JURNAL KEDOKTERAN DIPONEGORO
(*DIPONEGORO MEDICAL JOURNAL*)
Online : http://ejournal3.undip.ac.id/index.php/medico
E-ISSN : 2540-8844
DOI : 10.14710/dmj.v12i6.38806
JKD (DMJ), Volume 12, Number 6, November 2023 : 350-355

THE ROLE OF MIDAZOLAM ON STATUS EPILEPTICUS: SYSTEMATIC REVIEW

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ABSTRACT

Background: Status epilepticus is a condition that results either in the failure of the mechanisms responsible for stopping seizures or in initiating mechanisms that cause seizures to be abnormally prolonged. Benzodiazepine is the first-line therapy for status epilepticus. The three usually used Benzodiazepines are Lorazepam, diazepam, and midazolam. **Objective:** This systematic review was undertaken to determine midazolam's role in managing patients with status epilepticus. **Methods:** A systematic search from PubMed, Science Direct, and Cochrane was conducted with predetermined keywords. Studies in randomized controlled trials assessing the impact of midazolam on epileptic status were included in the inclusion criteria. Articles are published in English, and the full text is accessible. The authors independently extracted data and assessed the risk of bias for each included study. **Results:** Of 6410 studies obtained from the search results, 13 studies were found that were relevant and matched the inclusion criteria. Benzodiazepines are the first line of SE therapy in an emergency. This group works by inhibiting GABA receptors and has a rapid effect in stopping seizures. Midazolam can be given intravenously, intramuscularly, or transmucosal (nasal, buccal, or rectal). Intravenous midazolam may be a good choice because of its short onset of action and, therefore, can effectively stop seizures. **Conclusion:** Effective and safe results have been seen with each Midazolam administration method. This suggests that Midazolam may be an excellent therapeutic option for SE. However, the type of Midazolam administration can be adjusted according to the guidelines and drug availability in each country.

Keywords: {use 4-6 keywords, alphabetical order}: Benzodiazepine, Epilepticus, Midazolam, Status epilepticus

INTRODUCTION

Status epilepticus is a condition that results either in the failure of the mechanisms responsible for stopping seizures or in initiating mechanisms that cause seizures to be abnormally prolonged (for periods of 5 minutes or longer). Status epilepticus is a condition with long-term effects (primarily if it occurs for more than 30 minutes), such as nerve death, nerve injury, and changes in nerve tissue, depending on the type and duration of the seizure.[1] SE is characterized as ongoing convulsive activity or recurring generalized convulsive seizure activity without recovering consciousness in the context of generalized tonic-clonic seizures. Different criteria apply for SE, including focal seizures with diminished awareness and absence of SE.[1] Each year, there are 150,000 SE cases recorded in the US, resulting in 55,000 fatalities. In 10 to 40 per 100,000 people experience status epilepticus each year.[2]

In order to prevent brain damage and additional systemic consequences, seizures must be quickly controlled.[3-5] Benzodiazepine is the first-line therapy for status epilepticus. The three usually used Benzodiazepines are Lorazepam, diazepam, and midazolam.[6] A water-soluble benzodiazepine, midazolam can be administered intravenously, intramuscularly, or transmucosal. Compared to rectal diazepam administration, midazolam transmucosal administration is more secure, efficient, simple to administer, and socially acceptable.[7] Midazolam works as GABA-A agonist.[2] Midazolam was the first line of defense against SE, followed by phenytoin, phenobarbitone, and levetiracetam. Its loading dose, provided in conjunction with continuous intravenous infusion at 0.05–0.2 mg/kg/h, equals 0.2 mg/kg of body weight up to a maximum of 10 mg intravenously. The adverse effects of midazolam include hypotension and apnea.[8] Contraindications to midazolam use include respiratory distress, hypersensitivity to benzodiazepines, or a history of substance abuse.

Based on the information above, SE patients have diverse treatment options. We conducted a

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systematic review to determine the role of midazolam on status epilepticus.

METHODS

This study was conducted according to the recommendations of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.

Study selection

A systematic search from PubMed, Science Direct, and Cochrane was conducted until January 2022. We use the keywords "midazolam" AND "status epilepticus" OR "epilepsy". This study was conducted in accordance with the Preferred Reporting Items for Systematic Examination and Meta-Analysis (PRISMA) guidelines. We imported all search results into the Mendeley reference manager and removed the duplicate and screen. We examined the titles and abstracts of the papers to identify eligible studies and then screened the full texts. Disagreements between the three researchers were discussed until a consensus was reached.

Eligibility criteria

The inclusion criteria of this study were (1) Studies assessing the impact of midazolam on refractory status epileptic; (2) Articles were published in English; (3) The full-text article was accessible; (4) Studies with randomized controlled trials; (5) Studies with sufficient information for analysis; (6) Studies were published in the last 10 years.

Exclusion criteria

The exclusion criteria were as follows: (1) duplicate studies; (2) Review and expert opinion; (3) Incomplete data; (4) Unavailable full text; (5) Unrelated titles and abstracts.

Data extraction

Two reviewers (AAF and VAP) independently extracted data using a standardized form. Discrepancies were discussed and resolved by the senior researcher (AM). The following information was collected from each paper: (1) author, (2) year of publication, (4) study design, (4) country of research team, (5) participant, (6) sample size, (7) midazolam type, (8) midazolam dose, (9) frequency of midazolam administration, (10) Status epilepticus type, (11) main finding.

Quality assessment

Two reviewers assessed the methodological quality independently (AAF and VAP) based on the checklist of the Jadad score. The Jadad score was composed of three components: randomization (0-2 points), blinding (0-2 points), and dropouts and withdrawals (0-2 points) (0-1 points). Each item's response was either "yes" (1 point) or "no" (0 points). Higher ratings indicated better reporting; the final score varied from 0 to 5. Studies with a Jadad score of two or fewer were considered low quality, while studies with a score of three or more were regarded as good quality. A senior researcher (AM) was consulted if a discrepancy was found.

RESULTS

In total, 6410 items were identified based on our reference lists, 314 duplicates were removed, and 6078 were excluded because of irrelevant titles, abstracts, and no full text available. In total, 17 studies were included for full-text review. two of them were eliminated due to not meeting the inclusion criteria. Finally, 13 studies were included in this review. Figure 1 illustrates the paper selection process in our review, and Table 1 shows the characteristics of included studies.

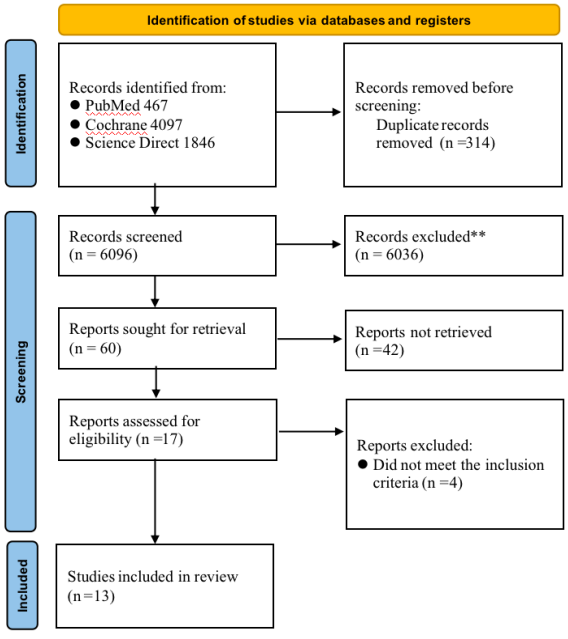

Figure 1. The PRISMA flow diagram of the literature search.

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Table 1. Characteristics of included studies

Authors and Year	Sample Size	Location	Study design	Jadad score	Main finding
Shaikh et al. 2022	31	India	RCT	7	Intramuscular midazolam more effective than intranasal midazolam for controlling status epileptic
Detynieki, et al. 2019	201	US	RCT	7	Midazolam nasal spray gives rapid and sustained seizure control compared placebo nasal spray
Wheless, et al. 2019	161	US	RCT	7	Nasal spray midazolam gives good results in treating seizure compared placebo nasal spray
Spencer, et al. 2020	62	USA	RCT	8	Midazolam nasal spray 5 mg may provide improvement over placebo nasal spray
Meng, et al. 2023	161	USA	RCT	5	Midazolam nasal spray effectiveness, convenience, minimal side effect, and reduced anxiety in patients and caregivers compared with placebo nasal spray
Berg, et al. 2017	30	US	RCT	7	Compared to non geriatrics, midazolam nasal spray has higher plasma concentration and longer t1/2 in geriatrics with a dose of 5.0 mg
Bancke, et al. 2015	25	USA	RCT	8	Intranasal midazolam improved bioavailability with similar pharmacodynamic effects and referable alternative to the currently approved rectal diazepam treatment
Silbergleit, et al. 2013	893	USA	RCT	4	IM route of midazolam is administered more rapidly after arrival than medication given IV, but that the onset of action after IV administration is more rapid than after IM administration
Abbaskhanian, et al. 2021	35	Iran	RCT	7	Compared to midazolam, sodium valproate more effective in controlling status epileptic
Momen, et al. 2014	50	Iran	RCT	8	Midazolam IM and rectal diazepam were effective for seizure control and no significant difference was found
Hamano, et al. 2019	34	Japan	RCT	8	Intravenous midazolam is suitable as first-line treatment either bolus or infusion
Portela, et al. 2013	16	Brazir	RCT	8	Compared to intravenous midazolam, Intramuscular midazolam is a great alternative for treating child seizures due to its effectiveness, simplicity, and quickness of administration
Alansari, et al. 2020	150	Qatar	RCT	8	Intramuscular midazolam is more effective and safe than buccal midazolam as a first-line treatment for childrens

DISCUSSION

Seizures are temporary signs or symptoms due to excessive or synchronic abnormal nerve activity in the brain. Status epilepticus is a condition that results either from failure of the mechanisms responsible for stopping seizures or from initiating mechanisms that cause seizures to be abnormally prolonged (for 5 minutes or longer). Status epilepticus is a condition that has long-term effects (especially if it occurs for more than 30 minutes), such as nerve death, nerve injury, and changes in nerve tissue, depending on the type and duration of the seizure.[21-23] Classification of status epilepticus is based on 4 axes: semiology, etiology, EEG correlation, and age. Therapy for status epilepticus should be given as soon as possible to stop the seizures before permanent nerve cell damage occurs. Status epilepticus becomes more challenging to treat as the duration of the seizure increases.[24]

Benzodiazepines are the first emergency treatment for status epilepticus. This group acts by blocking GABA receptors and has a rapid effect on stopping seizures. The benzodiazepines that are often used are lorazepam, diazepam, and midazolam.[2,6] Lorazepam 0.1 mg/kg or 4-8 mg intravenously (IV) is highly considered to be the first choice for acute management. But because IV lorazepam is unavailable in Indonesia, diazepam 0.2 mg/kg is considered to be the choice. Diazepam has a rapid onset of action with a very short duration of action because it is quickly redistributed to the body's fat reserves. Diazepam can be given rectally.[25] Midazolam can be given intravenously, intramuscularly, or transmucosal (nasal, buccal, or rectal).[26] All benzodiazepines cause sedation and respiratory depression, and repeated doses have a cumulative effect. The sedative effect can reduce the recovery of consciousness after SE stops. Midazolam can be given at a dose of 0.2 mg/kg with a maximum dose of 10 mg in adult patients.[26]

Intravenous midazolam is suitable as the first treatment.[20] Another study said that even compared to intravenous midazolam, intravenous sodium valproate was more effective and relatively safe for children with status epilepticus. In that study, patients receiving intravenous sodium valproate had a shorter stay in the PICU than those with intravenous midazolam. This can be given in small doses first to minimize side effects and then increased gradually to stop seizures.[18] Compared with intramuscular administration, intravenous midazolam has faster onset to stop seizures, but its administration is slower than intramuscular.[17,20] Intramuscular administration of midazolam 0.3 mg/kg was as effective as rectal diazepam 0.5 mg/kg in stopping seizures, and there

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were no serious side effects to the two drugs. But when compared with intravenous diazepam, intramuscular midazolam is more effective, simple, and easy to administer.[6,19] Administration of intramuscular midazolam is more effective and safe than transmucosal midazolam, especially in children with all types of epileptic status. Administering transmucosal midazolam (nasal, buccal, or rectal) is safer, more efficient, easier to administer, and easier to accept in the community. It increases the bioavailability of its pharmacodynamic effects compared to rectal diazepam.[7,15,16] Transmucosal administration of midazolam can be an alternative option to stop status epilepticus because it gives good results in treating seizures, is well tolerated for the long term, comfort, has minimal side effects, and reduces anxiety in patients and their families. The effective dose of transmucosal midazolam is 5 mg. In geriatric patients, plasma concentrations of midazolam tend to increase compared to non-geriatric patients, but there are no different side effects at the two ages.[9-13]

The limitations of this research include that some studies have small subjects, and some assess the effectiveness of a drug brand. We recommend more studies with larger samples and studies.

CONCLUSION

Midazolam comes from the benzodiazepine group, one of the recommended therapies for treating seizures in status epilepticus. Midazolam administration can be done through intramuscular, intravenous, and intranasal. Several studies have shown effective and safe results for each method of administration. However, this method can be adjusted according to each country's guidelines and drug availability.

ETHICAL APPROVAL

There is no ethical approval.

CONFLICTS OF INTEREST

The authors declare no conflict of interest.

FUNDING

No specific funding was provided for this article.

AUTHOR CONTRIBUTIONS

Conceptualization, AAF and VAP; methodology, AAF; validation, AAF, VAP, and AM; formal analysis, AAF and VAP; writing—original draft preparation, XXX; writing—review and editing, AAF and VAP; supervision, AM.

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