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Midazolam Versus Diazepam for the Treatment of Status Epilepticus in Children and Young Adults: A Meta-Analysis

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Abstract

Background—Rapid treatment of status epilepticus (SE) is associated with better outcomes. Diazepam and midazolam are commonly used, but the optimal agent and administration route is unclear.

Objectives—To determine by systematic review if non-intravenous midazolam is as effective as diazepam, by any route, in terminating SE seizures in children and adults. Time to seizure cessation and respiratory complications were examined.

Methods—Search of PubMed, Web of Knowledge, Embase, Cochrane Database of Systematic Reviews, Database of Abstracts of Reviews of Effects, American College of Physicians Journal Club, Cochrane Central Register of Controlled Trials, the Cumulative Index to Nursing and Allied Health Literature, and International Pharmaceutical Abstracts for studies published January 1, 1950 through July 4, 2009. English language quasi-experimental or randomized controlled trials comparing midazolam and diazepam as first-line treatment for SE, and meeting the Consolidated Standards of Reporting Trials (CONSORT)-based quality measures, were eligible. Two reviewers independently screened studies for inclusion and extracted outcomes data. Administration routes were stratified as non-intravenous (buccal, intranasal, intramuscular, rectal) or intravenous (IV). Fixed-effects models generated pooled statistics.

Results—Six studies with 774 subjects were included. For seizure cessation, midazolam, by any route, was superior to diazepam, by any route, (RR 1.52; 95% CI = 1.27 to 1.82). Non-IV midazolam is as effective as IV diazepam (RR 0.79; 95% CI = 0.19 to 3.36), and buccal midazolam is superior to rectal diazepam in achieving seizure control (RR 1.54; 95% CI = 1.29 to 1.85). Midazolam was administered faster than diazepam (mean difference 2.46 minutes; 95% CI = 1.52 to 3.39 min) and had similar times between drug administration and seizure cessation. Respiratory complications requiring intervention were similar, regardless of administration route (RR 1.49; 95% CI = 0.25 to 8.72).

Conclusions—Non-IV midazolam, compared to non-IV or IV diazepam, is safe and effective in treating status epilepticus. Comparison to lorazepam, evaluation in adults, and prospective confirmation of safety and efficacy is needed.

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Keywords

status epilepticus; seizures; benzodiazepines; midazolam; diazepam

INTRODUCTION

Seizures are a common medical emergency, accounting for 1–2% of all emergency department (ED) visits, and status epilepticus (SE) exists in approximately 6% of these encounters.¹ However, the optimal agent and route of administration for the treatment of SE remain unclear. Almost one in ten persons will suffer at least one seizure in their lifetime.² While most seizures are self-limited and short, every year 120,000 to 200,000 people have prolonged convulsions or rapidly recurrent convulsions without interval recovery, and these patients in SE have a true medical emergency.^{3,4} SE is associated with high morbidity and mortality, and contributes to 55,000 deaths each year in the United States.^{5–8} Common complications of SE include aspiration, anoxic brain injury, cardiac instability, metabolic and autonomic dysfunction, and direct neuronal damage.^{9–16}

Although clinical outcome in SE is primarily determined by the underlying etiology that caused the seizure, persistent seizure activity is associated with worse outcomes across the spectrum of precipitating conditions.^{16–19} In otherwise benign epilepsy, refractory SE can still be fatal, or result in neuronal injury and chronic brain damage. In SE resulting from acute trauma or stroke, persistent ictal activity is associated with increased secondary neuronal cell death and worse outcomes.²⁰ Although duration of seizure is associated with higher mortality and worse neurological recovery in survivors in clinical studies, these data do not provide rigorous proof of causality. However, studies of experimental SE in animal models directly demonstrate that neuronal loss increases with duration of seizure, and that kindling effects from persistent seizures are epileptogenic.^{19,21} Experimental status models also show that the effectiveness of anticonvulsant medications to terminate seizures rapidly decreases as the time between the start of convulsions and drug administration lengthens.²² If seizures are not terminated quickly, escalating doses of benzodiazepines are required to achieve seizure cessation, and seizures eventually become entirely refractory to anticonvulsant therapy.²³

Benzodiazepines have been the first line treatment of SE for the last 30 years, but the optimal drug and the best route of administration for seizure control outside of the hospital setting, or without intravenous (IV) access, remains unclear. Lorazepam is a clinical standard for initial treatment of SE in EDs.^{24,25} While shown to be safe for use by paramedics, lorazepam has a relatively short shelf-life without refrigeration, limiting its practicality in the prehospital setting.²⁶ Furthermore, lorazepam is only effective when given IV, and establishing IV access can be challenging, if not impossible, in convulsing patients.^{26–28} Diazepam is frequently used for treatment of SE, because it can be delivered either intravenously or rectally.^{26,27} However, the effectiveness of diazepam in terminating seizures is thought to be inferior to that of other benzodiazepines, especially when given rectally.²⁵ Additionally, diazepam is suspected to cause more complications than other benzodiazepines because of the risk for prolonged sedation and respiratory depression.^{26,29}

Midazolam is rapidly absorbed after intramuscular (IM) injection, does not require refrigeration, and is less expensive than lorazepam.³⁰ Requiring IV access before benzodiazepine administration may unnecessarily delay treatment of SE, placing the patient at risk, even when done in the ED. Non-IV midazolam administration for treatment of SE is an attractive idea, but there are few studies of its efficacy and safety.³¹ A recent Cochrane Review explored benzodiazepine treatment of pediatric SE, and included many different medication strategies.³² Important secondary outcomes, including time required for administration of medication and time to therapeutic effect, were not described, and the review did not include studies addressing out-of-hospital management of SE.

This meta-analysis compares the use non-IV midazolam to that of diazepam in the treatment of seizures. The specific objective was to determine the efficacy, rapidity, and safety of terminating seizures with non-IV midazolam, compared to either IV or non-IV diazepam, as an initial emergency treatment in pediatric and adult patients with SE.

METHODS

Data Sources and Search Strategy

A systematic review of the literature was conducted to identify studies comparing the use of non-IV midazolam to IV or non-IV diazepam in treating SE in pediatric and adult patients. For the purposes of this analysis, seizures lasting longer than 5 minutes are defined as SE, as has been suggested elsewhere.^{26,33} The following electronic databases were searched: PubMed, Web of Knowledge, Embase, all evidence-based medicine reviews (includes Cochrane Database of Systematic Reviews, Database of Abstracts of Reviews of Effects, American College of Physicians Journal Club, and Cochrane Central Register of Controlled Trials), the Cumulative Index to Nursing and Allied Health Literature (CINAHL), and International Pharmaceutical Abstracts. All studies published or in press between January 1, 1950 and July 4, 2009, were considered. Only reports published in English were included. The majority of articles were retrieved from PubMed and Web of Knowledge using a Boolean search strategy (Appendix 1). In addition to these automated searches, we conducted a hand search of bibliographies of key articles and abstracts presented at several major scientific conferences in 2006 through 2008. These included the annual meetings of the American College of Emergency Physicians, the American Neurological Association, the National Association of EMS Physicians, and the Society for Academic Emergency Medicine. Finally, references of key review articles were hand searched for other relevant articles.

Selection Criteria

Two reviewers (CS, RS) evaluated each full text article and determined exclusions based on *a priori* criteria to ensure the comparability of the groups and to allow for pooling of results. These criteria excluded any study that did not compare diazepam to non-IV administration of midazolam as a first line treatment for SE, animal studies, any study design other than randomized controlled or quasi-experimental, and any study that used diazepam or midazolam for sedation or prevention of seizures (Figure 1). Initial disagreements between reviewers regarding study inclusion were resolved by consensus.

Data Extraction and Quality Assessment

Studies that met our preliminary selection criteria were further evaluated by two independent reviewers (CS, JM) using the Consolidated Standards of Reporting Trials (CONSORT) Quality Scale, and the Randomized Controlled Trial (RCT) Checklist.³⁴ The CONSORT Quality Scale has been shown to be useful in determining the methodological quality of randomized clinical trials in a standardized format.³⁴ The 30-point scale assigns points for studies that report key concepts on randomization, allocation concealment, repeatability of observations, etc., and serves as a balance to the quality of writing to judge the strength and validity of findings. An a priori threshold score of at least 20 was established for inclusion. The RCT Checklist serves as a way to abstract data on specific interventions and to further assess key components of study design.

The following variables were extracted from the studies: type of study design, definition of SE, types of complications reported, absolute numbers of patients in the diazepam and the midazolam groups that had seizure activity terminated, route of administration, and dosage of drug administered.

Data Analysis

Study inclusion agreement between investigators was evaluated by kappa statistics. Pooled risk ratios were determined using both the Mantel-Haenszel fixed effects, and DerSimonian and Laird random-effects models.³⁵ Data were stratified into two subgroups, one comparing IV diazepam versus non-IV midazolam, and the other comparing non-IV diazepam to non-IV midazolam. Where study data were available, we assessed the mean differences in times between initial assessment and drug administration, and between drug administration and cessation of seizure activity based on route of administration. A fixed-effects model was used to pool times across studies.

Heterogeneity within the group was assessed using Cochran's Q test and I² statistic, which measures the degree of variation among studies.³⁶ Begg's test and a visual inspection of the funnel plot were conducted to evaluate publication bias. All statistical tests were two-sided. Stata version 10.0 (College Station, TX) and Review Manager 5.0 (RevMan, Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2008) were used to conduct the analyses. A meta-influence analysis was conducted to statistically omit one study at a time to determine the effect on the overall pooled estimate. A sensitivity analysis was performed to assess the effect of removing the most influential study from the pooled subgroup results.

RESULTS

Search and Study Characteristics

The initial literature search yielded 251 references, of which 44 met preliminary selection criteria for inclusion within the meta-analysis (Figure 1). Four authors were contacted to clarify the comparability of groups, to obtain more data, or to clarify definitions of SE. Thirty-eight articles were excluded because trial design was not randomized or controlled (n = 6); data included were not original (n = 5); there was no comparison group (n = 7); acute SE was not described (n = 7); the two drugs chosen for this review were not utilized (n = 5);

and the CONSORT score was <20 (n = 8).³⁴ The kappa for inter-rater reliability for inclusion into the study was 0.95.

The characteristics of the six studies included studies containing 774 subjects are shown in Table 1,^{37–42} and all are RCTs. Although the intent of our analysis was to include all age groups, all of the studies meeting the selection criteria happened to be studies of children and young adults. Five studies included children only; one study included children and adults, however the oldest subject was 22 years old.⁴² Routes of medication administration included IV and rectal (PR) diazepam and buccal, intranasal (IN), and IM midazolam. Dosing of medications varied slightly among studies: diazepam 0.2–0.3 mg/kg IV or 0.5 mg/kg PR, midazolam 0.2 mg/kg IM and IN, or 0.5 mg/kg buccal. One study used fixed doses of PR diazepam (10 mg) and buccal midazolam (10 mg).⁴² The determination of seizure cessation was clinically based, and used varying definitions based on time until convulsion stoppage and/or absence of seizure recurrence. Some studies included prolonged simple partial or focal convulsions.^{37,39,41,42} Despite these clinical and methodological differences, there was no significant statistical heterogeneity in pooled analysis of all included studies ($I^2 = 0\%$, Figure 2).

Seizure Cessation—Midazolam, by any route, was superior to diazepam, by any route, in achieving seizure cessation in pooled analysis (relative risk [RR] 1.52; 95% confidence interval [CI] = 1.27 to 1.82, n = 6, number needed to treat [NNT] = 7), Figure 2.

Three^{37–39} studies of 146 subjects compared IM or IN midazolam to IV diazepam. In pooled analysis, there is no apparent difference between non-IV midazolam and IV diazepam in achieving seizure cessation (RR 0.79; 95% CI = 0.19 to 3.26), Figure 3. Statistical heterogeneity of this sub-group of studies was very low ($I^2 = 0\%$).

Three^{40–42} studies of 628 subjects compared rectal diazepam to buccal midazolam. Buccal midazolam is more successful in achieving seizure cessation (RR 1.54; 95% CI = 1.29 to 1.85, $I^2 = 0\%$, NNT = 6).

Time to administration and time to seizure cessation—Early treatment of status epilepticus is likely to be most successful and relies on the time intervals of seizure onset to medical contact, medical contact to drug administration, and drug administration to therapeutic effect. These time intervals are separately evaluated when reported by individual studies. No studies reliably report the time from seizure onset to medical contact. Two^{37,38} studies demonstrate non-IV midazolam was administered 2.46 minutes (95% CI = 1.52 to 3.39) quicker than IV diazepam to seizing patients. Non-IV midazolam and IV diazepam were similar in the time between drug administration and seizure cessation in three^{37–39} studies (mean difference 0.68 minutes, 95% CI = –0.03 to 1.39).

Respiratory Complications—Respiratory complications were rarely reported. In five^{38–42} studies of 750 subjects only five instances of respiratory depression requiring intubation or ventilatory support (0.7%) were described, and these all came from a single study of non-IV benzodiazepines.⁴⁰ There is no apparent difference between the safety of

midazolam and diazepam (RR 1.49; 95% CI = 0.25 to 8.72, Figure 4). Causes of respiratory depression were described as multifactorial, but further detail was not provided.

Sensitivity Analysis—For each outcome, removing individual studies did not affect pooled risk ratios or measurements of statistical heterogeneity. There is also no apparent bias introduced by dose of medication, length of seizure required for inclusion, or inclusion of non-generalized seizures. Outcomes were also analyzed using a random-effects model, with no meaningful effect on the results.

A more broad pooled analysis including the eight studies with CONSORT scores between 15 and 19 yields similar results to all outcomes:^{27,43–49} overall success (RR 1.50; 95% CI = 1.30 to 1.73, n = 14), IV diazepam vs. non-IV midazolam (RR 0.90; 95% CI = 0.48 to 1.68, n = 5), PR diazepam vs. buccal midazolam (RR 1.51; 95% CI = 1.26 to 1.80, n = 4). Midazolam appears to be associated with fewer respiratory complications in this expanded group (RR 1.74; 95% CI = 1.23 to 2.46, n = 13, $I^2 = 69%$); however, this result is biased by a single study,⁴⁶ and exclusion resulted in no safety difference between the two medications (RR 1.31; 95% CI = 0.88 to 1.95, n = 12, $I^2 = 0%$).

Visual inspection of funnel plots shows no obvious signal of asymmetry, which suggests lack of significant publication bias; this is limited due to the small numbers of studies included. Begg's test was marginal, but not statistically significant ($p = 0.0724$).

DISCUSSION

This pooled meta-analysis of all published data from 774 subjects in six^{37–42} studies supports the use of midazolam by non-IV routes as a favorable alternative to diazepam in the initial treatment of SE. Midazolam, by any route, achieved seizure cessation more often than diazepam, by any route (RR 1.52; 95% CI = 1.27 to 1.82). This finding is even more apparent when comparing non-IV administration of diazepam and midazolam. The superior efficacy of midazolam as compared to diazepam likely reflects more favorable pharmacokinetics. Erratic absorption of rectal diazepam often results in low or delayed plasma peak drug concentrations, whereas IM and IN midazolam have a more consistent and higher bioavailability of 87% and 55%, respectively, with a short time to peak concentration.²⁹

Rapidity of seizure cessation is also a clinically important measure of performance that depends on both speed of administration and the onset of action. Earlier termination of seizure reduces the risk of complications due to convulsions, reduces neuronal injury, and is associated with decreased mortality. Rapid termination may also prevent kindling effects, where seizures become more refractory to treatment, and risk of recurrence increases as the duration of convulsions increases.¹⁹ Reliance on the IV route for benzodiazepine administration can be an important obstacle to rapid treatment of SE, because of difficulty or delay in obtaining IV access in a convulsing patient. As a result, our meta-analysis appears to favor non-IV midazolam, as its time to administration was more than 2 minutes faster, and seizure cessation less than 45 seconds slower than that of IV diazepam.

Respiratory depression is an expected and accepted side effect of benzodiazepine medications, and this meta-analysis suggests that midazolam is as safe as diazepam with regard to respiratory complications. Overall, 0.8% (3/375) of pediatric patients in this analysis receiving diazepam experienced complications, which is much less than the 10.3% previously observed with diazepam in a trial of the prehospital treatment of SE in adults.²⁶ Midazolam was associated with risk of respiratory complications in children similar to that found with diazepam (0.5%, 2/375). Respiratory depression in patients treated for SE can be a complication of either continued seizures, or an adverse medication effect. At least in the prehospital setting, failure to treat seizures is associated with much higher rates of respiratory complications. Twenty-two percent of placebo-treated patients in a prehospital trial of SE suffered a respiratory complication related to ongoing seizure.²⁶

Current clinical practice does not reflect the findings that non-IV midazolam is a safe and effective treatment for SE. There are no consensus guidelines addressing prehospital treatment of SE, and many large agencies rely solely on diazepam, or allow only restricted use of midazolam. Published professional guidelines for SE management rely on lorazepam or diazepam, and emphasize IV administration.⁵⁰⁻⁵³ Only the Royal College of General Practitioners acknowledges the role of buccal midazolam for use in the prehospital environment, but even in that guideline rectal diazepam is preferred.⁵² Recent surveys of parents and practitioners show a growing acceptance of IN and buccal midazolam over PR valium, but widespread adoption has not yet occurred.^{54,55} This analysis, in conjunction with previously published systematic reviews,^{32,56} may inform the development of future evidence-based guidelines. However, further prospective clinical trials are ultimately needed to confirm the efficacy and safety of non-IV midazolam in the treatment of patients with SE, especially in the adult population.

LIMITATIONS

As with all meta-analyses, the primary limitations of this study are those of the source data. The studies included here are relatively small, and contained differences in treatments, routes of medication administration, medication doses, outcome definitions, and inclusion criteria. However, the pooled results demonstrated low statistical heterogeneity, suggesting that comparisons are valid. Given the small numbers of studies included, the visual inspection of the funnel plot and measure of statistical heterogeneity should be interpreted with caution.⁵⁷⁻⁵⁹ A minimal I^2 does not guarantee homogeneity, but does provide evidence that there was no observed heterogeneity. Our finding of $I^2 = 0\%$ is consistent with many previously published Cochrane reviews.³⁶

Adults were virtually unrepresented in the included studies, and extrapolation of these results to the adult population should be done with caution. Future trials specifically targeting adult populations are required to confirm these findings. Studies also used differing definitions of adverse events, which were infrequent. However, this analysis is underpowered to detect differences in complication rates. Although a rigorous search strategy was employed, we did not attempt to identify or analyze non-English language studies. Comparisons with other anticonvulsants are lacking and were not identified or included in this meta-analysis. Despite these limitations, the effects identified here appear robust given

the magnitude of the findings and the rather small confidence intervals. Prospective confirmatory investigation, however, is warranted.

CONCLUSIONS

Published data support the efficacy and safety of non-intravenous routes of administration for midazolam, when compared to diazepam administered via any route in treating patients with status epilepticus, in the doses studied. Midazolam has characteristics that may make it an optimal choice for the treatment of seizing patients.

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Appendix A. Boolean Search Strategy

Date of Original Search- Aug. 20th, 2008

Search updated July 4th, 2009

PICO- In pediatric and adult patients with status epilepticus, is the administration of non-intravenous midazolam versus any route of diazepam more effective in ceasing seizures?

Exclusion Criteria:

1. Any study that does not compare diazepam to midazolam as a first line treatment for status epilepticus
2. Animal studies.
3. Studies that are not randomized controlled trials or quasi-experimental studies.
4. Any study that uses diazepam or midazolam as sedation, or prevention of seizures.

Search Strategy:

PubMed (62) 26 pulled for full text

("Seizures"[MeSH] OR "status epilepticus" [MeSH] AND ("diazepam"[MeSH Terms] OR "diazepam"[All Fields]) AND ("midazolam"[MeSH Terms] OR "midazolam"[All Fields])

EMBASE (15- all duplicates)

All EBM Reviews (Cochrane, ACP Journal Club) (20 titles- 13 full texts pulled)

CINAHL: (16-all duplicates)

International Pharmaceutical Abstracts: (14- all duplicates)

Web of Knowledge (124) (5 full texts)

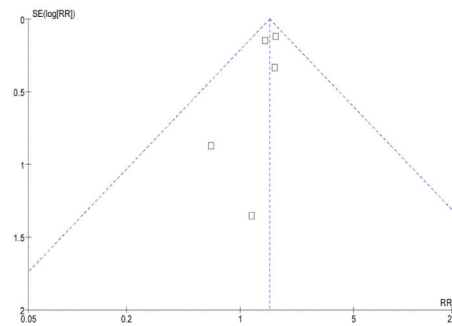
Hand Search of Review Article Bibliographies: all duplicates

TOTAL FULL TEXTS REVIEWED= 44

Total INCLUDED=6

Stratified by buccal vs. intranasal vs. intramuscular midazolam and rectal vs. intravenous diazepam

Appendix B: Funnel Plot



Funnel plot for Figure 2 (diazepam versus midazolam in failure to achieve seizure cessation). Kendall's rank correlation (Begg's test) = 0.77, $p = 0.0724$. As a comparison, the linear correlation (Egger's Test) = 0.27, $p = 0.24$.

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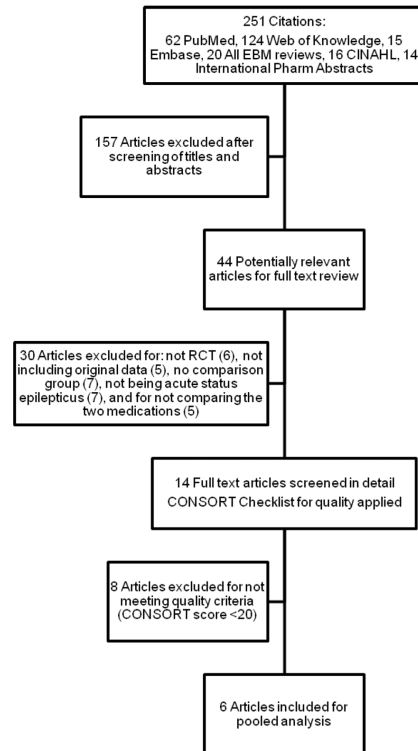


Figure 1.

Search strategy for articles reviewed for meta-analysis.

EBM = evidence-based medicine; CINAHL = Cumulative Index to Nursing and Allied Health Literature; RCT = randomized controlled trial; CONSORT = Consolidated Standards of Reporting Trials

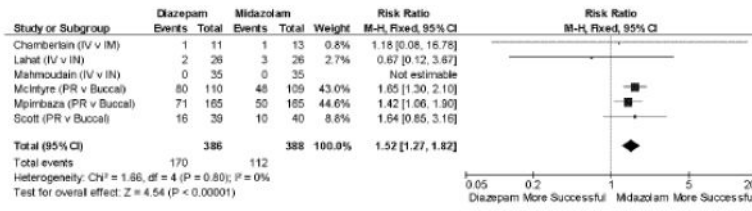


Figure 2. Diazepam versus midazolam in failure to achieve seizure cessation (all routes of administration). M-H = Mantel-Haenszel; IV = intravenous; IM = intramuscular; IN = intranasal; PR = per rectum

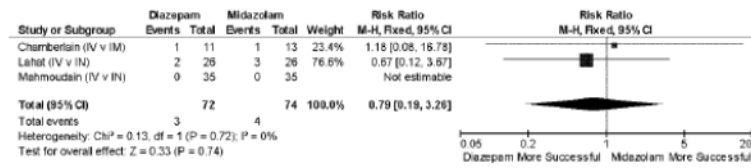


Figure 3. Intravenous diazepam versus non-intravenous midazolam in failure to achieve seizure cessation. M-H = Mantel-Haenszel; IV = intravenous; IM = intramuscular; IN = intranasal

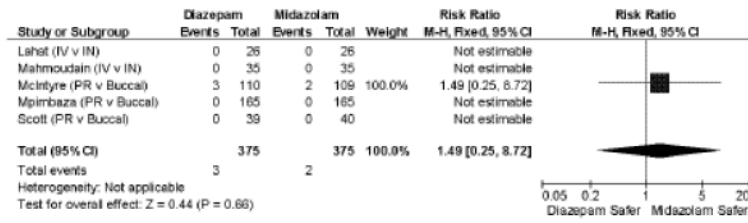


Figure 4. Respiratory complications requiring intervention (assisted ventilations, endotracheal intubation). M-H = Mantel-Haenszel; IV = intravenous; IM = intramuscular; IN = intranasal; PR = per rectum

Table 1

Characteristics of included studies.

Study, year	n	Age Range	Diazepam Dose/Route	Midazolam Dose/Route	Definition of "Status"	Definition of Success	CONSORT Score	Trial Design	Non Generalized Seizures Included?	History of Fever (%)	History of Prior Seizures (%)
Chamberlain, et al. 1997	24	0 mo. to 18 yr.	0.5mg/kg IV	0.2mg/kg IM	seizing >10 minutes	No seizure activity within 5 minutes	23	Randomized	Yes (11 partial motor)	0	57
Lahat, et al. 2000	52	6 mo. to 5 yr.	0.3mg/kg IV	0.2mg/kg IN	seizing >10 minutes	No seizure activity within 5 minutes; up to 10 minutes considered delayed success	24	Randomized	No	100	77
Mahmoudian, et al. 2004	70	2 mo. to 15 yr.	0.2mg/kg IV	0.2mg/kg IN	seizing at arrival to ED	No seizure activity within 10 minutes	22	Randomized	Yes (6 simple partial)	21	39
McIntyre, et al. 2005	219	6 mo. to 15 yr.	0.5mg/kg PR	0.5mg/kg Buccal	seizing at arrival to ED	No seizure activity within 10 minutes and no recurrent seizure within 1 hour	27	Randomized	Yes (5 partial included were protocol violations)	35	72
Mpimbaza, et al. 2008	330	3 mo. to 12 yr.	0.5mg/kg PR	0.5mg/kg Buccal	seizing at arrival to ED or >5 minutes	No seizure activity within 10 minutes and no recurrent seizure within 1 hour	28	Randomized	Yes (61 focal)	72	4
Scott, et al. 1999	79	5–22 yr.	10mg PR	10mg Buccal	seizing >5 minutes	Seizure cessation within 10 minutes	26	Randomized	Yes (17 complex partial, 10 myoclonic)	0	100

CONSORT = Consolidated Standards of Reporting Trials

PR = per rectum; IV = intravenous; IN = intranasal; IM = intramuscular; mo = month; yr = year; mg = milligram; kg = kilogram.