Non-intravenous midazolam versus intravenous or rectal diazepam for the treatment of early status epilepticus: a systematic review

PROTOCOL

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The review will be guided by the following protocol describing research questions, review methods, and plan for data extraction and synthesis.
Background
Prompt treatment of status epilepticus (SE) is associated with better outcomes. Diazepam (DZP) and midazolam (MDZ) are commonly used in the treatment of early (stage I) SE. Aim of this systematic review is to determine if non-intravenous (non-IV) MDZ is as effective and safe as intravenous or rectal DZP in terminating early SE in children and adults.

METHODS

Criteria for considering studies for this review
We will include randomized controlled trials, blinded or unblinded. Uncontrolled and non-randomized trials will be excluded. We will include patients of any age diagnosed with early (stage I) SE defined either as seizures lasting >5 min [Lowenstein, 1999] or as seizures at arrival to emergency department. We will consider all trials in which non-IV MDZ used as first-line agent in monotherapy was compared with DZP (first-line drug given singly) by any route. Following outcomes will be considered:

Efficacy
- The number of patients with clinical seizure cessation within 15 min after drug administration or number of patients with clinical seizure cessation before emergency medical service support arrived (only for studies conducted in prehospital setting).
- Time from arrival at the ED to drug administration (or time from seizure initiation to drug administration for studies conducted in prehospital setting);
- Time from drug administration to clinical seizure cessation;
- Time from arrival at the ED to clinical seizure cessation (or time from seizure initiation to clinical seizure cessation for studies conducted in prehospital setting).

Tolerability and safety
- The number of patients experiencing serious adverse effects (respiratory depression or hypotension).

Search methods for identification of studies
A comprehensive review of the literature of computerized databases as well as searches to find unpublished trials will be performed to minimize publication bias. Following electronic databases and data sources will be searched:
1. MEDLINE, accessed by PubMed;

Following search strategy for these databases will be adopted: ("Status Epilepticus"[Mesh] OR "status epilepticus" OR seizur*) AND midazolam). All resulting titles and abstracts will be evaluated, and any relevant article will be considered. There will be no language restrictions.

3. ClinicalTrials.gov (available at: https://clinicaltrials.gov/); following search strategy for this database will be adopted: ("Status Epilepticus" OR seizure OR seizures) AND midazolam.

There will be no language restrictions.

4. Handsearching of the references quoted in the identified trials.

5. Contact with pharmaceutical companies to identify unpublished trials or data missing from articles.

6. Contact with authors and known experts to identify any additional data.

**Data collection and analysis**

**Study selection**

Review authors will independently assess trials for inclusion. Disagreements will be resolved by discussion.

**Quality assessment**

Trials will be scrutinized, and the methodological quality of all included studies evaluated. Quality assessment will include following aspects of methodology: study design, definition and clinical relevance of outcomes, type of control, method of allocation concealment, total study duration, completeness of follow-up, intention-to-treat analysis, data concerning adverse effects, risk of bias, and conflict of interests. The randomized trials will be judged on the reported method of allocation concealment and on the risk of bias as outlined in the *Cochrane Handbook for Systematic Reviews of Interventions* Version 5.1.0 [updated March 2011] [Higgins, 2011].

**Data extraction**

Following trial data will be extracted: main study author and age of publication; country; definition of SE adopted; type of participants (children and/or adults); total number, age, and sex of participants for each treatment group; seizure type; intervention details (dose, way of administration); definition of successful treatment adopted in each trial; outcome measures proportion of patients with clinical seizure cessation after drug administration in each treatment group; time from arrival at the ED to drug administration; time from drug
administration to clinical seizure cessation; time from arrival at the ED to clinical seizure cessation; proportion of patients experiencing serious adverse effects (respiratory depression and/or hypotension) in each group. Data will be independently extracted by review authors and cross-checked. Disagreement about quality assessment and data will be resolved by discussion.

**Data analysis**

We will seek data on the number of participants in the treatment groups and with each outcome in the articles. Provided we think it clinically appropriate, and no important clinical and methodological heterogeneity is found, we plan to summarize results in a meta-analysis. The trials comparing the same drugs will be combined. Pooled risk ratios will be determined using the Mantel-Haenszel random-effects models. Data will be stratified into subgroups, comparing

1. non-IV midazolam by any route versus diazepam by any route;
2. Intranasal midazolam versus diazepam by any route;
3. Buccal midazolam versus diazepam by any route;
4. Intramuscular midazolam versus diazepam by any route;
5. Intranasal midazolam versus intravenous diazepam;
6. Intranasal midazolam versus rectal diazepam;
7. Buccal midazolam versus rectal diazepam;
8. Buccal midazolam versus intravenous diazepam;
9. Intramuscular midazolam versus intravenous diazepam;
10. Intramuscular diazepam versus rectal diazepam.

Where study data are available, we will assess the mean differences in times between arrival at the ED and drug administration (non-IV midazolam by any route versus diazepam by any route) or clinical seizure cessation, and between drug administration and cessation of seizure activity. Dichotomous outcomes (clinical seizure cessation and occurrence of serious adverse effects) will be analyzed by calculating relative risks (RR) for each trial with the uncertainty in each trial being expressed using 95% confidence intervals (CI). For each outcome, a weighted treatment effect across trials will be calculated. Continuous data (time intervals from arrival to the ED and drug administration or clinical seizure cessation) will be analyzed by calculating the mean difference for each trial, with the uncertainty in each study being expressed using 95% CI.
Homogeneity among study results will be evaluated using a standard Chi squared test, combined with the $I^2$ statistics, and the hypothesis of homogeneity will be rejected if the $p$ value is less than 0.10. The interpretation of $I^2$ for heterogeneity will be made as follows: 0–25 % represents low heterogeneity, 25–50 % moderate heterogeneity, 50–75 % substantial heterogeneity, 75–100 % high heterogeneity [Higgins, 2003]. Trial outcomes will be combined to obtain a summary estimate of effect (and the corresponding CI) using a random-effect model. Random-effects model is considered more conservative than a fixed-effect model, since it takes into account the variability between studies, thus leading to wider CIs. Statistical analyses will be performed with the Review Manager software developed by the Cochrane Collaboration (5.3).

References


Lowenstein DH, Bleck T, Macdonald RL. It’s time to revise the definition of status epilepticus. Epilepsia 1999; 40: 120–122