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. Benzodiazepine is the first-line therapy for status epilepticus. The three usually used Benzodiazepines are Lorazepam, diazepam, and midazolam.

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
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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.](image-url)
Table 1. Characteristics of included studies

<table>
<thead>
<tr>
<th>Authors and Year</th>
<th>Sample</th>
<th>Location</th>
<th>Study design</th>
<th>Jadad score</th>
<th>Main finding</th>
</tr>
</thead>
<tbody>
<tr>
<td>Shaikh et al. 2022</td>
<td>31</td>
<td>India</td>
<td>RCT</td>
<td>7</td>
<td>Intranasal midazolam more effective than intranasal midazolam for controlling status epilepticus</td>
</tr>
<tr>
<td>Ditrynicki, et al. 2019</td>
<td>201</td>
<td>US</td>
<td>RCT</td>
<td>7</td>
<td>Midazolam nasal spray gives rapid and sustained seizure control compared placebo nasal spray</td>
</tr>
<tr>
<td>Whelans, et al. 2019</td>
<td>161</td>
<td>US</td>
<td>RCT</td>
<td>7</td>
<td>Nasal spray midazolam gives good results in treating seizures compared placebo nasal spray</td>
</tr>
<tr>
<td>Spencer, et al. 2020</td>
<td>62</td>
<td>USA</td>
<td>RCT</td>
<td>8</td>
<td>Midazolam nasal spray 5 mg may provide improvement over placebo nasal spray</td>
</tr>
<tr>
<td>Mong, et al. 2023</td>
<td>161</td>
<td>USA</td>
<td>RCT</td>
<td>5</td>
<td>Midazolam nasal spray effective, convenient, minimal side effect, and reduced anxiety in patients and caregivers compared with placebo nasal spray</td>
</tr>
<tr>
<td>Bong, et al. 2017</td>
<td>30</td>
<td>US</td>
<td>RCT</td>
<td>7</td>
<td>Compared to non-geriatric, midazolam nasal spray has higher plasma concentration and longer 1/2 t in geriatrics with a dose of 5.0 mg</td>
</tr>
<tr>
<td>Buncic, et al. 2015</td>
<td>25</td>
<td>USA</td>
<td>RCT</td>
<td>8</td>
<td>Intranasal midazolam improved bioavailability with similar pharmacodynamic effects and preferable alternative to the currently approved rectal diazepam treatment</td>
</tr>
<tr>
<td>Silbergliet, et al. 2013</td>
<td>895</td>
<td>USA</td>
<td>RCT</td>
<td>4</td>
<td>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</td>
</tr>
<tr>
<td>Abbaaehami an, et al. 2021</td>
<td>35</td>
<td>Iran</td>
<td>RCT</td>
<td>7</td>
<td>Compared to midazolam, sodium valproate more effective in controlling status epilepticus</td>
</tr>
<tr>
<td>Mesiner, et al. 2014</td>
<td>50</td>
<td>Iran</td>
<td>RCT</td>
<td>8</td>
<td>Midazolam IM and rectal diazepam were effective for seizure control and no significant difference was found</td>
</tr>
<tr>
<td>Hizano, et al. 2019</td>
<td>34</td>
<td>Japan</td>
<td>RCT</td>
<td>8</td>
<td>Intravenous midazolam is suitable as first-line treatment other bolus of infarction</td>
</tr>
<tr>
<td>Portela, et al. 2013</td>
<td>16</td>
<td>Britain</td>
<td>RCT</td>
<td>8</td>
<td>Compared to intravenous midazolam, intramuscular midazolam is a great alternative for treating child seizures due to its effectiveness, simplicity, and quickness of administration</td>
</tr>
<tr>
<td>Alzahrani, et al. 2020</td>
<td>150</td>
<td>Qatar</td>
<td>RCT</td>
<td>8</td>
<td>Intramuscular midazolam is more effective and safe than buccal midazolam as a first-line treatment for children</td>
</tr>
</tbody>
</table>

DISCUSSION

Seizures are temporary signs or symptoms due to excessive or synchronous 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. 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.

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. 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.

Midazolam can be given intravenously, intramuscularly, or transtranusal (nasal, buccal, or rectal). 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.

Intravenous midazolam is suitable as the first treatment. 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. Compared with intramuscular administration, intravenous midazolam has faster onset to stop seizures, but its administration is slower than intramuscular. 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. 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. 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.

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.

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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.

REFERENCES


