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Nonintravenous midazolam versus intravenous or rectal diazepam for the treatment of early status epilepticus: A systematic review with meta-analysis

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ABSTRACT

Background: Prompt treatment of status epilepticus (SE) is associated with better outcomes. Rectal diazepam (DZP) and nonintravenous (non-IV) midazolam (MDZ) are often used in the treatment of early SE instead of intravenous applications. The aim of this review was to determine if nonintravenous MDZ is as effective and safe as intravenous or rectal DZP in terminating early SE seizures in children and adults.
Methods: We searched the Cochrane Central Register of Controlled Trials (CENTRAL), ClinicalTrials.gov, and MEDLINE for randomized controlled trials comparing non-IV MDZ with DZP (by any route) in patients (all ages) with early SE defined either as seizures lasting >5 min or as seizures at arrival in the emergency department. The following outcomes were assessed: clinical seizure cessation within 15 min of drug administration, serious adverse effects, time interval to drug administration, and time from arrival in the emergency department to seizure cessation. Outcomes were assessed using a random-effects Mantel–Haenszel meta-analysis to calculate risk ratio (RR), odds ratio (OR) and mean difference with 95% confidence intervals (95% CIs).
Results: Nineteen studies with 1933 seizures in 1602 patients (some trials included patients with more than one seizure) were included. One thousand five hundred seventy-three patients were younger than 16 years. For seizure cessation, non-IV MDZ was as effective as DZP (any route) (1933 seizures; RR: 1.03; 95% CIs: 0.98 to 1.08). No difference in adverse effects was found between non-IM MDZ and DZP by any route (1933 seizures; RR: 0.87; 95% CIs: 0.50 to 1.50). Time interval between arrival and seizure cessation was significantly shorter with non-IV MDZ by any route than with DZP by any route (338 seizures; mean difference: −3.67 min; 95% CIs: −5.98 to −1.36); a similar result was found for time from arrival to drug administration (348 seizures; mean difference: −3.56 min; 95% CIs: −5.00 to −2.11). A minimal difference was found for time interval from drug administration to clinical seizure cessation, which was shorter for DZP by any route than for non-IV MDZ by any route (812 seizures; mean difference: 0.56 min; 95% CIs: 0.15 to 0.98 min). Not all studies reported information on time intervals. Comparison by each way of administration failed to find a significant difference in terms of clinical seizure cessation and occurrence of adverse effects. The only exception was the comparison between buccal MDZ and rectal DZP, where MDZ was more effective than rectal DZP in terminating SE but only when results were expressed as OR (769 seizures; OR: 1.78; 95% CIs: 1.11 to 2.85; RR: 1.15; 95% CIs: 0.85 to 1.54). Only one study was entirely conducted in an adult population (21 patients, aged 31 to 69 years), showing no difference in efficacy or time to seizure cessation after drug administration between intranasal MDZ and rectal DZP.
Conclusions: Non-IV MDZ is as effective and safe as intravenous or rectal DZP in terminating early SE in children and probably also in adults. Times from arrival in the emergency department to drug administration and to seizure cessation are shorter with non-IV MDZ than with intravenous or rectal DZP, but this does not necessarily result in higher seizure control. An exception may be the buccal MDZ, which, besides being socially more acceptable and easier to administer, might also have a higher efficacy than rectal DZP in seizure control.

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1. Introduction

Status epilepticus (SE) can be regarded as the most extreme and severe form of seizure activity, being associated with high morbidity and mortality [1]. In clinical practice, SE has been traditionally defined as epileptic activity persisting for more than 30 min or as two or more sequential seizures without full interictal recovery [2]. However, over the years, this timeframe has been progressively shortened to the pragmatic definition of 5 min because of the seriousness of the condition and the urge to treat it as early as possible [3]. Its prompt treatment can prevent death or irreversible brain damage. In fact, early treatment is associated with lower morbidity and mortality, fewer drugs required in hospitals, and shorter overall seizure duration [4,5].

There are, however, several factors, including education regarding seizure emergencies and transferring of patients to the hospital, that may hinder prompt treatment, resulting in a significant treatment delay. Hence, prehospital management of SE might be beneficial provided that administered drugs are effective in terminating seizures, safe, and easy to use.

Diazepam (DZP) and midazolam (MDZ) are commonly used in the treatment of early (stage I) SE. Midazolam is a water-soluble benzodiazepine, which may be administered by different routes: intravenous, intramuscular, buccal, and intranasal. Conversely, DZP can be administered either intravenously or per rectum. Rectal DZP is the most common drug used in the prehospital management of early SE in Spain [6] and possibly also in other countries. However, its administration is most of the time socially unacceptable. Furthermore, its administration requires the removal of clothes and positioning the patient appropriately, which may result in relevant treatment delay. The same limitation holds true for intravenous administration of DZP or other drugs such as lorazepam, which requires the placement of an intravenous access.

Hence, MDZ, which can be administered by different and more practical routes (buccal, intranasal, intramuscular), has emerged as an alternative to drugs administered by intravenous or rectal route, such as lorazepam or DZP [7,8].

The aim of this systematic review was to determine if nonintravenous (non-IV) MDZ is as effective and safe as intravenous or rectal DZP in terminating early SE in children and adults. Furthermore, we aimed to evaluate whether non-IV MDZ administration is faster than intravenous or rectal DZP administration and, if so, whether this "time gain" results in higher seizure control.

2. Methods

This review was guided by a written prespecified protocol describing research questions, review methods, and a plan for data extraction and synthesis. The protocol is available at: http://www.crd.york.ac.uk/PROSPERO/DisplayPDF.php?ID=CRD42015016179.

2.1. Criteria for considering studies for this review

We included randomized controlled trials (RCTs), blinded or unblinded. Uncontrolled and nonrandomized trials were excluded. We included patients of any age diagnosed with early (stage I) SE defined either as seizures lasting >5 min [3] or as seizures at arrival to the emergency department.

We considered all trials in which non-IV MDZ used as a first-line agent in monotherapy was compared with DZP (first-line drug given singly) by any route. The following outcomes were considered:

Efficacy

- The number of status epilepticus episodes which were terminated within 15 min after drug (MDZ or DZP) administration or before emergency medical service support arrived (only for studies conducted in prehospital settings);
- Time from arrival at the emergency department to drug administration (or time from seizure initiation to drug administration for studies conducted in prehospital settings);
- Time from drug administration to clinical seizure cessation; and
- Time from arrival at the emergency department to clinical seizure cessation (or time from seizure initiation to clinical seizure cessation for studies conducted in prehospital settings).

Tolerability and safety

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

2.4. Search methods for identification of studies

A comprehensive review of the literature of computerized databases as well as searches to find unpublished trials were performed to minimize publication bias. The following electronic databases and data sources were searched:

1. MEDLINE (January 1966–20th of January 2015), accessed through PubMed;
2. Cochrane Central Register of Controlled Trials (CENTRAL) (Issue 12, *The Cochrane Library*, December 2014) (accessed 20th of January 2015); the following search strategy was adopted: (("Status Epilepticus"[Mesh] OR "status epilepticus" OR seizur*) AND midazolam). All resulting titles and abstracts were evaluated, and any relevant article was considered. There were no language restrictions;
3. ClinicalTrials.gov (available at: https://clinicaltrials.gov/; accessed 20th of January 2015); the following search strategy for this database was adopted: (("Status Epilepticus" OR seizure OR seizures) AND midazolam). There were no language restrictions;
4. Handsearching of the references quoted in the identified trials;
5. Contact with pharmaceutical companies (Viropharma and Accord Healthcare) to identify unpublished trials or data missing from articles (January 2015); and
6. Contact with authors and known experts to identify any additional data.

3. Data collection and analysis

3.1. Study selection

Retrieved articles were independently assessed for inclusion by two review authors; any disagreement was resolved through discussion.

3.2. Quality assessment

Trials were scrutinized, and the methodological quality of all included studies was evaluated. Quality assessment included the 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 were 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] [9]. We also evaluated whether authors disclosed their conflict of interest and whether pharmaceutical companies sponsored the studies.

3.3. Data extraction

The following trial data were extracted: main study author and age of publication; country; definition of SE applied in the study; type of participants (children and/or adults); total number, age, and sex of