	DZP+PHT	LZP	DZP+PHT
Sreenath et al., 2010, India [81]	Open label RCT	1–12	90 88	LZP DZP+PHT	0.1 (IV) 0.2 + 18/15–30 min (IV)	84 1.1 (1 –1.23) *P = 0.05*	74	20 sec	20 sec	6 0.42 (0.17–1.04) *P = 0.06*	14

LZP: Lorazepam, DZP: Diazepam, PHT: Phenytoin

*** All additional doses are given within the first 10 minutes of the initial seizure**

E. Intravenous lorazepam vs. intranasal lorazepam

Two studies recruited a total of 650 children aged between 2 months and 14 years; one was conducted in India [69] and the other in Malawi [71].

Arya et al. (2011) conducted the randomised, open-label, single-centre study in India [69]. The researchers recruited 141 children aged between 6 and 14 years who attended the emergency department with an acute tonic-clonic convulsion, over a 7 month period, and compared intravenous to intranasal lorazepam administration. The primary outcome was clinical termination of the seizure activity within 10 minutes of drug administration. If the seizure continued or recurred after 10 minutes from the initial dose, phenytoin was given at 20 mg/kg over 20 minutes. Secondary outcomes were persistent termination of seizures for 1 hour after drug administration, time for seizure control, incidence of hypotension within 1 hour of drug administration, and incidence of respiratory depression needing ventilation. Children were excluded if they were hypersensitive to benzodiazepine, had received intravenous AEDs within 1 hour prior to being admitted to the emergency room, or appeared to have cerebrospinal fluid rhinorrhoea or upper respiratory tract infection. Advance randomisation was performed using blocks of variable lengths and storing the medication in opaque sealed envelopes.

Four years later, Lissauer et al. (2015) conducted a randomised, open-label study at a single centre in Malawi comparing intravenous to intranasal lorazepam. The study period was not documented. Five hundred and nine children aged from 2 months to 14 years who attended the emergency department with acute generalised seizures lasting at least for 5 minutes were included. Lorazepam was given intravenously to 264 children

and intranasally to 245. Randomisation was computer-generated via a number table, in blocks of 10, and stratified depending on whether IV access was available, already established or could not be obtained. The primary endpoint was control of seizures within 10 minutes of the initial dose. The secondary outcomes included the time to stop seizure after the first dose, number of doses, additional AEDs, recurrence within 24 hours, length of seizure, side effects and the patients' health status at discharge. Treatment was considered effective if the presenting seizure terminated within 10 minutes of the initial dose. If the seizures were still active after 10 minutes, a second dose was given by the same route. If the seizure lasted for 20 minutes or more, the following medications were used: intramuscular paraldehyde (0.2ml/kg) followed by intravenous phenobarbital (18 mg/kg), then intravenous phenytoin (18 mg/kg/10minutes) as necessary, according to local guidelines.

The seizure ended in 274 of 334 children (82%) who received intravenous lorazepam and in 198 of 316 children (63%) who received intranasal lorazepam (Table 3.14). There was no difference statistically (RR: 1.19; 95% CI: 0.78 to 1.81; p = 0.42). Seizure termination was statistically higher with intravenous lorazepam in one study (RR: 1.46 & $p < 0.00001$) [71]. In the other study, however, there was no difference between the 2 routes (RR: 0.96 & p = 0.64)[69]. Seizure termination occurred 3 to 5 minutes after treatment with intravenous lorazepam, and 3 to 10 minutes after intranasal lorazepam.

One of the studies involving 509 children recorded whether an additional dose(s) and additional AEDs were needed [71]. Forty-six of the 264 children (17%) receiving intravenous lorazepam required additional dose(s) compared to 99 of the 245 children

(40%) who received intranasal lorazepam (Table 4.16); the difference was statistically significant (RR: 0.4; 95% CI: 0.32 to 0.58; $p < 0.00001$) (Table 3.14).

The intravenous route had a lower likelihood of requiring a different AED to terminate the seizure (23 children, 9%) than the intranasal route (56 children, 23%) (RR: 0.38; 95% CI: 0.24 to 0.6; $p < 0.0001$) (Table 3.14).

Eighty-eight of the 334 children (26%) on intravenous lorazepam experienced a further seizure after drug administration compared to 106 of the 316 children (34%) on intranasal lorazepam; the difference was not significant (RR: 0.7; 95% CI: 0.61 to 1.12; $p = 0.23$) (Table 3.14).

In conclusion, intravenous lorazepam appeared to be more effective than the intranasal lorazepam in the treatment of acute seizures with a lower recurrence rate of seizures. These differences however did not reach statistical significance. There was however a statistically lower risk of needing treatment with additional dose(s) and additional AEDs, favouring intravenous lorazepam (Table 3.14 and Figure 3.6).

Table 3. 14: Lorazepam (IV) versus lorazepam (IN)

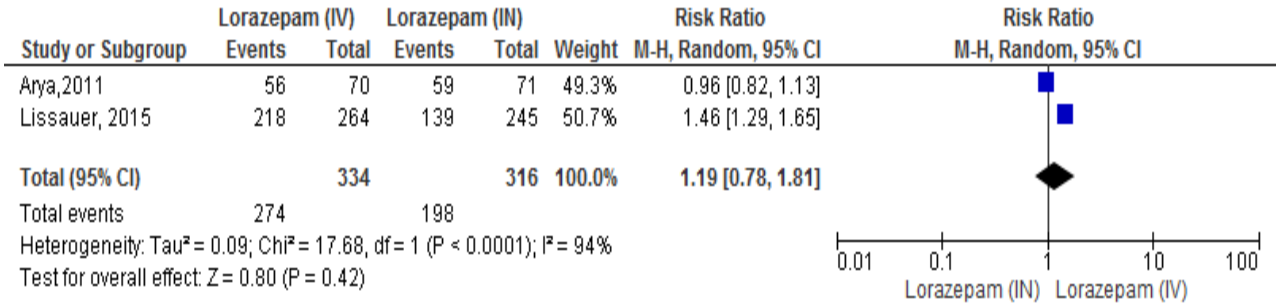
Reference, country	Study design	Age (Y)	No. of children	AED	Dose (mg/kg)	Seizure control (No. of children) RR (95% CI) *P-value* IV	IN	Time to seizure control (median) IV	IN	Additional dose(s) (No. of children) RR (95% CI) *P-value* IV	IN	Additional AEDs (No. of children) RR (95% CI) *P-value* IV	IN	Recurrence* (No. of children) RR (95% CI) *P-value* IV	IN
Arya et al., 2011, India [69]	Open label	6-14	70 71	LZP LZP	0.1 (IV), 4 mg max. 0.1/30-60 sec (IN)	56 0.96 (0.82-1.13) *p = 0.64*	59	3 min	3 min	NA	NA	NA	NA	41 0.95 (0.72-1.24) *p = 0.68*	44
Lissauer et al. ,2015, Malawi [71]	Open label	0.2-14	264 245	LZP LZP	0.1 (IV) 0.1(IN)	218 1.46 (1.29-1.65) *p < 0.00001*	139	5 min	10 min	46 0.4 (0.32-1.58) *p < 0.00001*	99	23 0.38 (0.24-0.6) *p < 0.0001*	56	47 0.7 (0.5-0.99) *p = 0.04*	62
Total	2	0.2-14	334 316	LZP LZP	0.1 (IV), 4 mg max. 0.1/30-60 sec (IN)	274 1.19 (0.78-1.81) *p = 0.42*	198	3-5 min	3-10 min	46 0.4 (0.32-1.58) *p < 0.00001*	99	23 0.38 (0.24-0.6) *p < 0.0001*	56	88 0.83 (0.61 – 1.12) *p = 0.23*	106

IV: Intravenous, IN: Intranasal

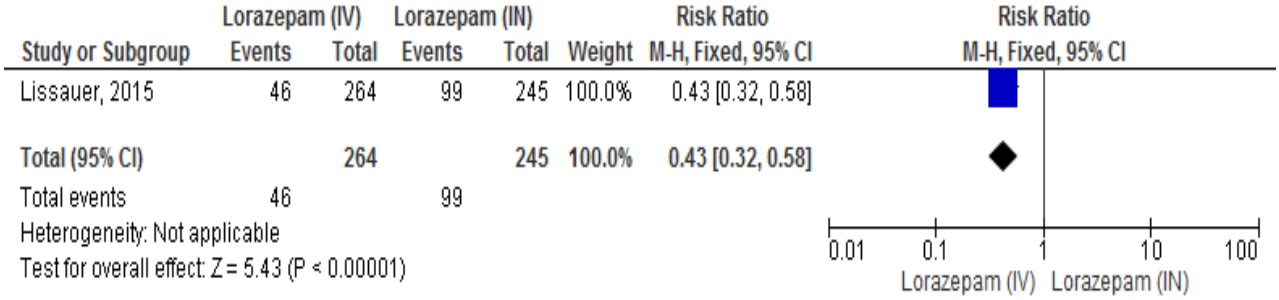
*** The first study documented the rate within 1 hour while the second study within 24 hours.**

Figure 3. 6: The effectiveness of lorazepam at different route of the administration (IV vs IN)

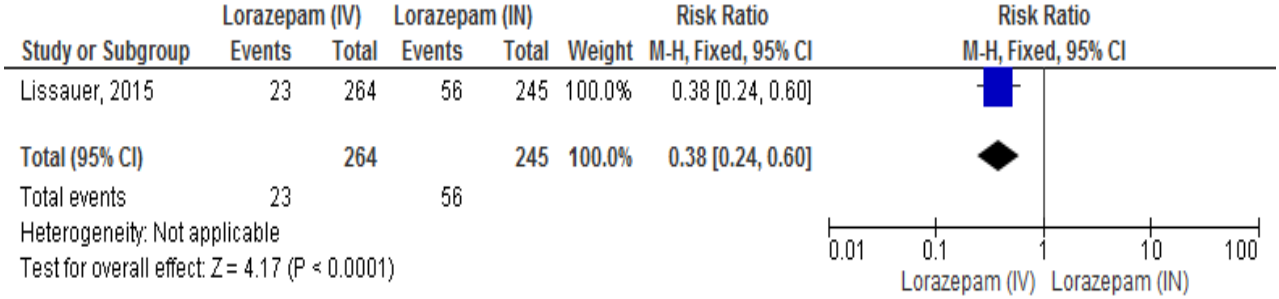
1. **Successful seizure control**



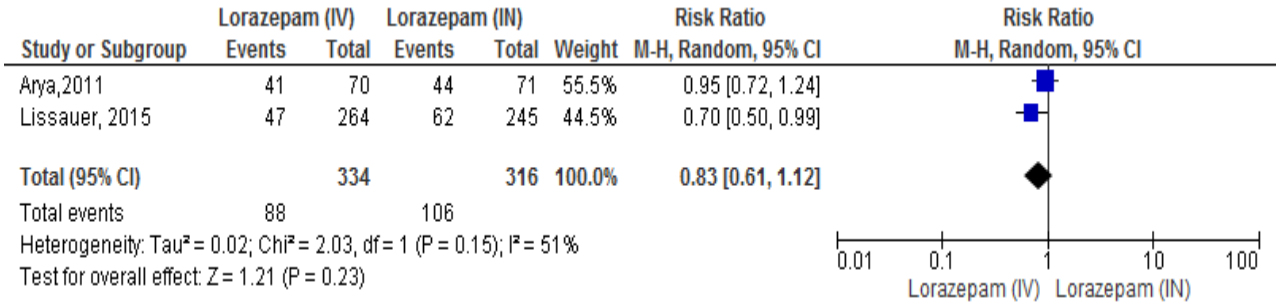
2. **Additional dose(s)**



3. **Additional AEDs**



4. **Seizure recurrence**



F. Intravenous lorazepam vs. buccal lorazepam

The Lissauer et al. (2015) study described in the previous section (intravenous vs. intranasal lorazepam) also compared intravenous vs. buccal lorazepam[71].

Seizures ended in 218 of 264 children (83%) who received intravenous lorazepam, and in 115 of 252 children (46%) after buccal lorazepam (Table 3.15 and appendix A). The results favoured intravenous lorazepam over the buccal route for seizure termination (RR: 1.81; 95% CI: 1.56 to 2.09; $p < 0.00001$) (Table 3.15 and appendix A).

Forty-six children (17%) receiving intravenous lorazepam required additional dose(s) compared to 130 children (51.5%) who received buccal lorazepam. The result revealed that children treated with intravenous lorazepam were significantly less likely to need a second dose (RR: 0.34; 95% CI: 0.25-0.45; $p < 0.00001$) (Table 3.15 and appendix A).

The intravenous route also had a significantly lower likelihood of requiring a different AED to terminate the seizure (23 children, 9%) than the buccal route (80 children, 32%) with significant differences between both routes, favouring intravenous (RR: 0.27; 95% CI: 0.18-0.42; $p < 0.00001$) (Table 3.15 and appendix A).

The seizure recurrence rate within 24 hours was similar between the administration routes, 47 children for intravenous and 48 for buccal and the risk ratio did not prove to be significant (RR: 0.7; 95% CI: 0.61 to 1.12; $p = 0.23$) (Table 3.15 and appendix A).

In summary, intravenous lorazepam was found to be superior to buccal lorazepam for the treatment of acute seizures in children. It was more effective and less likely to require additional dose(s) or further AEDs to terminate seizures (Table 4.17 and

appendix A). This suggests that buccal lorazepam is poorly absorbed. As previously mentioned, a pharmacokinetic study conducted by Anderson et.al (2012) has shown that lorazepam was slowly absorbed following buccal administration [85]. Peak absorption following buccal administration was at 180 minutes, suggesting that this may not be the best route for treating acute seizures [85]. The findings in relation to buccal lorazepam are similar to those described earlier for sublingual lorazepam. (See section B part B.3 & B.4).

Table 3. 15: Lorazepam (IV) versus lorazepam (buccal)

Reference, country	**Study design**	**Age (Y)**	**No. of children**	**AED**	**Dose (mg/kg)**	**Seizure control (No. of children)** RR (95% CI) *P-value* **IV**	**BUC**	**Time to seizure control (median) IV**	**BUC**	**Additional dose(s) (No. of children)** RR (95% CI) *P-value* **IV**	**BUC**	**Additional AEDs (No. of children)** RR (95% CI) *P-value* **IV**	**BUC**	**Recurrence* (No. of children)** RR (95% CI) *P-value* **IV**	**BUC**
Lissauer et al. ,2015, Malawi [71]	Open label	0.2-14	264	LZP	0.1 (IV)	218	115	5 min	12 min	46	130	23	80	47	48
			252	LZP	0.1(BUC)	1.81 (1.56-2.09) *p < 0.00001*				0.34 (0.25-0.45) *p < 0.00001*		0.27 (0.18-0.42) *p < 0.00001*		0.93 (0.65-1.34) *p = 0.72*	

IV: intravenous; BUC: buccal

*** Within 24 hours**

G. Intravenous valproate vs. intravenous phenytoin

The efficacy of intravenous valproate and intravenous phenytoin were compared in a 15-month, single-centre, mixed-population, randomised study conducted by Agarwal et al. (2007) in India [77]. A group of 100 adults and children who had benzodiazepine-resistant status epilepticus was divided into 2 sets of 50 patients. Group A, with a subset of 22 patients aged below 18 years, were given intravenous valproate (20mg/kg at 40mg/min). Group B, with a subset of 16 patients aged below 18 years, were given intravenous phenytoin (20mg/kg at maximum 50mg/min). Treatment was considered successful if the convulsion terminated within 20 minutes after starting the infusion and if there was no recurrence over the next 12 hours. If the seizures were still active after 20 minutes, or recurred after 12 hours of treatment, the crossover treatment was applied. Patients were excluded if they were aged under 2 years or had hepatic encephalopathy, myoclonic status epilepticus, or a history of benzodiazepine or barbiturate contraindication.

The only data for the paediatric population in this study was seizure termination. The seizure stopped in 20 of 22 children (91%) who received intravenous valproate, and in 14 of 16 children (88%) who received intravenous phenytoin; the difference was not significant (RR: 1.04; 95% CI: 0.8 to 1.3; p = 0.74) (Table 3.16 and appendix A).

Table 3. 16: Valproate (IV) versus phenytoin (IV) in one study

Reference, country	**Study design**	**Age (Y)**	**No. of children**	**AED**	**Dose (mg/kg)**	**Seizure control (No. of children)** RR (95% CI) *P-value* **VAP** **PHT**	**Time to seizure control (median)** **VAP** **PHT**	**Additional dose(s) (No. of children)** RR (95% CI) *P-value* **IV** **PHT**	**Additional AEDs (No. of children)** RR (95% CI) *P-value* **IV** **PHT**	**Recurrence (No. of children)** RR (95% CI) *P-value* **IV** **PHT**
Agarwal et al. ,2007, India [77]	Open label RCT	0-18	22 16	VAP PHT	20 (IV) 20 (IV)	20 14 1.04 (0.8-1.3) *p = 0.74*	***Data was not available***	***Data was not available***	***Data was not available***	***Data was not available***

VAP: Valproate, PHT: Phenytoin

H. Valproate versus phenobarbital

An Iranian study compared intravenous valproate to intravenous phenobarbital in the treatment of acute prolonged seizures at 2 centres in 2012 [67]. This randomised, double-blind study took place over 2 years and involved 60 children aged between 3 and 16 years old who attended the emergency room with seizures lasting more than 5 minutes, which had not been controlled by intravenous diazepam (0.2mg/kg).

The children were excluded if they had a history of an adverse reaction to sodium valproate, or coagulopathy, hepatic, or cardiovascular problems, or were on lamotrigine at more than 200 mg/day. Advance randomisation was allocated by a random number of tables in a quaternary block and children received either intravenous valproate (20 mg/kg at maximum 5-6 mg/min) as a rapid loading dose over 5-10 minutes or intravenous phenobarbital (20 mg/kg at maximum 60-100 mg/min). Treatment was considered successful if the seizure stopped within 20 minutes of the start of infusion of the initial study medication, without respiratory depression, hypotension, or recurrent seizure within 24 hour.

The seizure stopped in 27 of 30 children (90%) who received intravenous valproate, and in 23 of 30 children (77%) who received intravenous phenobarbital; the difference was not significant (RR: 1.17; 95% CI: 0.93 to 1.48; p = 0.17) (Table 3.17 and appendix A).

There was no difference in the time to end seizures which was less than 20 minutes for each medication.

Whether additional dose(s) or antiepileptic drugs were required to terminate seizures was not documented.

Four of the 30 children (13%) in the intravenous valproate group experienced a further seizure within 24 hours, compared to 12 of the 30 children (40%) who received intravenous phenobarbital; the difference was statistically significant (RR: 0.33; 95% CI: 0.12 to 0.92; p = 0.03) (Table 3.17).

This study showed that children receiving intravenous valproate were significantly less likely to have seizure recurrence within 24 hrs compared to those receiving intravenous phenobarbital. It appeared to be more effective, but this difference was not statistically significant (Table 3.17 and appendix A).

Table 3. 17: Valproate (IV) versus phenobarbital (IV) in one study

Reference, country	**Study design**	**Age (Y)**	**No. of children**	**AED**	**Dose (mg/kg)**	**Seizure control (No. of children)** **RR (95% CI)** ***P-value*** **VAP** **PB**	**Time to seizure control (median)** **VAP** **PB**	**Additional dose(s) (No. of children)** **RR (95% CI)** ***P-value*** **VAP** **PB**	**Additional AEDs (No. of children)** **RR (95% CI)** ***P-value*** **VAP** **PB**	**Recurrence* (No. of children)** **RR (95% CI)** ***P-value*** **VAP** **PB**
Malamiri et al. ,2012, India [67]	Double-blind RCT	3-16	30 30	VAP PB	20 at 5 - 6mg/min (IV) 20 at 60 - 100 mg/min (IV)	27 23 1.17 (0.93 -1.48) *p = 0.17*	< 20 min <20 min	***Data was not available***	***Data was not available***	4 12 0.33 (0.12 - 0.92) *p = 0.03*

VAP: Valproate, PB: Phenobarbital

*** Within 24 hours.**

3.3.2.2 Additional studies

Lewena and Young (2006) conducted a retrospective study in Australia, which involved 37 children ages 2 months to 7 years old who presented at an emergency department with convulsive status epilepticus lasting at least 10 minutes [83]. The primary aim of the study was to determine the effectiveness of second-line treatment. There was no clear definition of a successful treatment rate.

All the children received benzodiazepines as first-line treatment; 30 intravenous diazepam, (0.1 - 0.2 mg/kg). The seizure ended in 5 of 37 children (14%). Thirty-two children (86%) required further treatment; as a second-line treatment; 11 phenytoin, 10 phenobarbital, and 7 both agents (the doses were not documented). The seizure terminated in only 6 of the 28 children (21%) who received the second-line treatment.

The low response rate suggests that either the doses given were inadequate or possibly the notes were reviewed incorrectly. However, as the doses of the second line treatments and other benzodiazepines were not stated, and it was a retrospective study, it has been excluded from further analysis.

Garr et al. (1999) conducted a retrospective study to compare the effectiveness of rectal and intravenous diazepam (0.4 mg/kg, max 10 mg) in children aged 1 month to 15 years with tonic-clonic convulsions in the UK [82]. No specific definition of tonic-clonic convulsions was given in this study. The primary outcome was to identify at what stage of treatment protocol the seizure was controlled. The secondary outcome was to determine the safety of the medication used.

Of the 81 children, 48 received rectal diazepam, while 33 received intravenous diazepam. The seizure was terminated in 41 out of 48 children (85%) in the rectal diazepam group and 28 out of 33 children (85%) in the intravenous diazepam group after the first dose. Two children in each group required a second dose. Ten children were treated with paraldehyde and phenytoin (the doses were not documented) as additional AEDs to control their seizure, resulting in termination of the seizure in 5 children. The result of this study suggested that rectal diazepam was effective as intravenous diazepam.

3.4 Discussion

This systematic review has shown that buccal midazolam was more effective in terminating seizures in children suffering from acute tonic-clonic seizures than rectal diazepam, with a success rate ranging from 53 to 100% (RR: 1.23; 95% CI: 1 to 1.5; $p < 0.04$). The important aim in treating acute tonic clonic convulsions in children is to control the seizures as quickly as possible, thereby preventing the seizures from developing into the refractory or super refractory status epilepticus phase, which may lead to neuronal damage [30, 31]. The children receiving rectal diazepam need to be laid in the appropriate position, which may cause a delay in drug administration; this does not happen with the administration of buccal midazolam [21]. The means of administering buccal midazolam is easier and is more socially acceptable in comparison to the rectal method [27]. The results of this systematic review also showed that seizure recurrence is lower in children receiving buccal midazolam than in those who receive rectal diazepam. This could be because buccal midazolam acts over a long duration. The half-life of midazolam ranges from two to three hours for a healthy child and more than five hours for ill children, while the half-life of diazepam is one hour [32, 33]. Therefore, buccal midazolam should be the first choice for treating acute tonic clonic convulsion in children when intravenous access is difficult or is yet to be obtained [21].

When evaluating intravenous AEDs, our results showed that intravenous lorazepam and intravenous diazepam are equally effective in treating acute tonic-clonic seizures in children. The study by Appleton had suggested that lorazepam may be more effective, showing the need for less additional AEDs and a lower recurrence rate. However, the number of patients in this study were small [76].

Pharmacologically, one would expect a longer duration of action with lorazepam. More studies are needed to determine whether IV lorazepam is more effective than IV diazepam.

Sublingual/buccal lorazepam, however, was inferior to rectal diazepam and intravenous lorazepam for the treatment of acute seizure in children. It was less effective and more likely to require additional dose(s) or further AEDs to terminate the seizures. This suggests that sublingual/buccal lorazepam is poorly absorbed. A pharmacokinetic study conducted by Anderson et al. (2012) showed that lorazepam was slowly absorbed following buccal administration [27]. Sublingual absorption is likely to be similar to buccal absorption. Peak absorption following buccal administration was at 180 minutes, suggesting that this may not be the best route for treating acute seizures [27].

Only one study was identified in this review which evaluated the effectiveness of intramuscular paraldehyde. It was as effective as intranasal lorazepam for treating acute tonic-clonic seizures in children but those children treated with intramuscular paraldehyde were more likely to require additional dose(s) or alternative AEDs. This could be because of the slower absorption of paraldehyde when given by the intramuscular route which delays the circulation of paraldehyde to the brain [14].

Fewer randomised controlled trials evaluating the second-line treatments (VAP, PB and PHT) were identified in this systematic review. Our results showed that intravenous valproate appeared to be more effective than intravenous phenytoin and phenobarbital; however, this was not statistically significant. Several studies have recommended levetiracetam instead of sodium valproate or phenytoin as a second-line treatment

following the failure of benzodiazepines [6, 34-38]. However, to date, no randomised control studies have been published comparing the effectiveness of intravenous levetiracetam with other second-line agents for treating convulsive status epilepticus in children. More RCTs should be conducted to evaluate the effectiveness of these agents in treating children's convulsive status epilepticus.

3.5 Limitations

The studies included in this review have a number of limitations. The majority of studies were open label, which may affect the quality of a study. In general, the number of studies included was small, and the definitions of the effectiveness and the measurement of seizure recurrence varied amongst them. Therefore, the interpretation of these outcomes is subjective (depends on the time of follow-up). Fewer studies were identified in this systematic review for second-line treatment; thus, the results of these studies should be interpreted with caution.

3.6 Conclusions

Buccal midazolam was more effective in seizure termination in children suffering from acute tonic-clonic seizures than rectal diazepam, and it was associated with a lower rate of seizure recurrence. This suggests that the buccal route may the best route of administration when children are initially admitted to the emergency department. However, the intravenous route is the better route of administration for lorazepam compared to the buccal, sublingual, or intranasal routes. More randomised control trials are required to compare second-line treatments.

CHAPTER 4: SYSTEMATIC REVIEW TWO

4.1 Introduction

The mortality associated with status epilepticus ranges from approximately 3% to 40%, and the prolonged convulsions can be associated with hypoxia, hypotension, respiratory depression and increased intracranial pressure [1, 88]. Because the mortality and morbidity that results from acute tonic seizures are correlated with the duration of the seizures, the first priority for treatment is to control the seizure as quickly as possible [89]. Therefore, the best treatment for acute tonic clonic seizure should be characterised by safe and rapid effectiveness with minimal recurrence. Not all treatments that are currently used to manage acute tonic clonic seizure meet all these criteria [76].

Benzodiazepines are commonly used as the first line treatment for acute tonic clonic seizures. Lorazepam is the best choice as it has good effectiveness and a low incidence of respiratory depression [76, 90]. In contrast, diazepam has a higher risk of respiratory depression [65, 73, 76].

When two doses of benzodiazepine fail to control seizures, phenytoin or phenobarbital are the recommended second line treatments [38]. The Status Epilepticus Working Party preferred phenytoin over phenobarbital, as it caused less respiratory depression [91].

Several studies have recommended levetiracetam instead of phenytoin or phenobarbital or sodium valproate as a second-line treatment following the failure of benzodiazepines [51, 53, 92-94]. Recent cohort studies of intravenous levetiracetam in children have reported no serious AEs such as respiratory depression [51, 95, 96]. However, to date,

no randomised control studies comparing the safety of intravenous levetiracetam with other second-line agents for treating convulsive status epilepticus in children have been published.

The primary aim for this review was to evaluate the safety of the following antiepileptic drugs, irrespective of the administration routes, for the treatment of acute tonic-clonic seizures including convulsive status epilepticus in children: benzodiazepines, paraldehyde, phenobarbital, phenytoin, sodium valproate and levetiracetam.

4.2 Methods

The methods used for this review are the same as those described in Chapter 2.

4.3 Results

Based on the specified inclusion and exclusion criteria (Figure 4.1 and Table 4.1), 1,851 studies were identified initially and following further inspection of the abstract, 34 were retained for evaluation. Twenty-five of these studies were analysed, however, 8 studies could not be evaluated as they were published in Japanese or Turkish.

Figure 4. 1: Flow chart for the systematic review

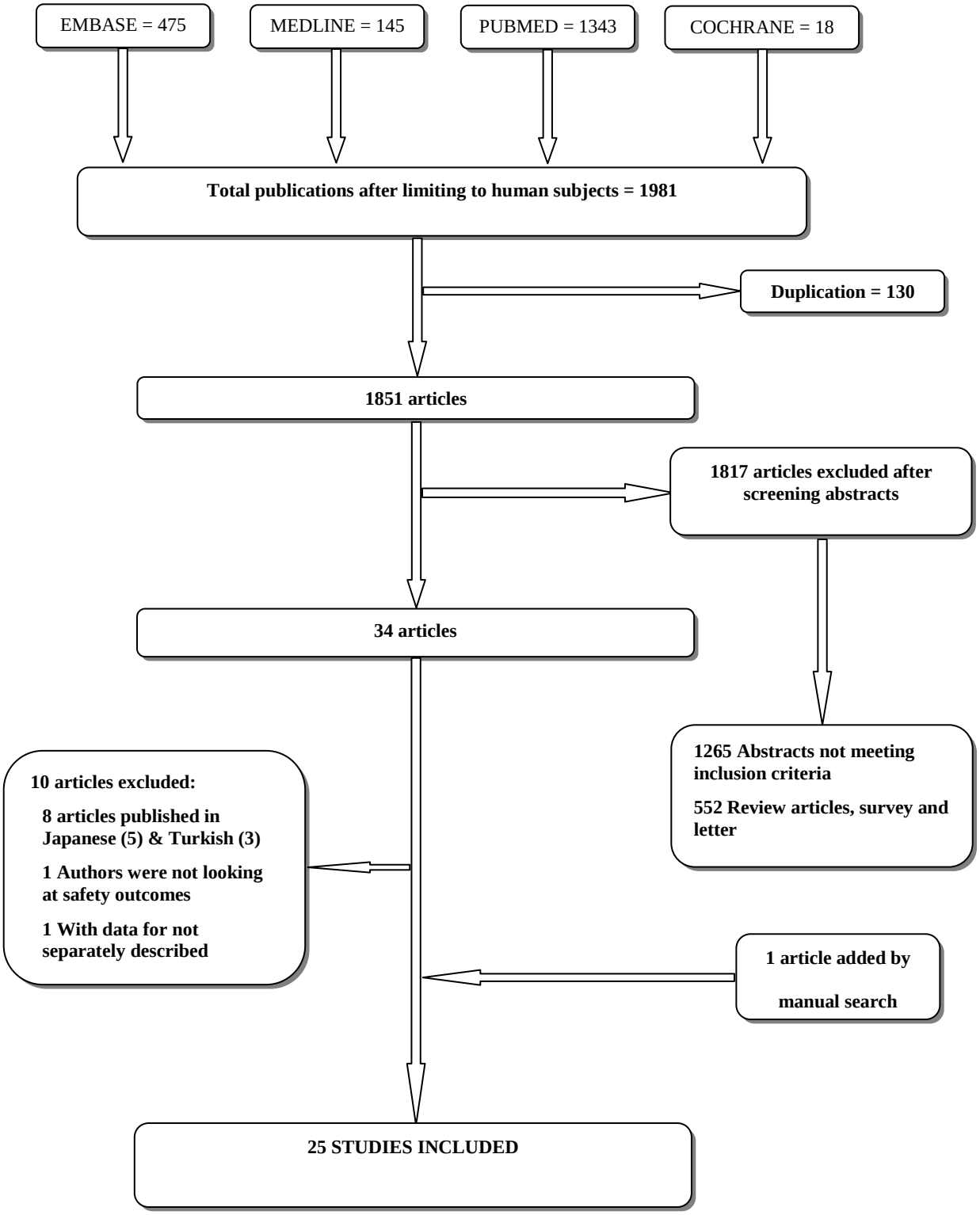


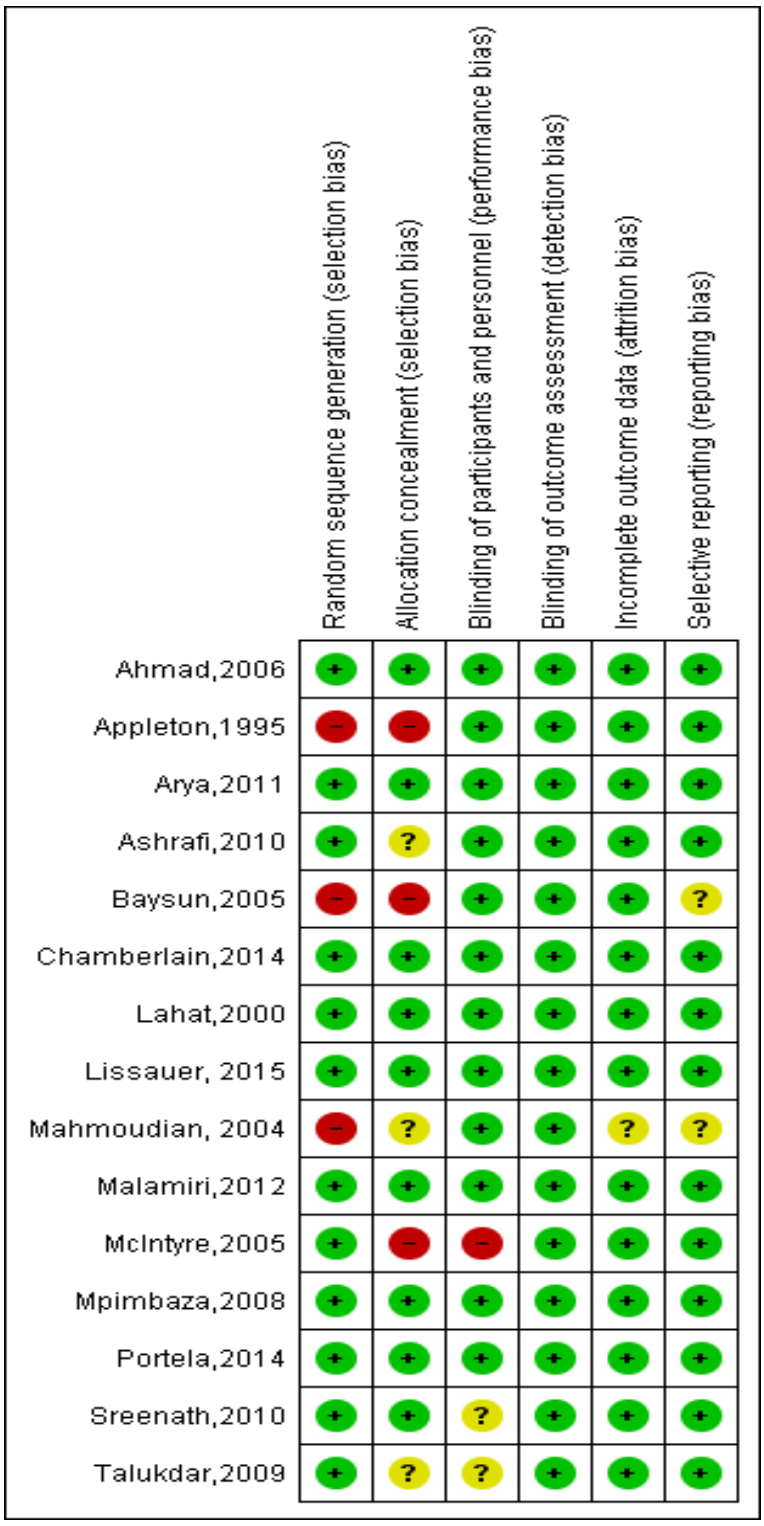
Table 4. 1:Reasons for exclusion from the systematic review

Reason	Total
Irrelevant article	1265
Review, conference, survey	552
Studies in Turkish and Japanese	8
Studies not looking at safety outcomes	1
Studies reporting the safety but the data for children not described separately	1
Total	**1827**

4.3.1 Quality assessment

The 25 studies that remained after screening were assessed; 15 RCTs with the Cochrane risk of bias tool [58] and 9 observational studies (4 prospective and 5 retrospective studies) with STROBE tool [60]. Eight RCTs were rated low-risk for all criteria [65-72]. The method of randomisation was inadequately described in 3 studies [73, 74, 76]. In 3 RCTs, the risk of bias in the allocation concealment was high [73, 76, 78]. One RCT was rated high-risk in blinding of participants and personnel [78] (Figure 4.2). None of these RCTs were excluded from the systematic review. None of the observational studies (prospective and retrospective studies) were excluded. All studies were of sufficiently good quality for inclusion. There were no quality tools to assess the case report/series and determine the quality of these types of studies.

Figure 4. 2: Risk of bias summary



4.3.2 The study descriptions

Twenty-five studies were included; 15 were randomised controlled trials [65-74, 76, 78-81], 9 were cohort studies [51, 82, 84, 95-100] and one case series[101]. These studies involved more than 2,000 children aged from birth to 18 years. Most of the children were treated with lorazepam (1263, 42%) (Table 4.2).

Table 4. 2: Antiepileptic drugs used in 25 studies

Anti-epileptic drug used	No. of studies (N =25)*	No. of children (N = 2983)*
Lorazepam	7	1263
Diazepam	10	551
Midazolam	9	418
Levetiracetam	4	243
Paraldehyde	2	93
Diazepam + phenytoin	1	88
Sodium valproate	3	60
Phenobarbital	1	30

*** Some children and studies accounted more than once**

Of the 25 studies that monitored AEs, 19 reported more than one AE. The other 6 studies reported none (Table 4.3 and 4.4). A total of 203 AEs were reported, mainly associated with lorazepam (65 AEs) and diazepam (53 AEs). The most common AE reported was respiratory depression (101 children), mainly reported with diazepam (46 children) and lorazepam (38 children) (Table 4.5).

Table 4. 3: Summary of 19 studies that reported AEs

Reference	Study design (no. of study)	Age (Y)	No. of children	No. of AEs
Midazolam vs diazepam	Open label RCT (2) Single blind RCT (2)	0.2-14	MDZ (Buccal): 280 MDZ (IM): 16 DZP (PR): 270 DZP (IV): 16 **Total: 592**	MDZ (Buccal): 8 MDZ (IM): 1 DZP (PR): 9 DZP (IV): 7 **Total: 25**
Lorazepam vs diazepam	Open label RCT (1) Double blind RCT (1) Prospective non randomised (1)	0.1<18	LZP (IV): 191 LZP (PR): 6 DZP (IV): 174 DZP (PR): 19 **Total: 390**	LZP (IV): 30 LZP (PR): 0 DZP (IV): 33 DZP (PR): 1 **Total: 64**
Lorazepam vs diazepam + PHT	Open label RCT (1)	1-12	LZP (IV): 90 DZP+PHT (IV): 88 **Total: 178**	LZP (IV): 4 DZP+PHT (IV): 5 **Total: 9**
Lorazepam vs paraldehyde	Open label RCT (1)	0.2-12	LZP (IN): 80 Paraldehyde (IM): 80 **Total: 160**	LZP (IN): 29 Paraldehyde (IM): 21 **Total: 50**
Lorazepam vs Lorazepam	Open label RCT (1)	6-14	IV: 70 IN: 71 **Total: 141**	IV: 2 IN: 0 **Total: 2**
Valproate vs phenobarbital	Double blind RCT (1)	3-18	VAP (IV): 30 PB (IV): 30 **Total: 60**	VAP (IV): 7 PB (IV): 22 **Total: 29**
Diazepam vs diazepam	Retrospective non randomised (1)	0.1-15	PR: 48 IV: 33 **Total: 81**	PR & IV: 3
Levetiracetam	Prospective (2) Retrospective (2)	38 weeks-18 Y	243 (IV)	8
Valproate	Retrospective (2)	< 9.6	30 (IV)	10
Paraldehyde	Case series	0.2-17	IV: 9 PR: 3 Both routes: 1 **Total: 13**	IV: 3 PR: 0 Both routes: 0 **Total: 3**

Table 4. 4: Summary of six studies that reported no AEs

Reference	Study design (no. of study)	Age (Y)	No. of children
Midazolam vs diazepam	Open label RCT (3) Single blind RCT (1)	0-15	MDZ (Buccal): 109 MDZ (IN): 56 DZP (PR): 49 DZP (IV): 118 **Total: 332**
Lorazepam vs Lorazepam	Open label RCT (1)	0.2-14	IV: 264 Buccal: 252 IN: 245 **Total: 761**
Midazolam	Prospective (1)	0.9-12	IN: 20

Table 4. 5: Reported AEs from 19 studies

Body system	ADRs	LZP	DZP	MDZ	Others	Total
Respiratory	Respiratory depression	38*	46	7	DZP+PHT (5) Paraldehyde (4)* PB (1)	101
Cardiovascular	Hypotension	27	-	1	Paraldehyde (20) VAP (2)	50
CNS	Lethargy	-	-	-	PB (17) VAP (3)	20
	Behavioural changes	-	-	-	LEV (7)	7
	Hyperactivity	-	2	-	-	2
	Somnolence	-	-	-	VAP (2)	2
Others	Nausea & vomiting	-	3	-	VAP (5) PB (4)	12
	Salivation	-	2	-	-	2
	↑ Ammonia	-	-	-	VAP (2)	2
	Abnormal LFTs	-	-	-	VAP (1)	1
	Purities	-	-	1	-	1
	Thrombocytopenia	-	-	-	VAP (1)	1
	Leukopenia	-	-	-	VAP (1)	1
	Pain at injection site	-	-	-	LEV (1)	1
Total		**65**	**53**	**9**	**76**	**203**

*** Include three cases of hypoxia; two with lorazepam (LZP) and one with paraldehyde**

4.3.2.1 Evidence from RCTs

Fifteen randomised controlled trials published between 1995 and 2015 were analysed, including 10 open-label studies [66, 69, 71-74, 76, 78, 79, 81], 3 single-blind studies [65, 68, 80], and 2 double-blind studies [67, 70]. All of these were 2-armed clinical trials except 2 studies – one of these had 3 arms [71] and the other had 4 arms [76]. Eight studies compared midazolam and diazepam. All randomised control trials included were conducted solely in the paediatric population (Table 4.6).

Table 4. 6: Randomised controlled studies characteristics

Study characteristics	No. of studies (N = 15)	No. of children (N = 2548)
Type of blinding		
Open label	10	1733
Single blinded	3	482
Double blinded	2	333
Antiepileptic drugs compared		
Midazolam vs. diazepam	8	914
Lorazepam vs. diazepam	2	334
Lorazepam vs. paraldehyde	1	160
Lorazepam vs. diazepam + phenytoin	1	178
Intravenous lorazepam vs. intranasal lorazepam	1	141
Intravenous lorazepam vs. intranasal & buccal LZP	1	761
Sodium valproate vs. phenobarbital	1	60

A. Midazolam versus diazepam

Eight studies compared the safety between midazolam and diazepam; they involved over 800 children (466 on midazolam) aged between birth and 14 years old; five were open-label [66, 73, 74, 78, 79] and three single-blinded [65, 68, 80]. Four studies documented one or more AE(s) [65, 68, 73, 78], and four studies did not report any AEs in either group [66, 74, 79, 80] (Table 4.7).

Table 4. 7: Summary of four studies that did not report AEs

Reference, country	Study design	Age (Y)	No. of children	AEDs	Dose (mg/kg)
Ashrafi et al., 2010, Iran [79]	Open label RCT	0-12	49 49	MDZ DZP	0.3-0.5 BUC 0.5 PR
Talukdar et al, 2009, India, [80]	Single blind RCT	< 12	60 60	MDZ DZP	0.2 BUC 0.3 IV
Mahmoudian and Zadeh, Mohammadi, 2004, Iran [74]	Open label RCT	0.2-15	35 35	MDZ DZP	0.2 (IN) 0.2 (IV)
Lahat et al., 2000, Israel [66]	Open label RCT	0.6-12	21 (26 episodes) 23 (26 episodes)	MDZ DZP	0.2 (IN) 0.3 (IV)

A.1. Buccal midazolam versus rectal diazepam

Three studies compared the safety of buccal midazolam to rectal diazepam in more than 500 children aged between birth and 15 years. Two were open-label [73, 78] and one was single-blind[65].

The randomisation sequences, allocation concealment and definitions used in these three studies for convulsive status epilepticus and effective treatment were described in the previous chapter (the effectiveness of AEDs for CSE).

McIntyre et al. (2005) conducted a three-year, multicentre randomised controlled, open-label study in 177 children who attended an emergency department with active convulsions in the UK [78]. The safety outcome was the incidence of respiratory depressions within 1 hour of the initial dose of the study medications. The oxygen saturation and respiratory rate were documented at 5, 15 and 40 minutes of the initial dose of the study medications. The authors defined respiratory depression as a decrease of oxygen level or respiratory rate which leads to oxygen supply either by using face-mask inflation or intubation after the initial dose of the study medications.

Baysun et al. (2005) performed a prospective, single-centre study in Turkey involving 43 children aged between 2 months and 12 years with acute tonic clonic seizures [73]. They did not specify the safety outcomes in the methods. However, respiratory rate, heart rate and blood pressure were recorded at 5 and 10 minutes after the administration of the study medications. The definition of respiratory depression was not specified by the authors.

Mpimbaza et al. (2008) assessed buccal midazolam against rectal diazepam in 330 children, aged between 3 months and 12 years, who attended an emergency department with prolonged seizures [65]. This was an eight-month, single-blind, single-centre study in Uganda. The safety outcome was the incidence of respiratory depression after the administration of the AEDs. The peripheral oxygen saturation was recorded at 0, 5, 10, 20, 40 and 60 minutes after the administration of the study medications. Respiratory definition was defined as a fall in oxygen saturation to < 92% or a decrease in respiratory efforts which needs breathing to be supported.

Eight of the 280 children who received buccal midazolam experienced AEs; 7 cases of respiratory depression and one case of pruritus. Nine of the 270 children who received rectal diazepam experienced respiratory depression. The total incidence of AEs was similar between the two groups (3% midazolam and 3.3% diazepam). The difference was not significant (RR: 0.84; 95% CI: 0.33 to 2.12; p = 0.7) (Table 4.8).

The incidence of respiratory depression was lower with buccal midazolam in two studies [73, 78] and higher in the other study [65]. None of the differences were significant (Table 4.8). The pooled risk ratio showed no significance between the two groups (RR: 0.73; 95% CI: 0.28 to 1.91; p= 0.52).

One study reported pruritus as an AE with midazolam [65] (Table 4.8).

Admission to intensive care unit was documented in one study [78]. Two of the 92 children (2%) who received buccal midazolam were admitted to ICU due to respiratory depression compared to three of the 85 children (3.5%) who received rectal diazepam (RR: 0.62; 95% CI: 0.11 to 3.6; p= 0.59).

The mortality rate was documented in one study [65]. Eight of the 165 children (5%) who received buccal midazolam died compared to 12 of the 165 children (7%) who were treated with rectal diazepam (RR: 0.67; 95% CI: 0.28 to 1.59; p= 0.35). However, all the deaths were documented to be due to status epilepticus itself (Table 4.8).

In summary, the three studies showed no difference in the toxicity between buccal midazolam and rectal diazepam. The incidence of respiratory depression was 3-3.3%.

Table 4. 8: Buccal midazolam versus rectal diazepam

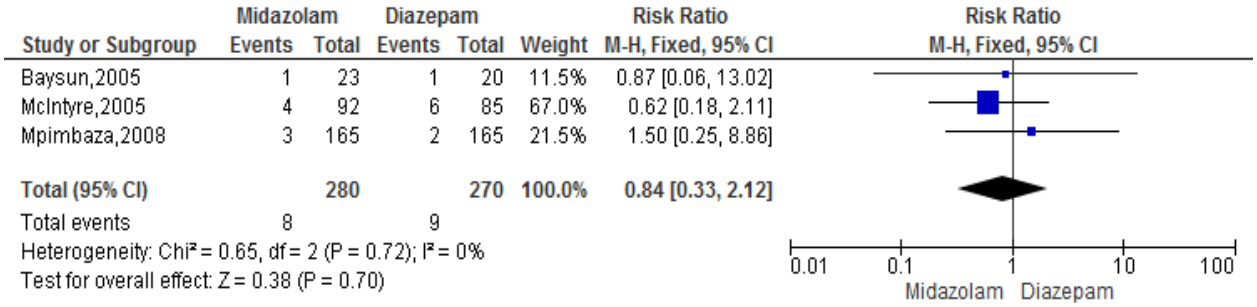
Reference, country	Study design	Age (Y)	No. of children	AEDs	Dose (mg/kg)	All AEs (No. of children, %) RR (95% CI) *P-value*		Resp. depression (No. of children, %) RR (95% CI) *P-value*		Other AEs (No. of children, %) RR (95% CI) *P-value*		ICU admission (No. of children) RR (95% CI) *P-value*		Deaths (No. of children) RR (95% CI) *P-value*	
						MDZ*	**DZP***	**MDZ**	**DZP**	**MDZ**	**DZP**	**MDZ**	**DZP**	**MDZ**	**DZP**
McIntyre et al, 2005, UK [78]	Open label RCT	0.7-15	92 85	MDZ DZP	0.5 BUC 0.5 PR	4 (4%) 0.62 (0.18-2) *p = 0.44*	6 (7%)	4 (4%) 0.62 (0.18-2) *p = 0.44*	6 (7%)	0	0	(2) 0.62 (0.11-3.6) *p = 0.59*	(3)	***Data not available***	
Baysun et al, 2005, Turkey [73]	Open label RCT	0.2-12	23 20	MDZ DZP	0.25 BUC 0.3-0.5 PR	1 (4%) 0.87 (0.06-13) *p = 0.92*	1 (5%)	1 (4%) 0.87 (0.06-13) *p = 0.92*	1 (5%)	0	0	***Data not available***		***Data not available***	
Mpimbaza et al 2008, Uganda [65]	Single blind RCT	0.3- 12	165 165	MDZ DZP	0.5 BUC 0.5 PR	3 (2%) 1.5 (0.25-8.9) *p = 0.65*	2 (1%)	2 (1%) 1 (0.14-7) *p = 1*	2 (1%)	1 (0.6%)[88**] 3 (0.12-73.1) *p = 0.5*	0	***Data not available***		(8) 0.67 (0.28-1.6) *p = 0.35*	(12)
Total	3	0.3-15	280 270	MDZ DZP	0.25- 0.5 BUC 0.3-0.5 PR	8 (3 %) 0.84 (0.33-2.12) *p = 0.7*	9 (3.3%)	7 (3%) 0.73(0.28-1.91) *p = 0.52*	9 (3.3%)	1 (0.6%)** 3 (0.12-73.1) *p = 0.5*	0	(2) 0.62 (0.11-3.6) *p = 0.59*	(3)	(8) 0.67 (0.28-1.6) *p = 0.35*	(12)

*** MDZ: Midazolam, DZP: Diazepam**

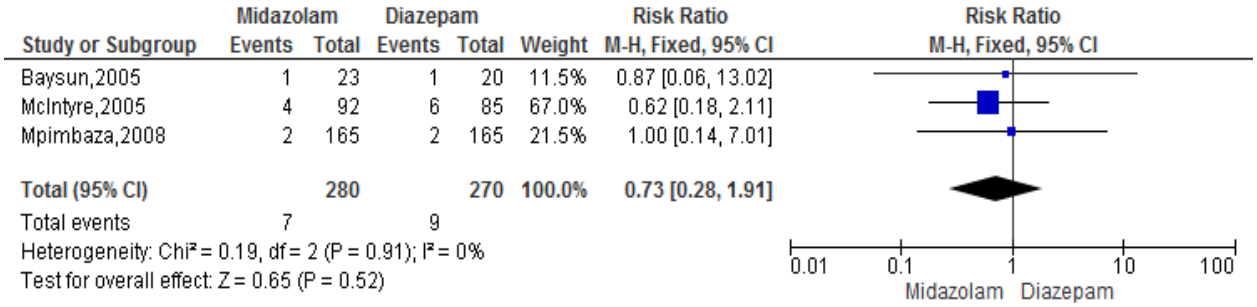
**** Pruritus**

Figure 4. 3: The safety of buccal midazolam versus rectal diazepam

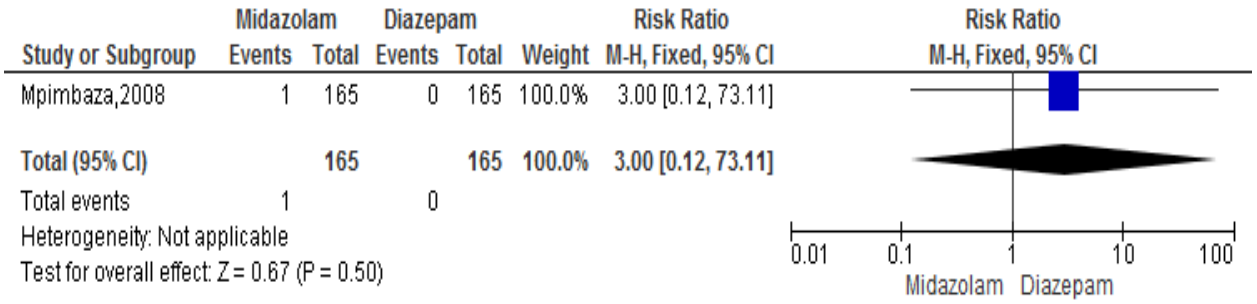
1. All AEs



2. Respiratory depression



3. Pruritus



4. ICU

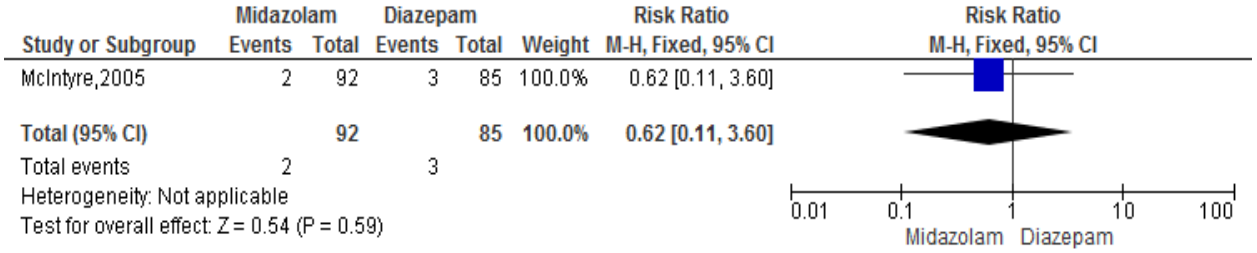
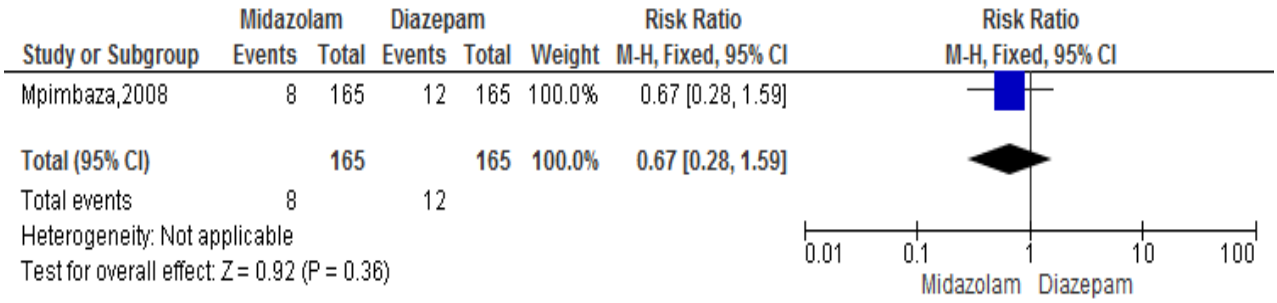


Figure 3.4: The safety of buccal midazolam versus rectal diazepam (continue..)

5. Deaths



A.2. Intramuscular midazolam versus intravenous diazepam

Portela et al. (2014) conducted a single-centre randomised controlled, single-blind study in Brazil involving 32 children aged between 2 months and 14 years[68]. The randomisation sequences, allocation concealment, convulsive status epilepticus definition and treatment successful definition for this study were described in the previous chapter (the effectiveness of AEDs for CSE).

The authors did not specify the safety outcome however; any AEs were assessed in the first 10 minutes after drug administration. The following parameters were monitored from admission and every 5 minutes thereafter until seizure cessation and discharge; heart rate and oxygen level by pulse oximetry. The definition of respiratory depression was not given.

One of the 16 children who received intramuscular midazolam experienced hypotension. Seven of the 16 children who received intravenous diazepam experienced AEs; 2 cases each of hyperactivity, vomiting and salivation and one case of nausea. The incidence of any AE was lower following intramuscular midazolam (6%) than

intravenous diazepam (44%); borderline statistically significant (RR: 0.14; 95% CI: 0.02 to 1.03; p = 0.05) (Table 4.9).

No children in either group required ICU admission and there were no reported cases of death.

In summary, there was a borderline statistical difference in the risk of all AEs, favouring intramuscular midazolam.

Table 4. 9: Intramuscular midazolam versus intravenous diazepam

Reference, country	**Study design**	**Age (Y)**	**No. of children**	**AEDs**	**Dose (mg/kg)**	**All AEs (No. of children, %)** **RR (95% CI)** ***P-value*** **MDZ DZP**	**Hyperactivity (No. of children, %)** **RR (95% CI)** ***P-value*** **MDZ DZP**	**Vomiting (No. of children, %)** **RR (95% CI)** ***P-value*** **MDZ DZP**	**Hypotension (No. of children, %)** **RR (95% CI)** ***P-value*** **MDZ DZP**	**Salivation (No. of children, %)** **RR (95% CI)** ***P-value*** **MDZ DZP**	**Nausea (No. of children, %)** **RR (95% CI)** ***P-value*** **MDZ DZP**
Portela et al, 2014, Brazil [68]	Single blind RCT	0.2-14	16 16	MDZ DZP	0.5 IM (max. 15mg) 0.5 at 5mg/min IV (max. 10mg)	1 (6%) 7 (44%) 0.14 (0.02-1.03) *p = 0.05*	0 2 (13%)* 0.29 (0.01-3.86) *p = 0.29*	0 2 (13%) 0.29 (0.01-3.86) *p = 0.29*	1 (6%) 0 3 (0.13-86.57) *p = 0.49*	0 2 (13%)* 0.29 (0.01-3.86) *p = 0.29*	0% 1 (6%) 0.33 (0.01-7.62) *p = 0.49*
Total	1	0.2-14	16 16	MDZ DZP	0.5 IM (max. 15mg) 0.5 at 5mg/min IV (max. 10mg)	1 (6%) 7 (44%) 0.14 (0.02-1.03) *p = 0.05*	0 2 (13%)* 0.29 (0.01-3.86) *p = 0.29*	0 2 (13%) 0.29 (0.01-3.86) *p = 0.29*	1 (6%) 0 3 (0.13-86.57) *p = 0.49*	0 2 (13%)* 0.29 (0.01-3.86) *p = 0.29*	0 1 (6%) 0.33 (0.01-7.62) *p = 0.49*

MDZ: midazolam, DZP: diazepam
*** Same children**

B. Lorazepam versus diazepam

Two studies that compared the safety between lorazepam and diazepam involved over 300 children; one was open label [76], and one was double-blind [70].

Respiratory depression was the only AE reported in both studies. It was most common in children who received intravenous diazepam (33 children).

B.1.Lorazepam (IV) versus diazepam (IV)

Two studies compared the safety of intravenous lorazepam to intravenous diazepam, they recruited a total of 334 children aged between one month and <18 years.

The randomisation sequences, allocation concealment, convulsive status epilepticus definition and treatment successful definition for these studies were described in the previous chapter (4); section (2, I).

Appleton et al. (1995) conducted a 12-month, single-centre, randomised, open-label study of 61 children aged between one month and 16 years who attended the emergency department with an acute tonic-clonic convulsion[76].

The safety outcome was the incidence of respiratory depression. The authors defined respiratory depression as requiring oxygen by using face-mask inflation or a decrease of respiratory effort and rate following seizure termination.

In the second study, Chamberlain and colleagues assessed 273 children, aged from 3 months through 17 years. One hundred and forty patients were given diazepam and 133 lorazepam [70]. This was a 4-year, double-blind, randomised clinical trial conducted in the U.S. at 11 paediatric hospitals. The primary safety outcome was any respiratory

depression within 10 minutes of the initial dose of the study medications. Respiratory depression was defined as a decrease in the respiratory effort and rate which led to oxygen supply. The secondary outcomes were incidences of aspiration pneumonia, time to recover consciousness, and incidence of sedation and agitation.

Twenty-seven of the 160 children who received intravenous lorazepam experienced respiratory depression. Thirty-three of the 174 children who received intravenous diazepam experienced respiratory depression. The total incidence of respiratory depression was slightly lower with intravenous lorazepam (17%) than intravenous diazepam (19%), however, the difference was not statistically significant (RR: 0.57; 95% CI: 0.11 to 3.07; p = 0.52) (Table 4.10).

The data of other AEs and mortality rate were not reported.

ICU admission was reported in one study[76]. Only children on intravenous diazepam were admitted to ICU due to the respiratory depression (8/34 children; RR: 0.07; 95% CI; 0 to 1.22; p = 0.07) (Table 4.10).

In summary, these two studies showed no difference in the incidence of respiratory depression. However, no children on intravenous lorazepam were admitted to ICU due respiratory depression. The incidence of respiratory depression was 17-19%.

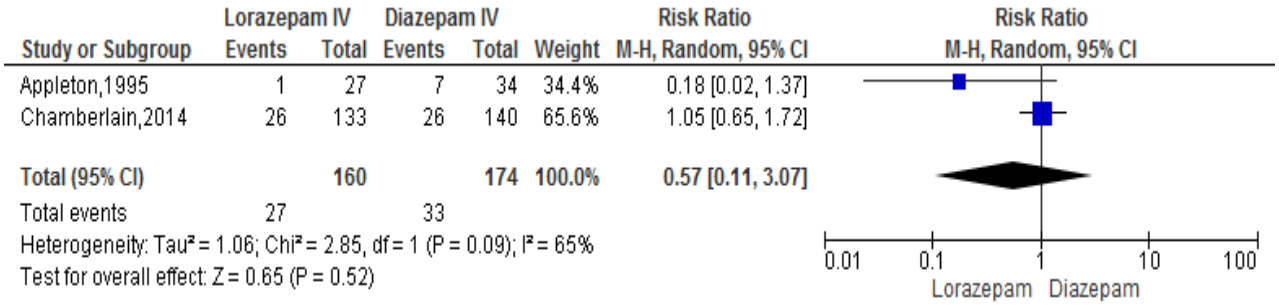
Table 4. 10: Intravenous lorazepam vs intravenous diazepam

Reference, country	**Study design**	**Age (Y)**	**No. of children**	**AEDs**	**Dose (mg/kg)**	**Respiratory depression (No. of children, %)** **RR (95% CI)** ***P-value*** **LZP** **DZP**	**ICU admission (No. of children)** **RR (95% CI)** ***P-value*** **LZP** **DZP**
Appleton et al, 1995, UK [76]	Open label Quasi-RCTs	0.1-16	27 34	Lorazepam Diazepam	0.05-0.1 (IV) 0.3-0.4 (IV)	1 (4%) 7 (21%) 0.18 (0.02 – 1.39) *p = 0.1*	0 8 0.07 (0 – 1.22) *p = 0.07*
Chamberlain et al., 2014, USA [70]	Double blind RCT	0.3-<18	133 140	Lorazepam Diazepam	0.1 (IV), 4 mg max. 0.2 (IV), 8 mg max.	26 (20%) 26 (19%) 1.05 (0.65 – 1.72) *p = 0.84*	***Data was not available***
Total		0.1<18	160 174	LZP DZP	0.05-0.1 (IV) Max 4 mg 0.2-0.4 (IV) Max. 8 mg	27 (17%) 33 (19%) 0.53 (0.14 – 2.03) *p = 0.35*	0 8 0.07 (0 – 1.22) *p = 0.07*

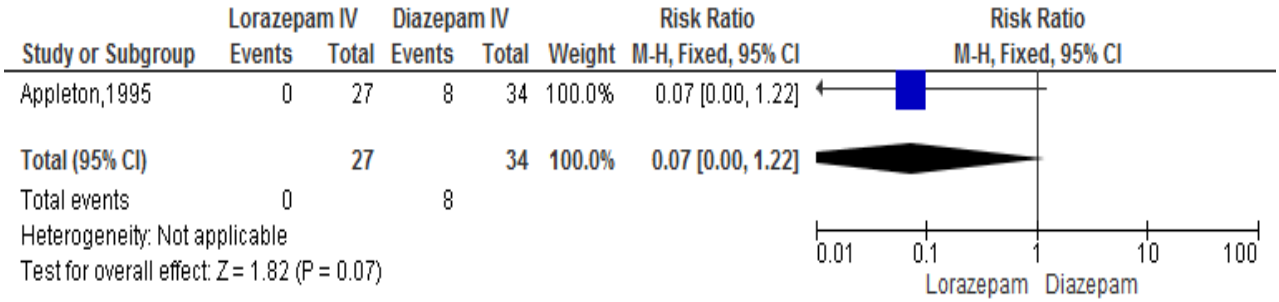
LZP: Lorazepam, DZP: Diazepam

Figure 4. 4: The safety of lorazepam (IV) compared with diazepam (IV)

1. **Respiratory depression**



2. **ICU admissions**



B.2. Lorazepam (PR) versus diazepam (PR)

The study by Appleton et al. (1995) also compared rectal lorazepam and rectal diazepam in 25 children (a concurrent portion of this study, that examined intravenous lorazepam vs. intravenous diazepam, was described in the previous section) [18]. Six children received lorazepam and 19 received diazepam.

Respiratory depression was only documented in one child treated with diazepam. A RR of 0.95 (95% CI: 0.04 to 20.78, p = 0.98), and he was admitted to ICU (RR: 0.57; 95% CI: 0.03 to 10.51, p = 0.71) (Table 4.11)

The data of other AEs and mortality rate were not reported. This study showed no statistical difference in the incidence of respiratory depression between lorazepam and diazepam.

Table 4. 11: Lorazepam (PR) versus diazepam (PR) in one study

Reference, country	Study design	Age (Y)	No. of children	AEDs	Dose (mg/kg)	Respiratory depression (No. of children, %) RR (95% CI) *P-value* LZP DZP	ICU admissions (No. of children) RR (95% CI) *P-value* LZP DZP
Appleton et al., 1995, UK [76]	Open label Quasi-RCT	0.1-16	6 19	LZP DZP	0.05-0.1 (PR) 0.3-0.4 (PR)	0 1 (5%) 0.95 (0.04 – 20.78) *p = 0.98*	(0) (1) 0.57 (0.03 - 10.51) *p = 0.71*

LZP: Lorazepam, DZP: Diazepam

C. Lorazepam versus paraldehyde

Shafique and colleagues conducted a 12-month, single-centre, randomised, open-label study in sub-Saharan Africa to compare intranasal lorazepam and intramuscular paraldehyde [14]. One hundred and sixty children aged 2 months to 12 years who attended the paediatric emergency department with generalized convulsions continuing for at least 5 minutes were included.

The randomisation sequences, allocation concealment, convulsive status epilepticus definition and treatment successful definition were described in the previous chapter.

The safety outcomes were the incidence of hypotension or hypoxia. Hypotension was defined as a reduction of 5 mm Hg or more for systolic and diastolic pressure. Hypoxia was defined as oxygen saturation (SpO2) level of <92% within 30 minutes of drug administration.

Twenty-eight of the 80 children who received intranasal lorazepam experienced 29 AEs; 27 cases suffered from hypotension and two from hypoxia (i.e. one child had 2 AEs).

Twenty-one of the 80 children who received intramuscular paraldehyde experienced AEs; 20 hypotension and one hypoxia. The total incidence of any AE following treatment with intranasal lorazepam was higher (35%) than with intramuscular paraldehyde (26%), but not statistically different (RR: 1.33; 95% CI: 0.83 to 2.14; p = 0.23) (Table 4.12).

The total incidence of hypotension was higher in the lorazepam group (34%) than the paraldehyde group (25%). Meta-analysis did not reveal any significant difference between the two groups (RR: 1.35, 95% CI: 0.83 to 2.2; p = 0.23) (Table 4.12).

The risk of hypoxia was 2 times greater with lorazepam than paraldehyde. However, our meta-analysis showed no significant difference between the two groups (95% CI: 0.19 to 21.62; p= 0.57) (Table 4.12).

The data of other AEs, mortality rate and ICU admissions due to AEs were not reported.

In summary, children receiving intranasal lorazepam as opposed to intramuscular paraldehyde were seen more often to have hypotension and hypoxia, however, this difference was not statistically significant.

Table 4. 12: Lorazepam (intranasal) vs paraldehyde (intramuscular) in one study

Reference, country	Study design	Age (Y)	No. of children	AEDs	Dose	All AEs (No. of children, %) RR (95% CI) *P-value* LZP Paraldehyde	Hypotension (No. of children, %) RR (95% CI) *P-value* LZP Paraldehyde	Hypoxia (No. of children, %) RR (95% CI) *P-value* LZP Paraldehyde
Shafique et al., 2006, sub-Saharan Africa [72]	Open label RCT	0.2-12	80 80	LZP Paraldehyde	100 µg/kg (IN) 0.2 ml/kg (IM)	28 (35%) 21 (26%) 1.33 (0.83 – 2.14) *P = 0.23*	27 (34%) 20 (25%) 1.35 (0.83 – 2.2) *P = 0.23*	2 (3%) 1 (1%) 2 (0.19 – 21.62) *p = 0.57*

LZP: Lorazepam

D. Intravenous lorazepam versus intravenous diazepam plus phenytoin (IV)

A 2010 study compared the intravenous use of lorazepam with an intravenous combination of diazepam and phenytoin in a tertiary hospital in India [1]. The study was randomised and open-label. Phenytoin was given, 15 to 30 minutes after diazepam administration, even if seizures had not recurred. The study recruited 178 children aged between 1 and 12 years with convulsive status epilepticus lasting for at least 5 minutes. If IV access could not be obtained, the same dose of lorazepam and diazepam was given rectally.

The safety outcome was incidence of respiratory depression. Respiratory depression was defined as a decrease in the respiratory effort and rate following the seizure termination, which needs oxygen supply or oxygen saturation less than 92%.

Four of the 90 children who received intravenous lorazepam experienced respiratory depression compared to 5 of the 88 children who received the intravenous combination of diazepam and phenytoin. The total incidence of respiratory depression was slightly lower with intravenous lorazepam (4%) than intravenous diazepam (6%), but not statistically significant (RR: 0.78; 95% CI: 0.22 to 2.82; p = 0.71) (Table 4.13). There were no cases required ICU admissions for mechanical ventilation due to respiratory depression.

The data of other AEs and mortality rate were not reported.

In summary, intravenous lorazepam was seen less often to be associated with respiratory depression compared to the intravenous combination of diazepam and phenytoin; however, this difference was not statically significant.

Table 4. 13: Intravenous lorazepam versus intravenous diazepam plus phenytoin

Reference, country	Study design	Age (Y)	No. of children	AEDs	Dose (mg/kg)	Respiratory depression (No. of children, %) RR (95% CI) *P-value* LZP	DZP+PHT
Sreenath et al., 2010, India [81]	Open label RCT	1–12	90 88	LZP DZP+PHT	0.1 (IV) 0.2 + 18/15–30 min (IV)	4 (4%) 0.78 (0.22–2.82) *P = 0.71*	5 (6%)

LZP: Lorazepam, DZP: Diazepam, PHT: Phenytoin

E. Intravenous lorazepam versus intranasal lorazepam

Two open-label studies compared the safety of intravenous and intranasal lorazepam; they involved over 600 children (334 on intravenous lorazepam) aged between 2 months and 14 years. Of these, one study reported two AEs for intravenous lorazepam[69] while the other study did not report AEs in either group (Table 4.14) [71].

Table 4. 14: Summary of study that did not report AEs

Reference, country	Study design	Age (Y)	No. of children	AEDs	Dose (mg/kg)
Lissauer et al. ,2015, Malawi [71]	Open label	0.2-14	264 245	LZP LZP	0.1 (IV) 0.1 (IN)

Arya et al. (2011) conducted the 7-month, randomised, open-label, single-centre study in India [11]. The researchers recruited 141 children aged between 6 and 14 years who attended the emergency department with an acute tonic-clonic convulsion and compared the administration of intravenous versus intranasal lorazepam. The safety outcomes were hypotension within 1 hour of the drug's administration and incidence of respiratory depression needing ventilation.

Two of the 70 children (3%) who received intravenous lorazepam experienced respiratory depression. There were no other AEs reported in either group (Table 4.15).

The intranasal route appeared to be safer than the intravenous route in terms of respiratory depression; however, the difference was not significant (p = 0.29).

Table 4. 15: Intravenous lorazepam versus intranasal lorazepam

Reference, country	**Study design**	**Age (Y)**	**No. of children**	**AED**	**Dose (mg/kg)**	**Respiratory depression (No. of children, %)** **IV** **IN**	**RR (95% CI)** ***P-value***
Arya et al., 2011, India [69]	Open label	6-14	70 71	LZP LZP	0.1 (IV), 4 mg max. 0.1/30-60 sec (IN)	2 (3%) 0	5.07 (0.25-103.76) *p = 0.29*

F. Intravenous lorazepam versus buccal lorazepam

The Lissauer study described in the previous section (intravenous vs. intranasal lorazepam) also compared intravenous versus buccal lorazepam [13]. No children had respiratory depression nor required ventilation. The other AEs were not reported.

Forty-seven (18%) of the 264 children received intravenous lorazepam and died compared to 39 (15.5%) of the 252 children treated with buccal lorazepam (RR: 1.15; 95% CI: 0.78 to 1.7; p = 0.48) (Table 4.16). However, it was documented to be due to status epilepticus itself.

Table 4. 16: Intravenous lorazepam versus buccal lorazepam

Reference, country	**Study design**	**Age (Y)**	**No. of children**	**AED**	**Dose (mg/kg)**	**Deaths (No. of children, %)**		**RR (95% CI)** ***P-value***
						IV	**BUC**	
Lissauer et al. ,2015, Malawi [71]	Open label	0.2-14	264 252	LZP LZP	0.1 (IV) 0.1 (BUC)	47 (18%)	39 (15.5%)	1.15 (0.78-1.7) *p = 0.48*

G. Valproate versus phenobarbital

An Iranian study compared intravenous valproate to intravenous phenobarbital in the treatment of acute prolonged seizures at 2 centres in 2012 [67]. This randomised, double-blind study took place over 2 years. It involved 60 children aged between 3 and 16 years who attended the emergency room with seizures lasting more than 5 minutes, that had not been controlled by intravenous diazepam (0.2mg/kg).

The following parameters were measured from the starting of treatment to seizure termination: pulse, blood pressure, respiratory effort (before treatment, at the end of treatment and at 5, 10, 20, and 30 minutes after starting treatment), and electrocardiogram baselines. Children who experienced hypotension or cardiac dysrhythmias were excluded and treatment was stopped. The authors did not define the respiratory depression, hypotension, and cardiac dysrhythmia.

Seven of the 30 children who received intravenous valproate experienced 7 AEs; 3 cases each of lethargy and vomiting and one case of hypotension. By contrast, 22 of the 30 children who received phenobarbital experienced 22 AEs; 17 cases of lethargy, 4 cases of vomiting, and one case of respiratory depression (Table 4.17).

The total incidence of AEs following treatment with intravenous valproate was significantly lower (23%) than those following treatment with intravenous phenobarbital (73%) (RR: 0.32; 95% CI: 0.16 to 0.63; p = 0.001).

Lethargy was the most common AE reported in both groups, with a lower occurrence in the valproate group (3 children, 10%) compared to the phenobarbital group (17 children,

57%). This was a statistically significant difference (RR: 0.18, 95% CI: 0.06 to 0.54, p = 0.002).

Vomiting was the second most common AE, with a similar occurrence between both groups, 10% in the valproate group and 13% in the phenobarbital group (RR: 0.75, 95% CI: 0.18 to 3.07, p = 0.69).

Respiratory depression was reported in one case of intravenous phenobarbital; however, it was not reported amongst the valproate group (RR: 0.33, 95% CI: 0.01 to 7.87, p = 0.5). Hypotension was only documented in one child treated with intravenous valproate with a risk ratio of 3 (95% CI: 0.13 to 70.83; p = 0.5).

The data for mortality and ICU admission due to AEs were not available (Table 4.17).

In summary, no child receiving intravenous valproate experienced respiratory depression as opposed to a single child receiving intravenous phenobarbital, the difference was not significant. However it appeared overall, when looking at all AEs, that valproate is significantly safer (p = 0.001).

Table 4. 17: Valproate (IV) versus phenobarbital (IV) in one study

Reference, country	**Study design**	**Age (Y)**	**No. of children**	**AED**	**Dose (mg/kg)**	**All AEs (No. of children, %)** **RR (95% CI)** ***P-value*** **VAP** **PB**	**Lethargy (No. of children, %)** **RR (95% CI)** ***P-value*** **VAP** **PB**	**Vomiting (No. of children, %)** **RR (95% CI)** ***P-value*** **VAP** **PB**	**Respiratory depression (No. of children, %)** **RR (95% CI)** ***P-value*** **VAP** **PB**	**Hypotension (No. of children, %)** **RR (95% CI)** ***P-value*** **VAP** **PB**
Malamiri et al. ,2012, India [67]	Double-blind RCT	3-16	30 30	VAP PB	20 at 5 - 6mg/min (IV) 20 at 60 - 100 mg/min (IV)	7 (23%) 22 (73%) 0.32 (0.16 – 0.63) *p = 0.001*	3 (10%) 17 (57%) 0.18 (0.06 – 0.54) *p = 0.002*	3 (10%) 4 (13%) 0.75 (0.18 – 3.07) *p = 0.69*	0 1 (3%) 0.33 (0.01 – 7.87) *p = 0.5*	1 (3%) 0 3 (0.13 – 70.83) *p = 0.5*

VAP: Valproate, PB: Phenobarbital

4.3.2.2 Evidence from prospective observational studies

Four prospective observational studies involved 156 children aged between 2 months and 18 years; one compared 2 AEDS (lorazepam and diazepam) [84]. All included studies, except one [99], were conducted solely in the paediatric population. Levetiracetam was the most frequently studied drug (Table 4.18). Seven AEs were reported; 4 were associated with intravenous levetiracetam. Respiratory depression that resulted in PICU admission was reported in 3 children who were administered intravenous lorazepam.

Table 4. 18: Prospective observational studies characteristics

Study characteristics	No. of studies (N = 4)*	No. of children (N = 156)*
Antiepileptic drugs used		
levetiracetam	2	88
diazepam	1	17
lorazepam	1	31
midazolam	1	20

*** Some children and studies accounted more than once.**

The first of the these four studies was a prospective, comparative, non-randomised study conducted in the UK by Wassmer and colleagues which compared intravenous lorazepam and intravenous diazepam [84]. This study involved 48 children aged 5 months to 11 years with convulsive status epilepticus.

Of these 48 children, 31 received intravenous lorazepam and 17 intravenous diazepam. AEs were reported in 3 children (10%) who experienced respiratory depression after

receiving intravenous lorazepam and were transferred to PICU. No other AEs were reported (Table 4.19).

The second observational study, conducted in the UK by McTague and colleagues evaluated the safety of intravenous levetiracetam [51]. This study involved 45 children who were aged between 2 months and 18.8 years (mean 7.1 years) with acute repetitive seizure or status epilepticus. Two children had non-convulsive status epilepticus and were excluded from the analysis. Three of 43 children exhibited changed, aggressive behaviour. The treatment was discontinued in one of these three children. There were no other AEs reported (Table 4.19).

The third study, conducted in the US by Wheless and colleagues evaluated the safety of intravenous levetiracetam [99]. This study involved 45 patients aged between 4 and 32 years (mean 14 years). One child aged 16 years with mental retardation experienced pain at the site of intravenous administration. The levetiracetam was discontinued and the child was removed from the study. No AEs were reported in the other children (Table 4.19).

The fourth study, conducted in the UK by Conroy and colleagues evaluated the safety of intranasal midazolam in 20 children aged 10 months to 12 years who attended the emergency department with seizures [100]. No AEs were reported in this study (Table 4.19).

Table 4. 19: The safety outcome in the prospective observational studies

Reference, country	Study design	Age (Y)	No. of children	AEDs	Dose (mg/kg) and route	All AEs	Respiratory depression	Behavioural change	Pain at the administration site	ICU admissions due to AEs
Wassmer et al, 2002, UK, [84]	Prospective comparative	0.5- 11	31	Lorazepam	0.1 IV	3	3	0	0	3
			17	Diazepam	0.3 IV	0	0	0	0	0
McTague, A., et al, 2012, UK[51]	Prospective	0.2-18.8 (Mean 7.1)	43	Levetiracetam	14.4 (median) IV	3	0	3	0	0
Wheless, J.W., et al, 2009, USA[99]	Prospective	4-32 (Mean 14)	45	Levetiracetam	20-60 IV	1	0	0	1	0
Conroy, S., et al, 2000, UK[100]	Prospective	0.9-12	20	Midazolam	0.2 IN	0	-	-	-	0

4.3.2.3 Evidence from retrospective observational studies

Five retrospective studies involved 266 children aged from birth to 18 years; one compared 2 routes (IV and PR diazepam) [82]. Levetiracetam was the most frequently studied drug (Table 4.20). Overall, seventeen AEs were reported; 10 were associated with intravenous valproate. Respiratory depression that resulted in PICU admission was reported in 3 children who were administered diazepam.

Table 4. 20: Prospective observational study characteristics

Study characteristics	No. of studies (N =5)*	No. of children (N = 266)*
Antiepileptic drugs used		
levetiracetam	2	155
diazepam	1	81
sodium valproate	2	30

*** Some children and studies accounted more than once.**

Garr and colleagues conducted a retrospective study to compare the effectiveness of rectal and intravenous diazepam, in children aged one month to 15 years with tonic-clonic convulsions in the UK [82]. This study involved 81 children, of whom 48 received rectal diazepam, while 33 received intravenous diazepam. The safety outcome was respiratory depression. Three of 81 children (4%) experienced respiratory depression and required admission to ICU; they all received two doses of diazepam in addition to rectal paraldehyde and intravenous phenytoin. Of these 3 children, one child received two doses of rectal diazepam and the authors did not state the route of administration for the other 2 children.

İşgüder and colleagues conducted a retrospective study to evaluate the effectiveness and safety of intravenous levetiracetam in Turkey [95]. This study involved 133 children aged one month to 18 years with acute repetitive seizures. Three of the 133 children (2%) experienced behavioural changes which resolved after dose reduction. No other AEs were reported.

Fallah and colleagues conducted a retrospective study in Iran to evaluate the effectiveness and safety of intravenous sodium valproate [97]. This study involved 11 children aged 3 to 9.6 years admitted to the emergency department with acute repetitive seizures. Two of the children (18%) experienced transient nausea and vomiting. There were no other AEs reported.

An American study conducted by Khan and colleagues compared the effectiveness and safety of intravenous levetiracetam in 22 neonates aged 37.5 to 41.2 weeks [96]. One child (5%) experienced irritability and subsequently received pyridoxine at 50 mg once daily.

The last study was conducted in Spain by Campistol and colleagues to evaluate the effectiveness and safety of intravenous sodium valproate [98]. This study involved 19 children aged less than 7 years. Seven of the 19 children (37%) experienced 8 AEs; two cases of hyperammonaemia, two cases of somnolence; one case of hypotension, and one case with abnormal liver function tests, thrombocytopenia and leukopenia. Intravenous valproate treatment was stopped in one child due to the abnormal liver function tests. None of the children were transferred to the ICU due to the AEs.

Table 4. 21: The safety outcome in the retrospective studies

Reference, country	Study design	Age (Y)	No. of children	AEDs	Dose (mg/kg) and route	All AEs	Hypotension	Respiratory depression	Behavioural change	Abnormal liver function tests	Others	ICU admissions due to AEs
Garr et al., 1999, UK, [82]	Retrospective comparative	0.1-15	48 33	Diazepam Diazepam	0.4 PR 0.4 IV	3	0	3	0	0	0	3
İşgüder, R., et al, 2014,Turkey [95]	Retrospective	0.1-18	133	Levetiracetam	10-20 over 15 min IV	3	0	0	3	0	0	0
Fallah et al., 2012, Iran [97]	Retrospective	3-9.6	11	Valproate	15 at 3mg/kg/min IV	2	0	0	0	0	Nausea and vomiting (2)	0
Khan et al., 2011, USA[96]	Retrospective	38-41 **weeks**	22	Levetiracetam	50 (20 pts) 20 (1 pt.) 10 (1 pt.) IV	1	0	0	1	0	0	0
Campistol et al., 1999, Spain [98]	Retrospective	0-7	19	Valproate	20 at 1mg/kg/hr IV	8	1	0	0	1	↑ Ammonia (2) Somnolence (2) Thrombocytopenia (1) leukopenia (1)	0

4.3.2.4 Case reports/series

This systematic review identified one case series which was reported by Curless and colleagues [101]. It discussed the effectiveness and safety of paraldehyde in 13 children aged from 2 months to 17 years, 9 children received the medicine intravenously and 3 rectally. One child received it by both routes .

Three of the children, with ages ranging from 7 months to 13 years, developed respiratory depression during or within a few minutes after receiving a loading dose of 0.3 ml/kg of intravenous paraldehyde. All these children were intubated and returned to normal breathing within one hour (Table 4.22).

One other child, aged one year, died. This was reported to be due to the status epilepticus.

Table 4. 22: Paraldehyde AEs in case series

Reference, country	Patient age (Y)	Dose of IV paraldehyde (ml/kg)	AE	Treatment
Curless et al. 1983, US [101]	13	2.5	Respiratory depression	Intubated
	2.4	0.35	Respiratory depression	Intubated
	0.7	0.3	Respiratory depression	Intubated

4.3.3 Respiratory depression

Respiratory depression is a serious AE. In the RCTs and prospective observational studies this occurred in 95 children. Table 4.23 showed the three most common AEDs associated with respiratory depression.

Table 4. 23: Respiratory depression in RCTs and prospective observational studies

Routes	**Midazolam** (No. of children experienced respiratory depression / No. of children receiving AEDs, %)	**Diazepam** (No. of children experienced respiratory depression / No. of children receiving AEDs, %)	**Lorazepam** (No. of children experienced respiratory depression / No. of children receiving AEDs, %)
Buccal	7/280 (2.5%)	-	-
PR	-	10/289 (3.4%)	-
IV	-	33/174 (19%)	38/502 (8%)
Total	7/280 (2.5%)	43/463 (9%)	38/502 (8%)

Buccal midazolam and rectal diazepam were associated with the lowest risk of respiratory depression (2.5%). Intravenous lorazepam was associated with a significantly lower risk of respiratory depression than intravenous diazepam (RR; 0.7; 95% CI: 0.55 to 0.87; $p < 0.0001$).

4.4 Discussion

The studies included in this review differed broadly in the reporting of AEs; some studies reported none whereas other studies reported at least one AE. In general, AEs were more frequently reported in the randomised control trials than in the cohort studies.

Respiratory depression was the most commonly reported AE, mainly in association with benzodiazepines. Variation in the reporting of respiratory depression, due to benzodiazepines, was noted. Respiratory depression following diazepam (PR or IV), lorazepam (IN), and midazolam (buccal, IV, IN or IM) was not reported in 6 studies [66, 68, 72, 74, 79, 80]. In contrast, it was reported following lorazepam (IV), midazolam (buccal), diazepam (PR, IV) in 5 studies [65, 73, 76, 78, 90]. This variation of the respiratory depression incidence may be due to the inclusion criteria of some of the studies. For example, studies that did not report respiratory depression excluded children who had received benzodiazepines as a prehospital treatment. Children who had received benzodiazepines, and whose seizures were not controlled before arriving at the hospital, are at a higher risk of respiratory depression. In children who suffered from acute tonic seizures, the respiratory depression may have been a complication either of their prolonged seizures or an AE of the benzodiazepine treatment [102].

Respiratory depression was most common with intravenous route however, its incidence was significantly lower with intravenous lorazepam (8%) compared to intravenous diazepam (19%) ($p< 0.0001$).

This review showed no difference in the rate of respiratory depression between buccal midazolam and rectal diazepam. However, based on the results of the previous systematic review (Chapter 4), buccal midazolam was more effective in controlling

seizures in children suffering from acute tonic-clonic seizures than rectal diazepam ($p<0.04$). Therefore, when comparing the safety and effectiveness of both medications, our results show that buccal midazolam should be the first choice for treating acute tonic-clonic seizures in children, if intravenous access is difficult to obtain [79].

Looking at the results reported in the previous chapter (Chapter 4), both intravenous medications were equally effective in treating acute tonic-clonic seizure. However, children given lorazepam were less likely to need additional dose(s) or AEDs to terminate their seizures, and were also less likely to have further seizures after drug administration. Therefore, intravenous lorazepam has better overall effectiveness and safety in treating acute tonic-clonic seizures compared to intravenous diazepam.

Respiratory depression was not reported in children who received buccal or intranasal lorazepam. These routes however, compared to intravenous lorazepam, were less effective and more likely to require additional dose(s) or further AEDs to terminate the seizure when compared to intravenous lorazepam, as discussed in Chapter 4. The main aim of treating acute tonic clonic seizures is to terminate the seizure quickly, to prevent the seizure from developing into status epilepticus, and to avoid the risk of respiratory depression due to the prolonged seizures [86, 87, 102]. Therefore, the effectiveness and safety profile of intravenous lorazepam suggest that intravenous delivery may be the best route for this drug [83].

Few studies that evaluated the safety of second line treatment (VAP, PB, LEV) were identified in this review. Our results identified one randomised control study that compared safety between intravenous valproate and intravenous phenobarbital; it showed that no child on intravenous valproate had respiratory depression. Moreover,

when looking at all AEs, it appeared that intravenous valproate was significantly safer than intravenous phenobarbital ($p = 0.001$). This could be because all children on intravenous valproate received a rapid loading dose (less than 20 minutes). Previous studies recommended that seizures be controlled in less than 30 minutes to reduce the risk of mortality and morbidity, suggesting that a rapid loading dose of intravenous valproate (less than 20 minutes) may the safest technique to stop seizures in children [103-105].

There were no cases of respiratory depression in children who received intravenous levetiracetam. However, no randomised control trials have been published that compared the safety of levetiracetam with other second-line agents for treating acute tonic-clonic seizures in children.

4.5 Limitations

There were limitations in the studies that were identified in this systematic review. The majority were open label, which may affect the quality of a study and introduce bias. Not all studies included a definition of respiratory depression. Also, there was a variation in respiratory depression in the studies that defined this AE. Few randomised control trials were identified for the safety of second-line treatments; thus, the results of these studies should be interpreted with caution.

4.6 Conclusions

Respiratory depression was documented mainly with benzodiazepines. There were no differences in the incidences of respiratory depression between buccal midazolam and rectal diazepam. However, buccal midazolam is more effective than rectal diazepam, so is the preferred choice for acute tonic-clonic including CSE as 1st line treatment. Intravenous lorazepam was less likely to be associated with respiratory depression when compared to intravenous diazepam. Intravenous lorazepam is the drug of choice where there is IV access. More randomised control trials are needed to compare the safety of second-line treatments.

CHAPTER 5: CONCLUSION

5.1 Introduction

Status epilepticus (SE) is a serious neurological emergency associated with mortality and morbidity [106-109]. Effective management of acute tonic-clonic seizures including CSE should be given to all patients whose seizures have lasted ≥ 5 minutes and certainly those who attend the emergency department to prevent progression to status epilepticus [59]. Acute tonic-clonic seizures including CSE often requires IV, IM, PR, IN or buccal AEDs. An understanding of the comparative effectiveness and safety of the different AEDs and routes will guide clinicians when selecting an appropriate treatment for children.

5.2 Summary of findings

In the first and the second systematic review, 25 studies were identified and were evaluated to assess the effectiveness and safety of AEDs for acute tonic-clonic seizures including CSE in children **(Chapter 3&4).**

Buccal midazolam was more effective than rectal diazepam in terminating seizures with success rate ranging from 53% to 100%. Moreover, it was associated with a lower recurrence rate of seizures (ranging from 6% to 8%) and significantly less likely to require an additional AED (ranging from 22% to 36%).

There were no differences in the incidence of respiratory depression between both groups; incidence was 3%-3.3%.

Also, administering buccal midazolam is easier for parents, healthcare and other professionals and is more socially acceptable in comparison to the rectal method. Therefore, buccal midazolam is the preferred choice for acute tonic-clonic seizures including CSE as 1st line treatment.

When assessing the intravenous AEDs, intravenous lorazepam and intravenous diazepam were equally effective (RR: 1.02 & p = 0.73). Respiratory depression was most common with the intravenous route; however, lorazepam was less likely to be associated with respiratory depression compared to intravenous diazepam (8% vs 19%). Intravenous lorazepam was superior to sublingual/buccal (83% vs 46%) or intranasal lorazepam (82% vs 63%). It was more effective and less likely to require additional dose(s) or AEDs to terminate the seizures. This suggests that buccal lorazepam is poorly absorbed. As previously mentioned, a pharmacokinetic study conducted by Anderson

et.al has shown that lorazepam was slowly absorbed following buccal administration [85]. Peak absorption following buccal administration was at 180 minutes, suggesting that this may not be the best route for treating acute seizures [85]. These results suggest that intravenous administration is the best route for lorazepam when treating seizures in children.

Few RCTs were identified that evaluated second-line treatment: intravenous valproate, phenobarbital and phenytoin.

5.3 Implications for practice

I would suggest the following recommendations for out of hospital use and for healthcare professionals working in children's hospitals:

- Buccal midazolam is the preferred choice for acute tonic-clonic seizures including CSE as 1st line treatment when intravenous access is difficult or is yet to be obtained.
- Intravenous lorazepam is the treatment of choice for children with CSE who have IV access.
- Training programmes are essential for paramedics and parents to deal with emergency treatment of status epilepticus. This will help medical professionals working in children's hospitals to decrease the risk of morbidity and mortality of status epilepticus.
- Based on this thesis, I am planning to establish a Saudi Arabia epilepticus working group. This group will involve pediatricians specialising in epilepsy and also emergency department physicians. It will work with authorised hospital committees to develop guidelines for status epilepticus treatment.
- Develop national guidelines for treatment of status epilepticus in Saudi Arabia.

5.4 Implications for future research

- Researchers need to agree a universal definition of the stages of status epilepticus; early stages, established, refractory and super-refractory status epilepticus.
- Researchers need to give a standard definition of treatment outcomes, especially the seizures recurrence rate; since 5 studies in this thesis did not define recurrence.

- Conduct surveys in Middle East countries about the AEDs used in status epilepticus in children.
- Conduct more RCTs in Middle East countries to evaluate the effectiveness and safety of AEDs for acute tonic-clonic seizures including CSE in children; since limited numbers of studies have been conducted in this region.
- More RCTs are needed to compare the effectiveness and safety of second-line treatment for acute tonic-clonic seizures including CSE in children.
- A previous study in adults has shown similar efficacy between intravenous levetiracetam and intravenous lorazepam[110]. However, no such study has been conducted in children. Therefore, it is important to compare the efficacy of intravenous levetiracetam with intravenous lorazepam in children.
- Intravenous lacosamide also is thought to have good effectiveness in the treatment of status epilepticus. There were up to 19 published articles on the use of intravenous lacosamide (10 case reports and 9 retrospective studies)[111]. Randomized controlled studies are needed to compare the effectiveness and safety of intravenous lacosmaide and other AEDs used for the management of acute tonic-clonic seizures such as intravenous diazepam, lorazepam, phenytoin, phenobarbital, sodium valproate and levetiracetam in children.
- More RCTs are required to evaluate the use of paraldehyde in children with convulsive status epilepticus.
- More studies are required to clarify the role of parents and paramedics in treating convulsive status epilepticus out of hospital.

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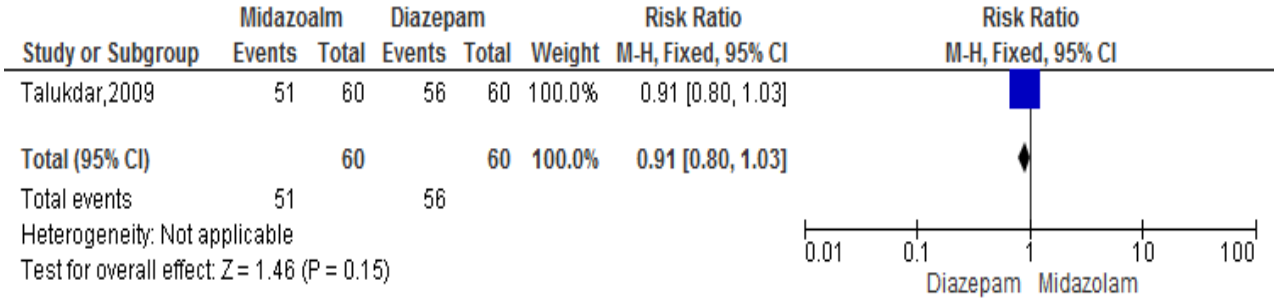
APPENDICES

APPENDIX A: SYSTEMATIC REVIEW ONE: FOREST PLOTS

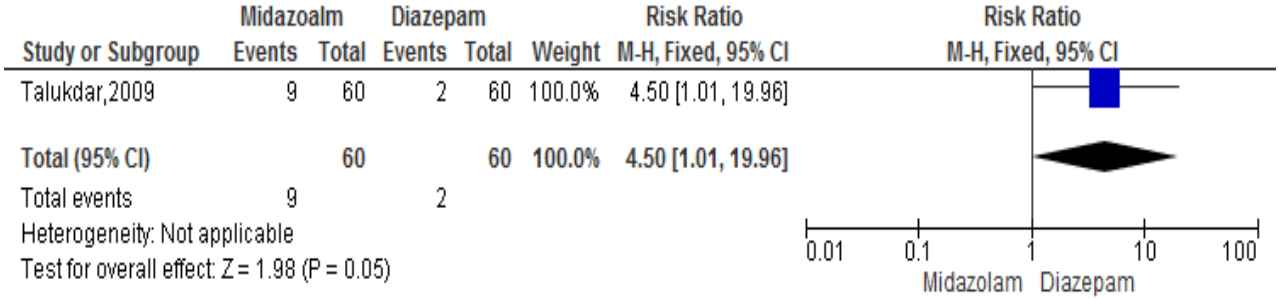
A. Midazolam versus diazepam

A.1. Buccal midazolam vs intravenous diazepam

1. Successful seizure control

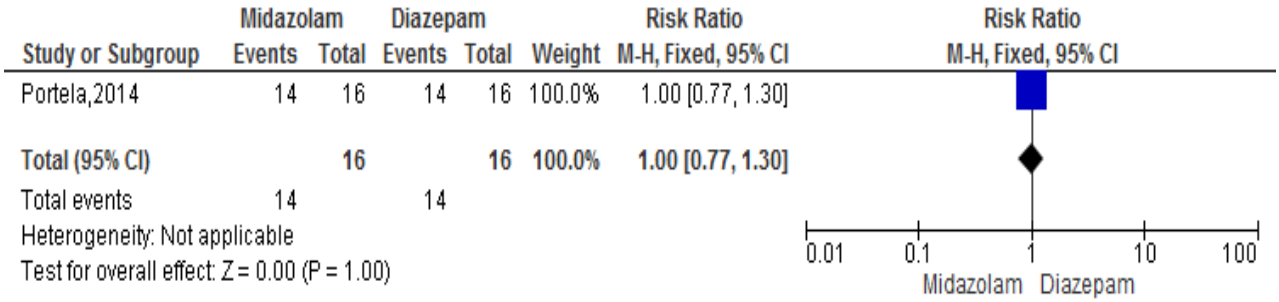


2. Additional AEDs

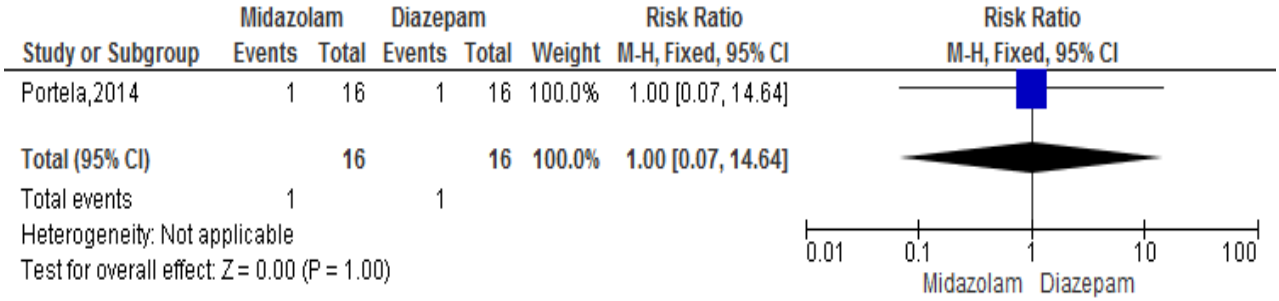


A.2. Intramuscular midazolam versus intravenous diazepam

1. Successful seizure control



2. Additional dose(s)



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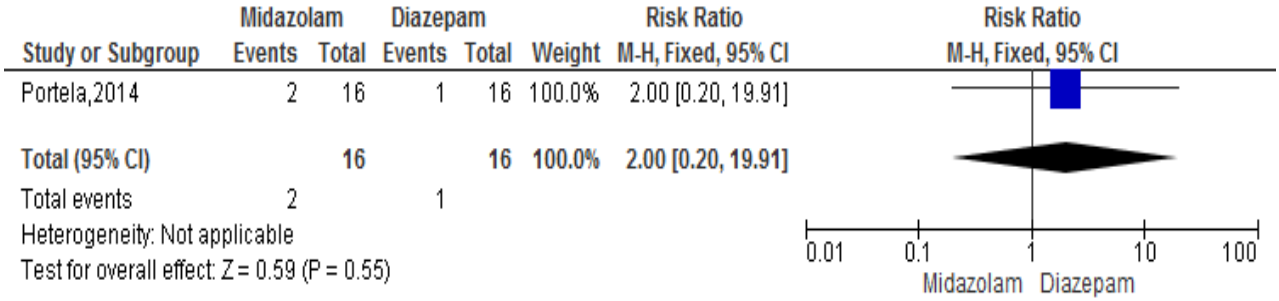
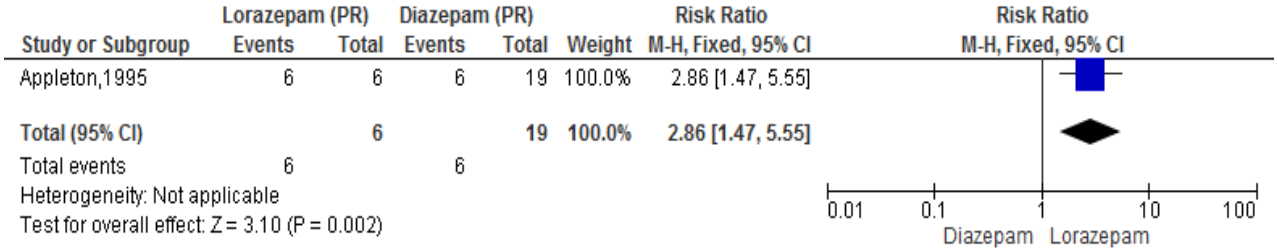


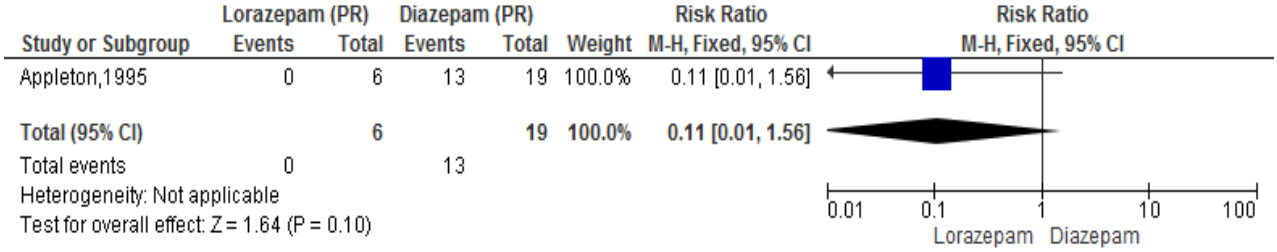
B. Lorazepam versus diazepam

B.1. Rectal lorazepam versus rectal diazepam

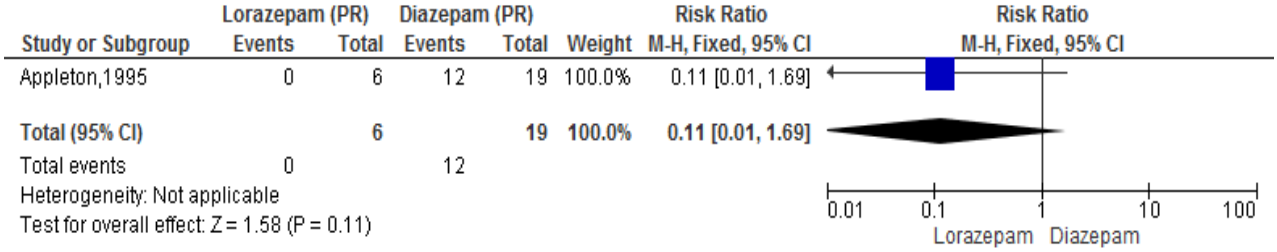
1. Successful seizure control



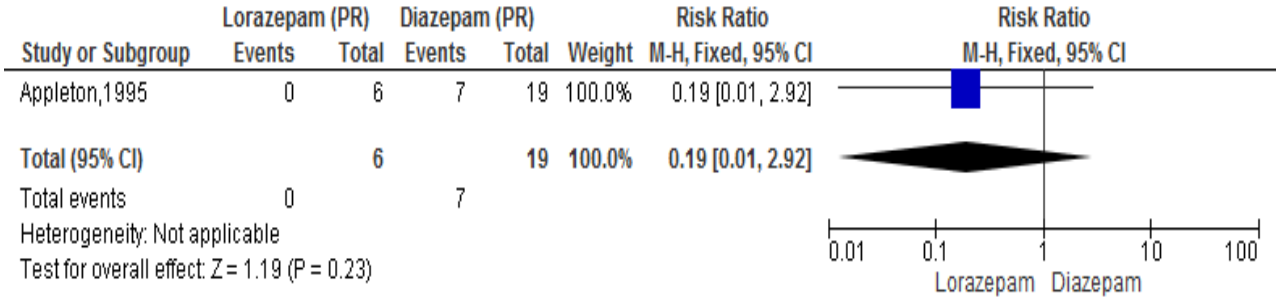
2. Additional dose(s)



3. Additional AEDs

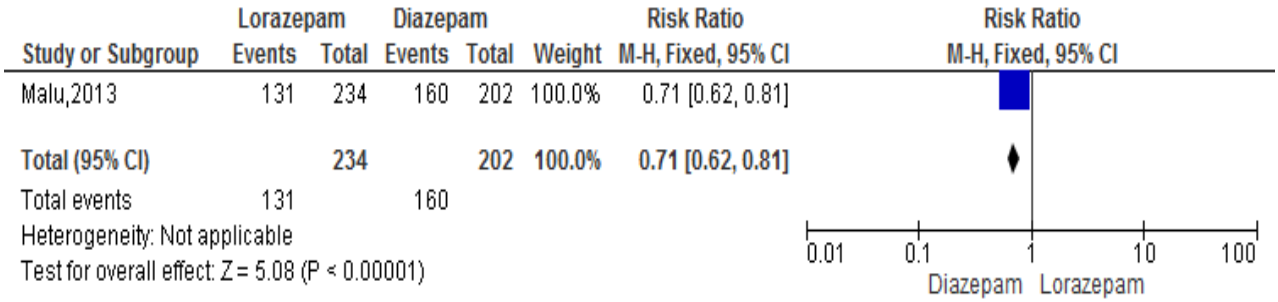


4. Seizure recurrence

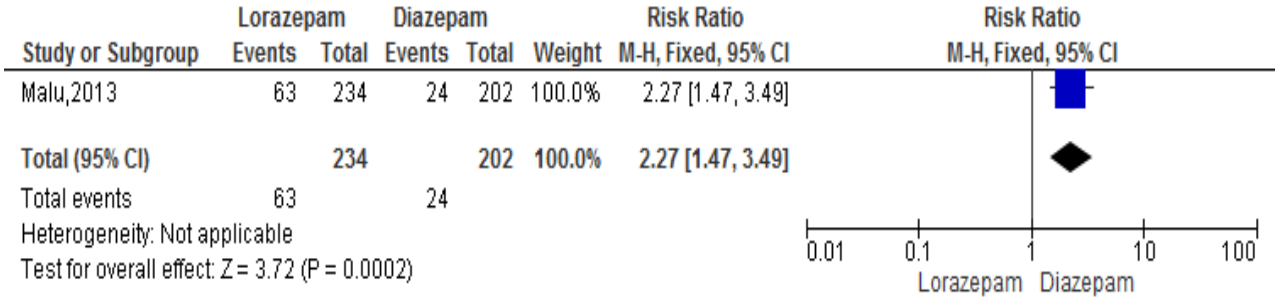


B.2. Sublingual lorazepam versus rectal diazepam

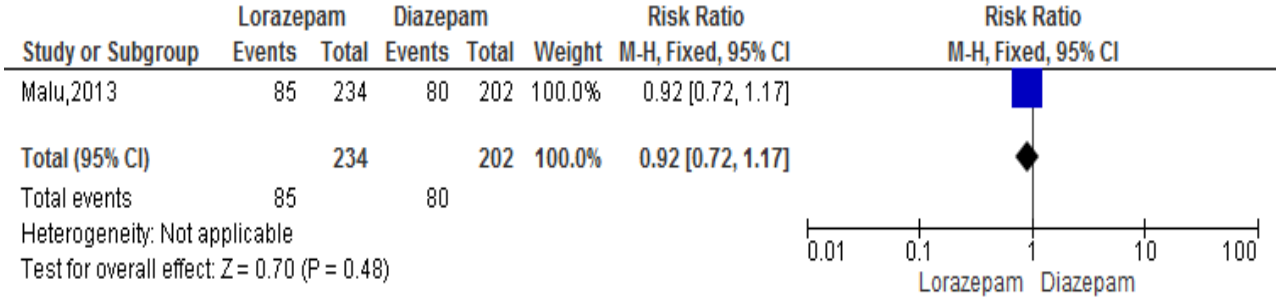
1. Successful seizure control



2. Additional dose(s)

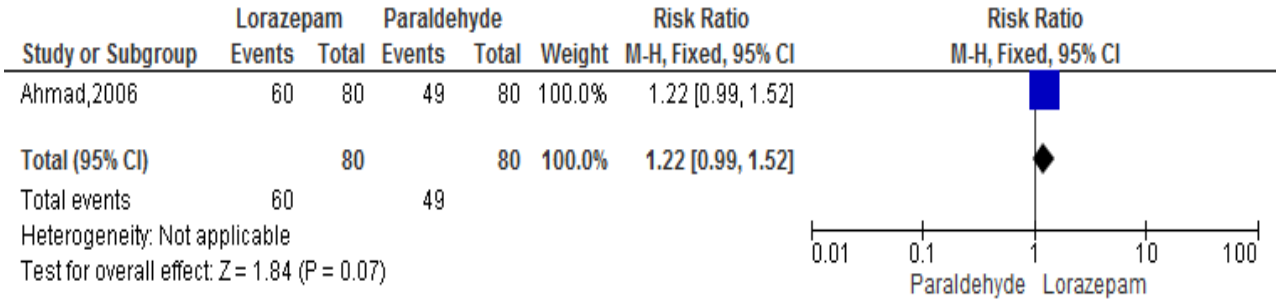


3. Seizure recurrence

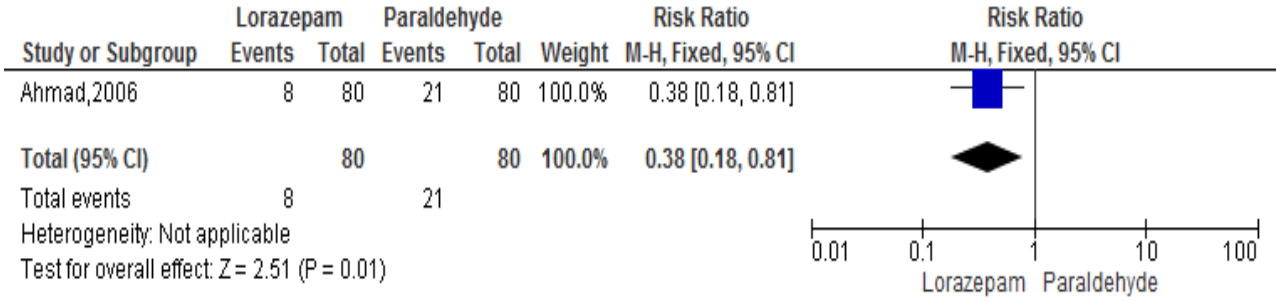


C. Intranasal lorazepam versus intramuscular paraldehyde

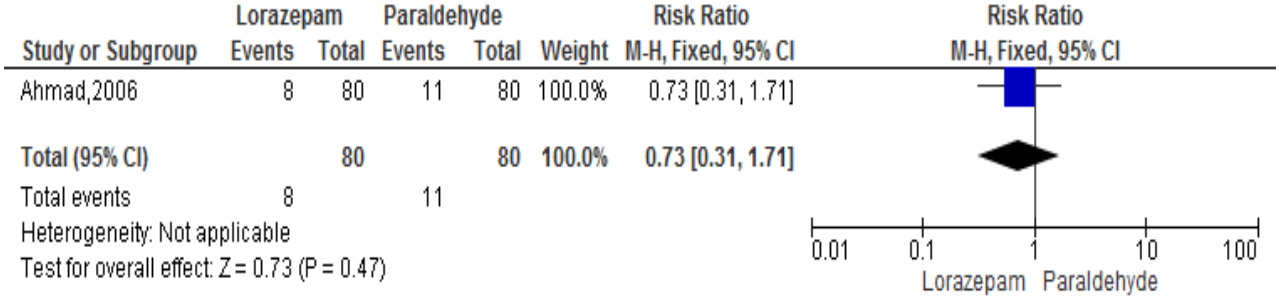
1. Successful seizure control



2. Additional AEDs

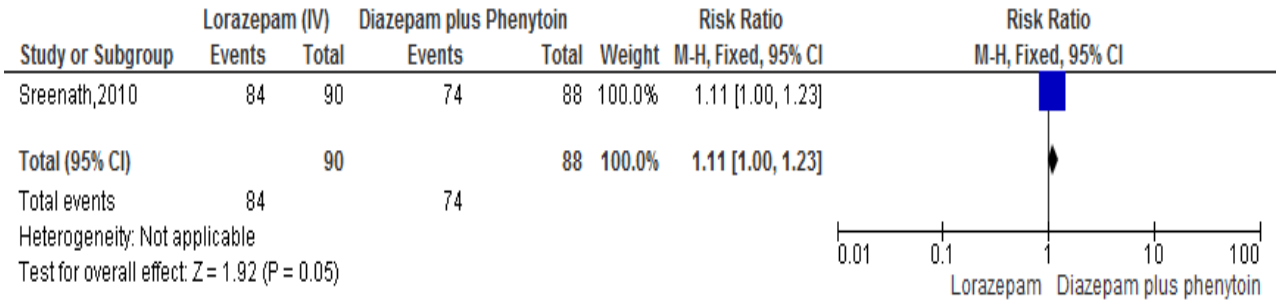


3. Seizure recurrence

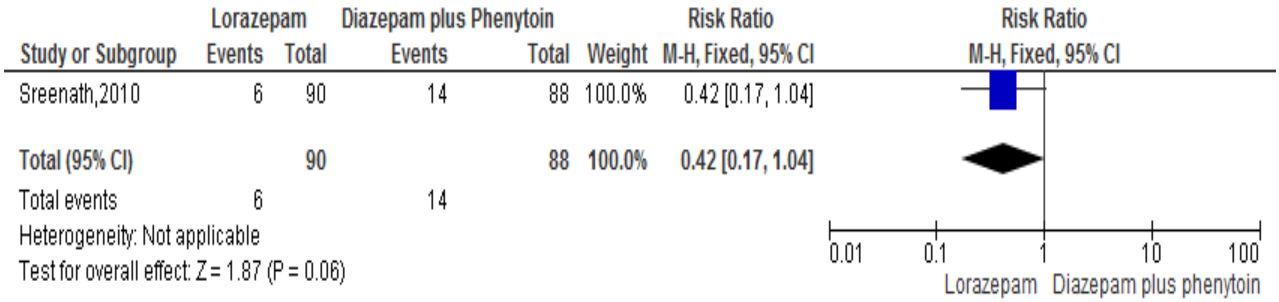


D. Intravenous lorazepam versus intravenous diazepam plus phenytoin

1. Successful seizure control



2. Additional dose(s)

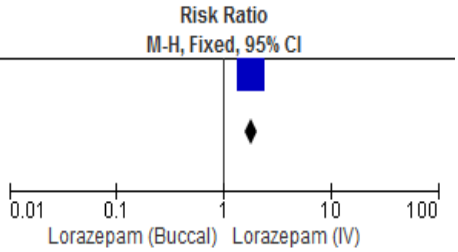


E. Intravenous lorazepam versus buccal lorazepam

1. Successful seizure control

Study or Subgroup	Lorazepam (IV) Events	Total	Lorazepam (Buccal) Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Lissauer, 2015	218	264	115	252	100.0%	1.81 [1.56, 2.09]
Total (95% CI)		**264**		**252**	**100.0%**	**1.81 [1.56, 2.09]**
Total events	218		115			

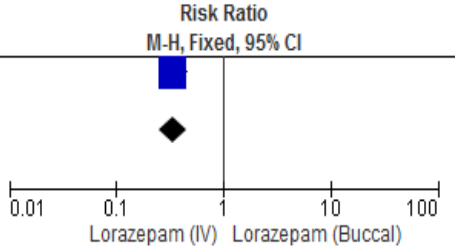
Heterogeneity: Not applicable
Test for overall effect: Z = 7.98 (P < 0.00001)



2. Additional dose(s)

Study or Subgroup	Lorazepam (IV) Events	Total	Lorazepam (Buccal) Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Lissauer, 2015	46	264	130	252	100.0%	0.34 [0.25, 0.45]
Total (95% CI)		**264**		**252**	**100.0%**	**0.34 [0.25, 0.45]**
Total events	46		130			

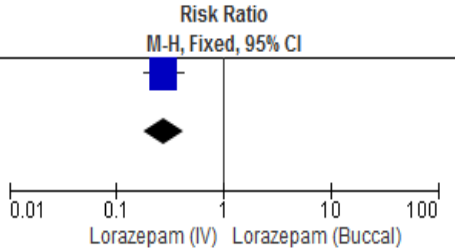
Heterogeneity: Not applicable
Test for overall effect: Z = 7.37 (P < 0.00001)



3. Additional AEDs

Study or Subgroup	Lorazepam (IV) Events	Total	Lorazepam (Buccal) Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Lissauer, 2015	23	264	80	252	100.0%	0.27 [0.18, 0.42]
Total (95% CI)		**264**		**252**	**100.0%**	**0.27 [0.18, 0.42]**
Total events	23		80			

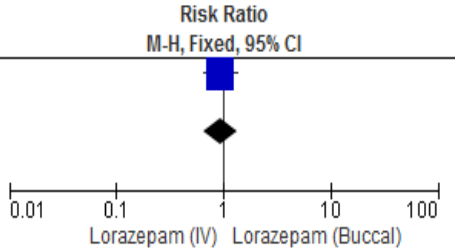
Heterogeneity: Not applicable
Test for overall effect: Z = 5.89 (P < 0.00001)



4. Seizure recurrence

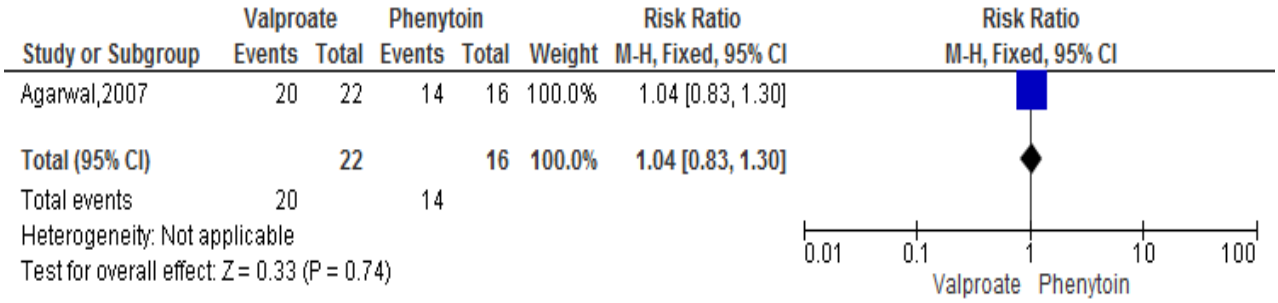
Study or Subgroup	Lorazepam (IV) Events	Total	Lorazepam (Buccal) Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Lissauer, 2015	47	264	48	252	100.0%	0.93 [0.65, 1.34]
Total (95% CI)		**264**		**252**	**100.0%**	**0.93 [0.65, 1.34]**
Total events	47		48			

Heterogeneity: Not applicable
Test for overall effect: Z = 0.36 (P = 0.72)



F. Intravenous valproate versus intravenous phenytoin

1. Successful seizure control

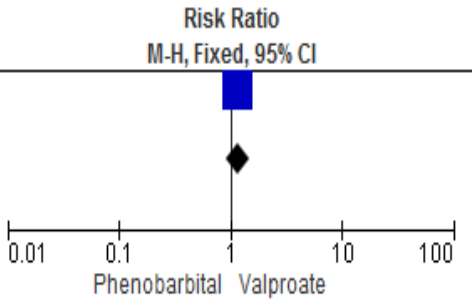


G. Intravenous valproate versus intravenous phenobarbital

1. Successful seizure control

Study or Subgroup	Valproate Events	Valproate Total	Phenobarbital Events	Phenobarbital Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Malamiri,2012	27	30	23	30	100.0%	1.17 [0.93, 1.48]
Total (95% CI)		**30**		**30**	**100.0%**	**1.17 [0.93, 1.48]**
Total events	27		23			

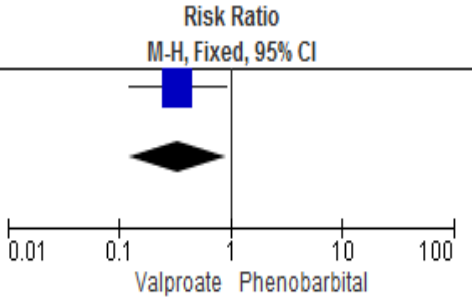
Heterogeneity: Not applicable
Test for overall effect: Z = 1.36 (P = 0.17)



2. Seizure recurrence

Study or Subgroup	Valproate Events	Valproate Total	Phenobarbital Events	Phenobarbital Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Malamiri,2012	4	30	12	30	100.0%	0.33 [0.12, 0.92]
Total (95% CI)		**30**		**30**	**100.0%**	**0.33 [0.12, 0.92]**
Total events	4		12			

Heterogeneity: Not applicable
Test for overall effect: Z = 2.13 (P = 0.03)



APPENDIX B: SYSTEMATIC REVIEW TWO: FOREST PLOTS

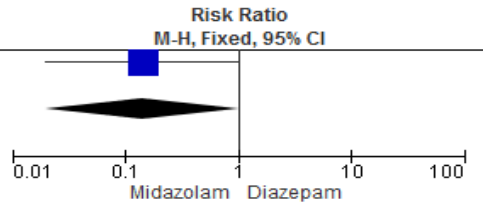
A. Midazolam versus diazepam

A.1. Intramuscular midazolam versus intravenous diazepam

1. All AEs

Study or Subgroup	Midazolam Events	Total	Diazepam Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Portela,2014	1	16	7	16	100.0%	0.14 [0.02, 1.03]
Total (95% CI)		**16**		**16**	**100.0%**	**0.14 [0.02, 1.03]**
Total events	1		7			

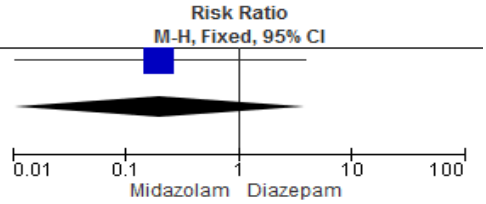
Heterogeneity: Not applicable
Test for overall effect: Z = 1.93 (P = 0.05)



2. Vomiting

Study or Subgroup	Midazolam Events	Total	Diazepam Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Portela,2014	0	16	2	16	100.0%	0.20 [0.01, 3.86]
Total (95% CI)		**16**		**16**	**100.0%**	**0.20 [0.01, 3.86]**
Total events	0		2			

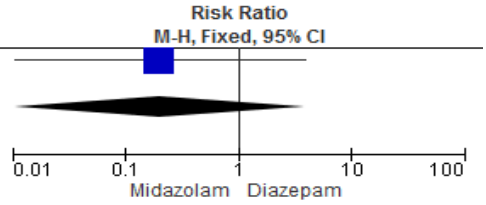
Heterogeneity: Not applicable
Test for overall effect: Z = 1.07 (P = 0.29)



3. Hyperactivity

Study or Subgroup	Midazolam Events	Total	Diazepam Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Portela,2014	0	16	2	16	100.0%	0.20 [0.01, 3.86]
Total (95% CI)		**16**		**16**	**100.0%**	**0.20 [0.01, 3.86]**
Total events	0		2			

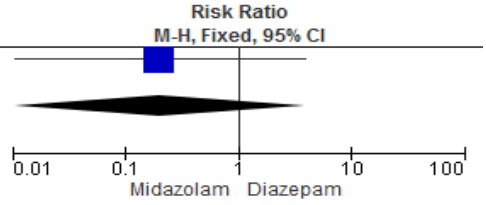
Heterogeneity: Not applicable
Test for overall effect: Z = 1.07 (P = 0.29)



4. Salivation

Study or Subgroup	Midazolam Events	Total	Diazepam Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Portela,2014	0	16	2	16	100.0%	0.20 [0.01, 3.86]
Total (95% CI)		**16**		**16**	**100.0%**	**0.20 [0.01, 3.86]**
Total events	0		2			

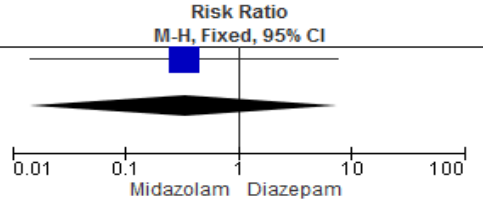
Heterogeneity: Not applicable
Test for overall effect: Z = 1.07 (P = 0.29)



5. Nausea

Study or Subgroup	Midazolam Events	Total	Diazepam Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Portela,2014	0	16	1	16	100.0%	0.33 [0.01, 7.62]
Total (95% CI)		**16**		**16**	**100.0%**	**0.33 [0.01, 7.62]**
Total events	0		1			

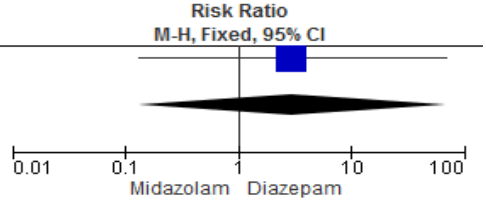
Heterogeneity: Not applicable
Test for overall effect: Z = 0.69 (P = 0.49)



6. Hypotension

Study or Subgroup	Midazolam Events	Total	Diazepam Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Portela,2014	1	16	0	16	100.0%	3.00 [0.13, 68.57]
Total (95% CI)		**16**		**16**	**100.0%**	**3.00 [0.13, 68.57]**
Total events	1		0			

Heterogeneity: Not applicable
Test for overall effect: Z = 0.69 (P = 0.49)

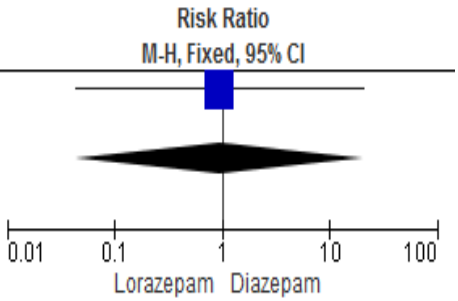


B. Lorazepam versus diazepam

1. Lorazepam (PR) versus diazepam (PR)

Study or Subgroup	Lorazepam (PR) Events	Total	Diazepam (PR) Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Appleton,1995	0	6	1	19	100.0%	0.95 [0.04, 20.78]
Total (95% CI)		**6**		**19**	**100.0%**	**0.95 [0.04, 20.78]**
Total events	0		1			

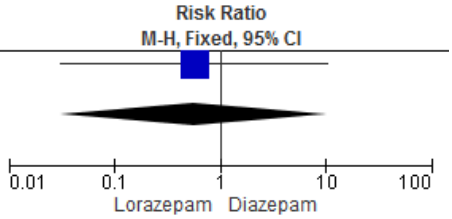
Heterogeneity: Not applicable
Test for overall effect: Z = 0.03 (P = 0.98)



2. ICU admission

Study or Subgroup	Lorazepam (PR) Events	Total	Diazepam (PR) Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Appleton,1995	0	6	2	19	100.0%	0.57 [0.03, 10.51]
Total (95% CI)		**6**		**19**	**100.0%**	**0.57 [0.03, 10.51]**
Total events	0		2			

Heterogeneity: Not applicable
Test for overall effect: Z = 0.38 (P = 0.71)

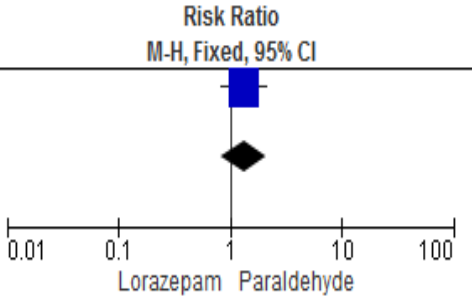


C. Intranasal lorazepam versus intramuscular paraldehyde

1. All AEs

Study or Subgroup	Lorazepam Events	Lorazepam Total	Paraldehyde Events	Paraldehyde Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Ahmad,2006	28	80	21	80	100.0%	1.33 [0.83, 2.14]
Total (95% CI)		**80**		**80**	**100.0%**	**1.33 [0.83, 2.14]**
Total events	28		21			

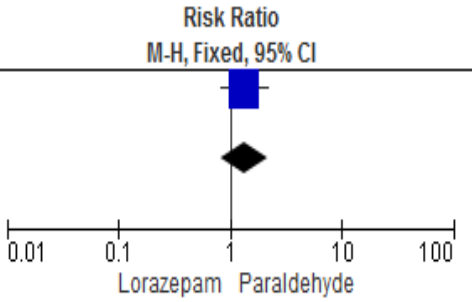
Heterogeneity: Not applicable
Test for overall effect: Z = 1.19 (P = 0.23)



2. Hypotension

Study or Subgroup	Lorazepam Events	Lorazepam Total	Paraldehyde Events	Paraldehyde Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Ahmad,2006	27	80	20	80	100.0%	1.35 [0.83, 2.20]
Total (95% CI)		**80**		**80**	**100.0%**	**1.35 [0.83, 2.20]**
Total events	27		20			

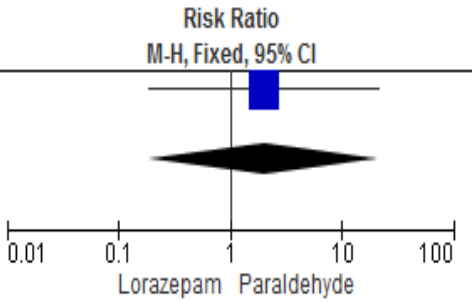
Heterogeneity: Not applicable
Test for overall effect: Z = 1.20 (P = 0.23)



3. Hypoxia

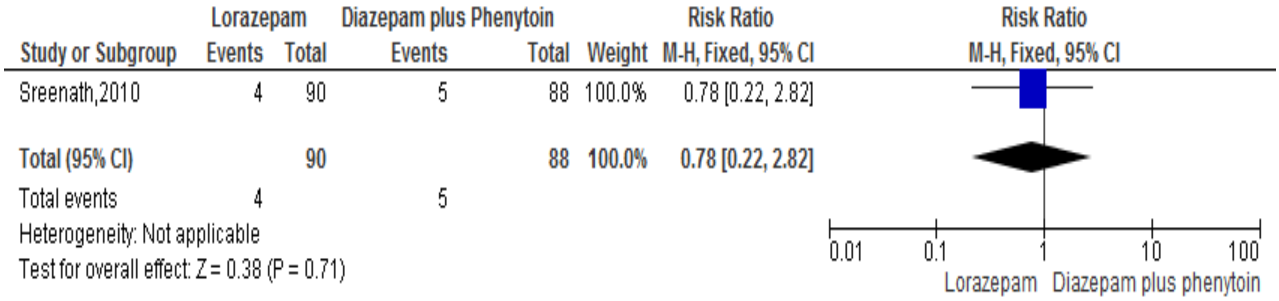
Study or Subgroup	Lorazepam Events	Lorazepam Total	Paraldehyde Events	Paraldehyde Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Ahmad,2006	2	80	1	80	100.0%	2.00 [0.19, 21.62]
Total (95% CI)		**80**		**80**	**100.0%**	**2.00 [0.19, 21.62]**
Total events	2		1			

Heterogeneity: Not applicable
Test for overall effect: Z = 0.57 (P = 0.57)



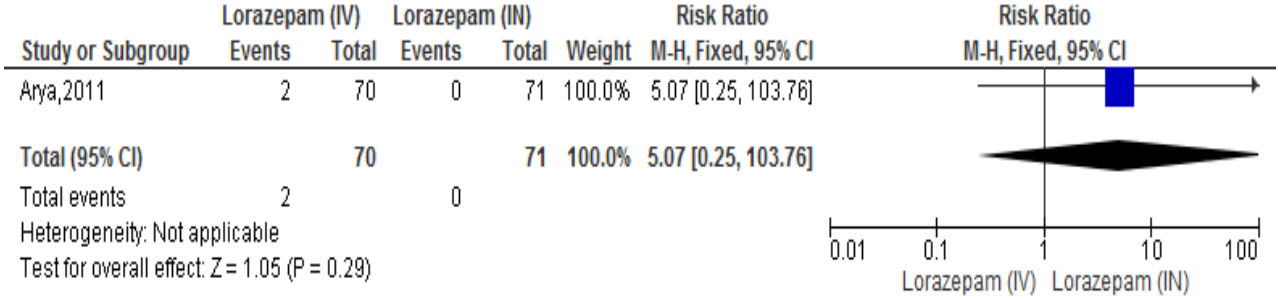
D. Intravenous lorazepam versus intravenous diazepam plus phenytoin (IV)

1. Respiratory depression



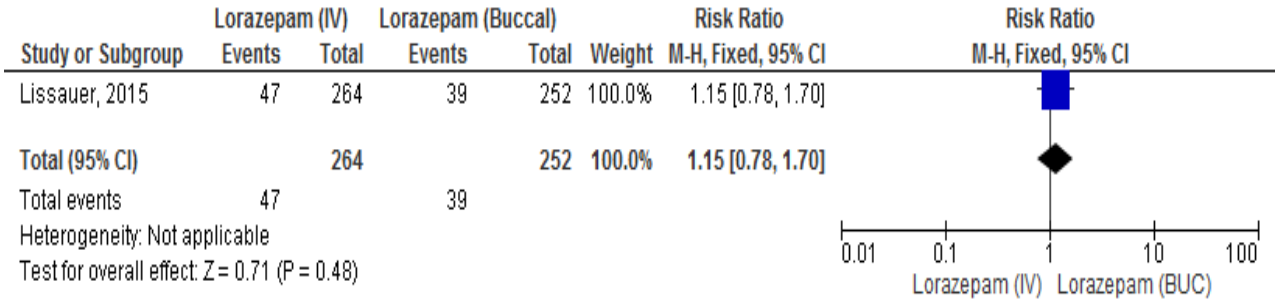
E. Intravenous lorazepam versus intranasal lorazepam

1. Respiratory depression



F. Intravenous lorazepam versus buccal lorazepam

1. Deaths

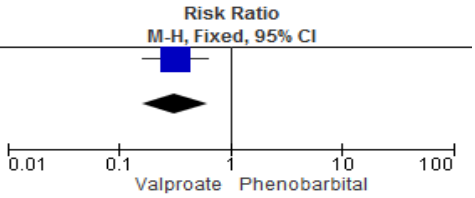


G. Valproate versus phenobarbital

1. All AEs

Study or Subgroup	Valproate Events	Valproate Total	Phenobarbital Events	Phenobarbital Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Malamiri,2012	7	30	22	30	100.0%	0.32 [0.16, 0.63]
Total (95% CI)		**30**		**30**	**100.0%**	**0.32 [0.16, 0.63]**
Total events	7		22			

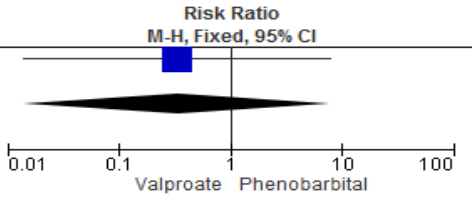
Heterogeneity: Not applicable
Test for overall effect: Z = 3.28 (P = 0.001)



2. Respiratory depression

Study or Subgroup	Valproate Events	Valproate Total	Phenobarbital Events	Phenobarbital Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Malamiri,2012	0	30	1	30	100.0%	0.33 [0.01, 7.87]
Total (95% CI)		**30**		**30**	**100.0%**	**0.33 [0.01, 7.87]**
Total events	0		1			

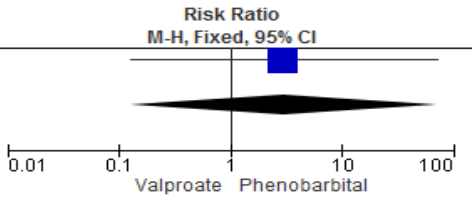
Heterogeneity: Not applicable
Test for overall effect: Z = 0.68 (P = 0.50)



3. Hypotension

Study or Subgroup	Valproate Events	Valproate Total	Phenobarbital Events	Phenobarbital Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Malamiri,2012	1	30	0	30	100.0%	3.00 [0.13, 70.83]
Total (95% CI)		**30**		**30**	**100.0%**	**3.00 [0.13, 70.83]**
Total events	1		0			

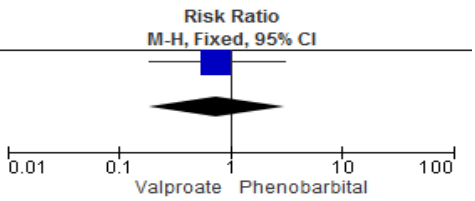
Heterogeneity: Not applicable
Test for overall effect: Z = 0.68 (P = 0.50)



4. Vomiting

Study or Subgroup	Valproate Events	Valproate Total	Phenobarbital Events	Phenobarbital Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Malamiri,2012	3	30	4	30	100.0%	0.75 [0.18, 3.07]
Total (95% CI)		**30**		**30**	**100.0%**	**0.75 [0.18, 3.07]**
Total events	3		4			

Heterogeneity: Not applicable
Test for overall effect: Z = 0.40 (P = 0.69)



5. Lethargy

Study or Subgroup	Valproate Events	Valproate Total	Phenobarbital Events	Phenobarbital Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Malamiri,2012	3	30	17	30	100.0%	0.18 [0.06, 0.54]
Total (95% CI)		**30**		**30**	**100.0%**	**0.18 [0.06, 0.54]**
Total events	3		17			

Heterogeneity: Not applicable
Test for overall effect: Z = 3.04 (P = 0.002)