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Evidence-Based Case Report

Efficacy and Safety Comparison Between Lorazepam and Diazepam in Treating Convulsive Status Epilepticus in Children: An Evidence-Based Case Report

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ABSTRACT

Introduction: Indonesia still recommends diazepam for epilepsy, but the International League Against Epilepsy increasingly favours lorazepam. Some reports indicate diazepam being less effective and causing side effects. This report presents a difficult-to-treat convulsive status epilepticus (CSE) case in a 10-month infant who received diazepam, questioning if intravenous/rectal lorazepam is a better initial therapy than diazepam for hospitalized children with CSE.

Methods: Following the patient-intervention-comparison-outcome (PICO) formula, we searched for evidence in four journal databases (Pubmed, Proquest, EBSCOHost, and Cochrane). Studies meeting inclusion and exclusion criteria were appraised.

Results: Through three systematic reviews and meta-analyses, our clinical query was addressed. One study revealed that rectal lorazepam was more effective in stopping seizures than rectal diazepam (RR 2.86). Meanwhile, two studies found that intravenous lorazepam exhibited similar efficacy in seizure cessation compared to intravenous diazepam (RR 1.04 and OR 1.03, respectively). Both drugs showed no significant difference in the time required to stop seizures or the necessity for additional doses or adjunctive medications to achieve such cessation, nor in the likelihood of refractory seizure within 24 hours. Two studies indicated that intravenous lorazepam had a reduced risk of respiratory depression (RR 0.71 and OR 0.62, respectively). Regardless of the administration route, lorazepam was linked to a lower probability of ICU admission (RR 0.15) than diazepam.

Conclusion: Intravenous lorazepam and diazepam are equally effective for treating CSE, but rectal lorazepam is considered better at stopping seizures and preventing their recurrence compared to diazepam. Furthermore, lorazepam is deemed safer, especially when given intravenously.

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INTRODUCTION

Epilepsy is one of the children's neurological diseases that causes debilitating outcomes, such as growth and development disorders, cognitive impairment, and decreased quality of life [1]. Most epilepsy is short-duration, and as it worsens, it gets more challenging to stop, leading to status epilepticus (SE) [2]. Repeated episodes of SE can cause irreversible nerve injury and thus requires urgent and appropriate early anticonvulsant treatment [3]. SE is characterised by at least two convulsions separated by 30 minutes or more without full recovery of consciousness (intermittent SE) or by a single prolonged seizure (continuous SE) [4]. SE is classified into two types: convulsive (CSE) and non-convulsive (NCSE). CSE, the most common type, is characterised by generalised tonic-clonic movements and mental status impairment [5]. The international consensus states that tonic-clonic seizures that have lasted at least 5 minutes must be given benzodiazepines as the first line, with up to 80% of patients achieving long-term seizure control [6,7].

However, the best initial drug treatment to stop seizures in children remains uncertain [3].

Rectal diazepam has been used as a primary drug to treat seizures pre-hospital and initially intra-hospital, as it was considered safe and easy, although it was less comfortable [8,9]. On the other hand, intravenous lorazepam has been used in the international consensus to treat adults [10,11] and children [12,13] with SE in the hospital setting. Several studies have found that lorazepam is preferable to diazepam as a first-line medication due to prolonged duration, better seizure outcomes and reduced incidence of respiratory depression [14,15]. Many specialists in developed countries have also endorsed lorazepam use as a first-line treatment of SE; however, its use in Indonesia for this indication is undocumented [16]. Today, lorazepam is still mainly prescribed for sleep disorders (such as insomnia) and as a preoperative medication, and it has not been extensively researched in treating seizures in Indonesian patients. Therefore, future studies and cost-benefit analyses are urgently needed to determine whether lorazepam is effective for treating epilepsy, especially in children. Ultimately, lorazepam preparation for seizure medication might be widely available in the future in the form of intravenous and rectal.

The American Epilepsy Society (AES) [17], International League Against Epilepsy (ILAE) [18], and National Institute for Health and Care Excellence (NICE) [19] also supported the benefits feature of lorazepam to treat SE among children. AES [17] stated that in children, intravenous lorazepam and diazepam are proven to be successful in stopping seizures in SE [17]. Looking at another research gap, although intravenous lorazepam has been recommended for SE in children, there was no adequate evidence for rectal lorazepam treating epilepsy in children [20–24]. Therefore, this evidence-based case report (EBCR) aimed to assess the therapeutic outcomes (i.e., efficacy and safety profile) of using intravenous and rectal lorazepam compared to diazepam for treating CSE in early recognition of seizure in hospital.

MATERIAL AND METHODS

Case Illustration

A 10-month-old boy with a seizure (>30 minutes) was admitted to the emergency department with a seizure 3 hours prior to admission and a worsening fever (temperature: 39.5˚C) since the previous day. Seizures started with staring and blinking rapidly, head-scratching, eyes blinking and squinting to the right side, the face turning to the right, mouth twitching, and drooling. The seizure was focal with right-hand stiffness, then immediately turned into a generalised seizure with tonic-clonic. His mother had once administered rectal diazepam at home, but the child became difficult to breathe and weaker. The patient was first diagnosed with epilepsy when he was 1 month old. The patient was admitted to the intensive care unit (ICU) at 7 months old with recurrent CSE >30 times.

The patient frequently experienced respiratory infections due to his laryngomalacia. There was no family history of epilepsy or genetic disorders. The patient was born at term with a healthy weight and length (3.1 kg and 44 cm, respectively). The antenatal examinations revealed no abnormalities. The patient did (routine USG) not require neonatal intensive care unit admission for respiratory or jaundice issues at birth.

Based on the paediatric assessment triangle (PAT), the patient appeared critically ill and experiencing respiratory failure, as evidenced by somnolence and inadequate TICLS parameters (tonus, interactiveness, consollability, look or gaze, and cry). Physical observations revealed tachypnea with a respiration rate of 64/min (regular) and oxygen saturation of 92% on room air, chest retraction, and snoring. However, the patient's pulse was regular and adequate at 200/min, with warm accrual and capillary refill test <3 second. No signs of pale skin, cyanosis, or mottling were observed. The child's head circumference was 43 cm, body weight was 7.1 kg, and body length was 68 cm.

During the physical examination, the patient exhibited a prominent hypertelorism feature, along with a fixed staring gaze and bilateral hypertrophy tonsil (T2/T2). Upon chest auscultation, crackles sounds were audible in the upper right and left lung, and stridor was observed during inspiration. However, the classic meningeal sign was negative, including nuchal rigidity and Brudzinski. The patient appeared unable to sit up or communicate effectively, displaying limited social engagement and motor function. Furthermore, the patient's immunisation status was incomplete, having only received two vaccines, specifically *Bacillus Calmette Guerin* (BCG) and hepatitis B.

The complete blood count test results showed an increase in haemoglobin (13.8 mg/dL) and hematocrit (44.7%), as well as leukocytosis (21,530/µL) with lymphocytosis (53.8%) in differential counts, and thrombocytosis (522,000/µL). The patient tested negative for COVID-19 based on the molecular test. Fig. 1. displays the patient's electroencephalogram (EEG) taken 3 months before the current evaluation, which led to the diagnosis of epilepsy of his seizure. Fig.2 of magnetic resonance imaging (MRI) revealed cerebral atrophy and incomplete myelination. In the emergency department, the patient was diagnosed with difficult-to-treat CSE due to epilepsy with a differential diagnosis of encephalitis and meningitis, prolonged fever due to suspected broncho-pneumonia and tonsils-pharyngitis), laryngomalacia, short stature, underweight, global delayed of development, and incomplete immunisation.

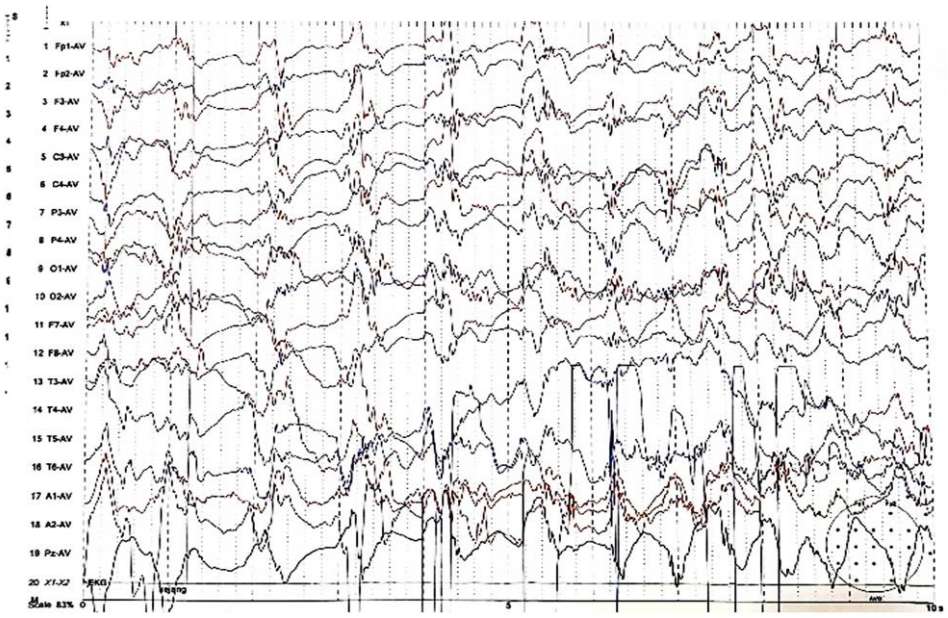


Fig. 1. Three-month prior electroencephalogram (EEG) of a patient with epilepsy and refractory status epilepticus. The figure revealed a spike-wave complex that started in the left occipital and expanded to both hemispheres with general slowing on long-term EEG.

The patient was given one 5 mg rectal dose of diazepam pre-hospital, and a second dose was administered upon admission due to challenges obtaining intravenous access caused by dehydration. However, the patient had difficulty breathing and experienced desaturation; thus, we provided oxygen supplementation through a nasal cannula at a rate of 1 litre per minute. Subsequently, we administered a slow bolus intravenous injection of diazepam 2 mg, intravenous paracetamol at a dosage of 70 mg per 6 hours, intravenous dexamethasone 1.5 mg per 8 hours, and crystalloid KaEN 1B infusion 35 ml/hour given. Catheter insertion was done to observe diuresis. After twice administration of intravenous diazepam, the CSE of the patient was still unresponsive, then was continued with intravenous loading of phenytoin 150 mg with monitoring.

Clinical Question

This presented case ignited the authors as a physician to formulate a clinical question: "*do intravenous/rectal lorazepam superior to intravenous/rectal diazepam for treating CSE in hospitalised children?*". This question was translated into a PICO formula for collecting evidence as follows:

- **P** : Pediatric patients with acute tonic-clonic seizures, including those in CSE
- **I** : Lorazepam
- **C** : Diazepam (current standard therapy)
- **O** : The efficacy measurement includes seizure cessation, time to the cessation of seizures since drug administration, the additional doses of drugs to stop seizures, the addition of other medications to stop seizures, and seizure recurrences within 24 hours. The safety profile includes the incidence of respiratory depression and ICU admission.

Patient's chart data were collected with consent from the family. Following the EBCR design [25,26] and case report reporting checklist (CARE) [27], we searched the highest evidence level of literature to answer our clinical question about the efficacy and safety profile of intravenous/rectal lorazepam compared to diazepam in treating acute tonic-clonic seizures, including CSE. A literature search was done in May – June 2022 using specific combined keywords in four large-scale journal databases (Pubmed, Proquest, EBSCOHost, Cochrane Library) following inclusion and exclusion criteria (Fig. 3).

After screening and full-text assessment, we found three eligible systematic reviews and meta-analyses (SRs-MAs) to be criticised using an appraisal sheet from the Center for Evidence-Based Medicine (CEBM) at the University of Oxford [25,28,29] and a Graphic Approach To Evidence-Based Practice (GATE-CAT) from the University of Auckland [30]. The quality of evidence was assessed independently by two authors for the aspect of 'importance', 'applicability', and 'validity' using the FAITH approach (find, appraise, include, total-up, heterogeneity) [28,31].

Heterogeneity interpretation in assessing the studies follows the criteria: 0–40% (not important); 30–60% (moderate); 50–90% (substantial); and 75–100% (considerable) [32]. We also looked for studies that

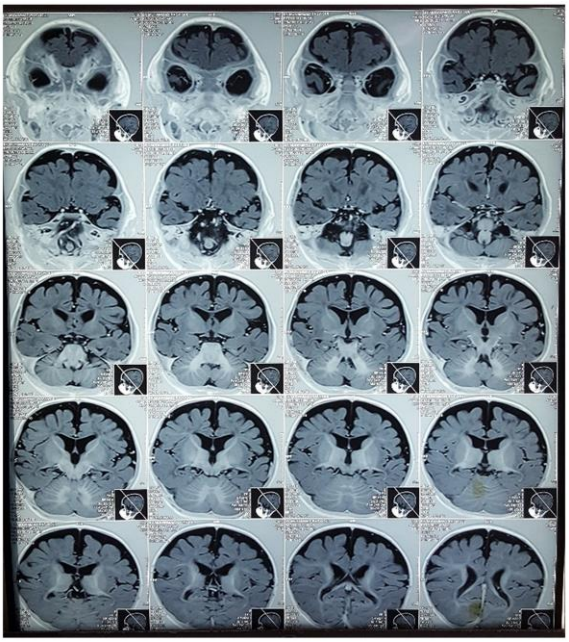


Fig. 2. Three-week magnetic resonance imaging (MRI) results of a patient with status epilepticus. MRI showed cerebral atrophy with incomplete myelination. There was no hippocampus atrophy and sclerosis and no focal cortical dysplasia. There was no appearance of infarction, haemorrhage, space-occupying lesion, or sign of intracranial pressure elevation.

could provide an explanation for the conceptual basis of the events that occur during the use of lorazepam and diazepam medications to treat SE, with a focus on their efficacy and safety. Ultimately, we summarised our findings to address the patient's problem and gave recommendations for clinical practice.

RESULTS

As shown in Table 1, three SR-MAs appraised were valid and eligible to be used as sources of evidence in answering clinical questions in this EBCR [33–35]. Three studies from McTague, et al. [33], Zhao et al. [34], and Wu et al. [35] matched our PICO, employed an extensive database in collecting their data, utilised a thorough searching method with explicit inclusion and exclusion criteria, provided a summary of findings with its heterogeneity assessment, and thus were eligible to be reviewed. Despite being valid and eligible, some studies had their shortcomings. McTague et al. [33] limited their diverse heterogeneity results for each subgroup analysis. Meanwhile, a study by Zhao et al. [34] was constrained due to their language restriction, thus possibly narrowing data collecting. Similarly, a study by Wu et al. [35] did not use the MeSH term and employed publication restriction, making them slightly lower performance in collecting the relevant study and might miss evidence during their search process.

Three acquired SR-MAs discussed the first-line anti-epileptic comparison in efficacy and safety profile [33–35]. McTague et al. [33] compared lorazepam and diazepam to treat tonic-clonic seizure and CSE with detailed subgroup analysis based on the intravenous administration route and per rectal. Similarly, Wu et al. [35] focused on therapy for CSE but not differentiating the route of administration. Meanwhile, due to limited studies, Zhao et al. [34] only assessed the comparison of lorazepam and diazepam in intravenous administration and did not differentiate CSE and NCSE in their analysis. The clinical and essential findings provided in the three valid studies were summarised in Table 2, focusing on the efficacy and safety profile of lorazepam compared to diazepam.

According to the critical appraisal for applicability in Table 3, all three studies were relatively applicable to answer our clinical question with the best evidence given by McTague et al. [33]. There are some important notes to consider regarding clinical applicability. First, Wu et al. [35] did not differentiate the route of administration in their analysis, making their applicability unclear. Moreover, the criteria age of children included in their study was not explicitly explained. Meanwhile, Zhao et al. [34] did not analyse the efficacy and safety comparison between rectal lorazepam and diazepam.

As our concern, although overall, lorazepam was superior to diazepam, we admitted that their drug preparation is not widely distributed Internationally for rectal form and in Indonesia for both parenteral and suppository [36–38]. To sum up, the three studies included in this EBCR were eligible and essential to explain the efficacy and safety comparison between lorazepam and diazepam in treating CSE in a hospital setting [33–35].

DISCUSSION

Our patient was diagnosed with difficult-to-treat CSE. His risk factor for seizure was presented, including abnormality in the brain, recurrent infection, and dehydration (as found in increased haemoglobin, hematocrit, and platelet counts). We gave him a second diazepam suppository at the admission because a once-shot had been given at home. However, the side effect (shortness of breath and desaturation) appeared, and the seizure was not stopped. It was still unresponsive after being administered diazepam intravenously. Thus, as clinicians, we questioned if there was another benzodiazepine (e.g., lorazepam) with more potent efficacy but fewer side effects than diazepam, the common first-line anticonvulsant.

Efficacy comparison

A significant parameter for selecting a SE drug is that it must effectively stop seizures in children. In 2015, Wu et al. [35] indicated equal efficacy in terms of seizure control in CSE between lorazepam and diazepam intravenous. In the subsequent year, an investigation of the efficacy of lorazepam and diazepam intravenous was done by Zhao Z et al. [34]. They found no difference in the intravenous administration of lorazepam and diazepam for seizure cessation in SE (OR 2.71, 95%CI: 1.25–5.89). A recent SR-MA published in Cochrane review by McTague A et al. [33] proved a similar conclusion for equal efficacy of lorazepam and diazepam administered intravenous (RR 1.04, 95%CI: 0.94–1.16) to stop a seizure in children with any acute tonic-clonic convulsion of any duration.

On the other hand, McTague A et al. [33] SR-MA study showed more effective seizure cessation after receiving per rectal lorazepam than per rectal diazepam (RR 2.86, 95%CI 1.47–5.55). When it disregards the route of administration, lorazepam and diazepam have equal efficacy (OR 0.95, 95%CI: 0.73–1.22) for treating CSE in children and can be used as first-line therapy [35]. McTague A et al. [33] also made a similar conclusion when rectal and intravenous were not differentiated (RR 1.08, 95%CI 0.98–1.20). However, their meta-analysis indicated a low-quality conclusion since there was a substantial heterogeneity (I^2=67%, p=0.003), which may have been due to differences in outcomes by different routes of administration.

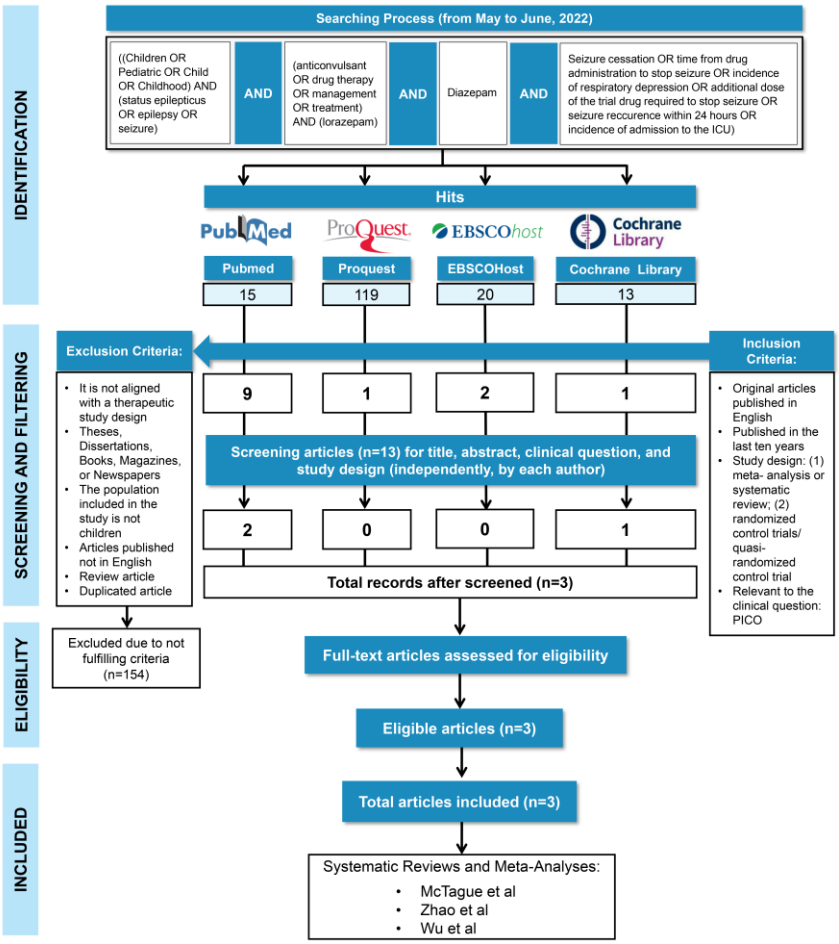


Fig. 3. Selection Process Flowchart of Evidence Answering the Formulated Clinical Question

Table 1. Summary of critical review of validity aspect for systematic reviews and meta-analyses (SRs-MAs) studies included in this EBCR using FAITH approach.

Studies, Year	Appraisal criteria									
	Find			Appraise			Include		Total Up	Heterogeneity
	Clearly defined PICO	Employing a large database	Using appropriate terminology and MeSH term?	All relevant evidence found	Appropriate inclusion-exclusion criteria	Valid and high-quality studies with a low risk of bias were assessed	A clear rationale for including/ excluding studies	Benefit and harm outcomes were assessed	Summary table or plot to total up the result	Heterogeneity analysis
McTague et al., 2018 [33]	🟢	🟢	🟢	🟢	🟢	🟢	🟢	🟢	🟢	🟡
Zhao et al., 2016 [34]	🟢	🟢	🟢	🟢	🟡	🟢	🟢	🟢	🟢	🟢
Wu et al., 2015 [35]	🟢	🟢	🟡	🟡	🟡	🟢	🟢	🟢	🟢	🟢

Abbreviation: PICO: P (patient, population, problem), I (intervention), C (comparison), and O (outcome); FAITH: find, appraise, include, total-up, and heterogeneity; EBCR: an evidence-based case report. **Notes:** Yes, clearly stated in the study (🟢); Unclear (🟡); No, definitely not matched with the criteria (🔴)

It was difficult to draw a firm conclusion regarding which one of these benzodiazepines is superior to another for the effective control of SE [39]. When intravenous access was not accessible, the same amount of diazepam or lorazepam might be administered rectally in three experiments [20,22,40]. Aligned with that, a recent SR-MA by McTague et al. [33] revealed a superiority of lorazepam compared to diazepam [33]. However, this SR-MA only included one study from Appleton et al. [20], indicating insufficient data on the practice of lorazepam rectally for treating SE. Meanwhile, this robust evidence did not include two more studies [20,38] that also investigated the role of rectal lorazepam in treating SE in children [33].

Concerning Appleton et al. [20] study, we noted indications of bias due to unclear criteria and protocol, as well as an insufficient number of participants (25 in total, with 19 in the diazepam group; and 6 in the lorazepam group), casting doubt on the efficacy of rectal diazepam. Despite this, a clinical study has suggested that rectal lorazepam may be effective, using a parenteral preparation of benzodiazepine (lorazepam) administered rectally as an innovative approach to overcome the unavailability of rectal preparation [40].

Rectal lorazepam peaked at 30 minutes to 2 hours, indicating good cessation and more extended control for SE. Whereas rectal diazepam reached peak concentration at 2 to 30 minutes, indicating an equal cessation effect (might be faster) but poorer control [40]. Rectal lorazepam is well tolerated [40], with good bioavailability (~80%) [41], but absorbed variably (50–100%) [41]. However, lorazepam parenteral solution administered rectally may be of limited usefulness because of the slow absorption rate [41]. In short, we suggest that the results of these findings should be carefully interpreted, and further study is demanded.

Concerning another parameter of efficacy, an SR-MA by McTague A et al. [33] also reported no significant difference in the time to seizure cessation, where the mean difference (MD) was 6.18 seconds faster for intravenous lorazepam compared to intravenous diazepam (95%CI: -7.83 to 20.19). Three studies were included in McTague et al. [33] also reported that when given intravenously or rectally, the number of children requiring an additional drug dose or medication to stop seizures was not different in both groups of given drugs [33]. McTague A et al. [33] Also, the number of children with seizure recurrence within 24 hours showed no difference between treatments, either when given intravenously, rectally, or for both routes of administration.

It is unclear how lorazepam, without considering the route of administration and specifically administering intravenously equal in efficacy compared to diazepam. In a pharmacokinetics study by Treiman et al. [39], all two benzodiazepines are lipid-soluble and enter the brain within seconds to minutes after intravenous administration. However, looking specifically at the pharmacokinetics of these two drugs used in the treatment of SE, lorazepam is much smaller lipid solubility than diazepam. Their octanol/buffer partition coefficient can indicate lipid solubility, an established method to predict the probability that molecules with molecular weights below 400–600 Dalton can be passively transported across a lipophilic membrane [39].

Lorazepam is less lipophilic than diazepam, with a partition coefficient considerably lower than diazepam (240 vs 840) [39]. However, their protein binding is similar, with lorazepam having slightly lower protein binding than diazepam (85–93% vs 90–99%). Consequently, the volume distribution of the total drug

Table 2. Summary of important findings in assessed systematic reviews and meta-analyses (SRs-MAs) in this EBCR

Studies, Year: Design of the study	Results and route of administration	Studies (N)	Patients (N)	Measure effect of lorazepam vs diazepam, (95% CI)	Heterogeneity analysis	Evidence quality
McTague et al., 2018 [33]: SR-MA (with homogeneity) of RCTs	1. Seizure cessation	3	439	RR 1.08 (0.98–1.20)	P=0.03, I^2=67.5% (Substantial heterogeneity)	Level 1a (High quality)
	1.1. Intravenous	3	414	RR 1.04 (0.94–1.16)	P=0.51, I^2=0% (No sig. heterogeneity)	
	1.2. Rectal	1	25	RR 2.86 (1.47–5.55)	N/A	
	2. Time taken from the drug administration to stop seizures with the intravenous route	1	80	MD 6.18 (-7.83–20.19)	N/A	
	3. Additional dose to stop the seizure	3	439	RR 0.88 (0.64–1.20)	P=0.11, I^2=50.01% (moderate heterogeneity)	
	3.1 Intravenous	3	414	RR 0.97 (0.71–1.33)	P=0.25, I^2=28.84% (No sig. heterogeneity)	
	3.2 Rectal	1	25	RR 0.11 (0.01–1.56)	N/A	
	4. Additional anti-epileptic drugs to stop the seizure	2	359	RR 0.75 (0.45–1.24)	P=0.11, I^2=54.32% (substantial heterogeneity)	
	4.1 Intravenous	2	334	RR 0.91 (0.54–1.55)	P=0.19, I^2=41.81% (moderate heterogeneity)	
	4.2 Rectal	1	25	RR 0.11 (0.01–1.69)	N/A	
	5. Recurrence of seizures within 24 hours of stopping	3	439	RR 0.86 (0.61–1.20)	P=0.40, I^2=0% (No sig. heterogeneity)	
	5.1 Intravenous	3	414	RR 0.91 (0.65–1.27)	P=0.44, I^2=0% (No sig. heterogeneity)	
	5.2 Rectal	1	25	RR 0.19 (0.01–2.92)	N/A	
	6. Adverse effects: respiratory depression/ arrest	3	439	RR 0.72 (0.55–0.93)	P=0.51, I^2=0% (No sig. heterogeneity)	
	6.1. Intravenous	3	414	RR 0.71 (0.55–0.92)	P=0.32, I^2=12.76% (No sig. heterogeneity)	
	6.2. Rectal	1	25	RR 0.95 (0.04–20.78)	N/A	
	7. Adverse effects: ICU admission	1	86	RR 0.15 (0.02–0.98)	N/A	
	7.1 Intravenous	1	61	RR 0.07 (0.00–1.22)	N/A	
	7.2 Rectal	1	25	RR 0.57 (0.03–10.51)	N/A	
Zhao et al., 2016 [34]: SR-MA (with homogeneity) of RCTs	1. Seizure cessation	2	359		P=0.347, I^2=10.8% (No sig. heterogeneity)	Level 1a (High quality)
	1.1 Intravenous lorazepam vs intravenous diazepam	2	359	OR 1.03 (0.62–1.70)		
	1.2 Lorazepam vs diazepam (Without differentiate route of administration) in network SR-MA	2	359	OR 1.32 (0.84–2.09)		
	2. Respiratory depression				P=0.347, I^2=10.8% (Not sig. heterogeneity)	
	2.1 Intravenous lorazepam vs intravenous diazepam	2	359	OR 0.62 (0.39–0.96)		
	2.2 Lorazepam vs diazepam (Without differentiate route of administration) in network SR-MA	2	359	OR 0.61 (0.39–0.95)		
Wu et al., 2015 [35]: SR-MA (with homogeneity) of RCTs	1. Seizure control Diazepam vs. lorazepam (Without differentiating route of administration)	3	574	OR 0.95 (0.73– 1.22)	P=0.677, I^2=0.0% (Not sig. heterogeneity)	Level 1a (High quality)
	2. Side effect (respiratory depression) Diazepam vs. lorazepam (Without differentiating route of administration)	3	574	OR 1.35 (0.92–1.99)	P=0.129, I^2=0.0% (Not sig. heterogeneity)	

Abbreviation: EBCR: an evidence-based case report; ICU: intensive care unit; CI: confidence interval; MD: mean difference; N: number; OR: odds ratio; RCT: randomised controlled trial; RR: relative risks; sig: significant; and SR-MA: a systematic review and meta-analysis.

Table 3. Summary of critical review of applicability aspect for systematic reviews and meta-analyses (SRs-MAs) studies included in this EBCR.

Studies, Year	Appraisal Criteria			
	Applicability of results to patient in this case report	The similarity of patient's characteristic	Findings are essential and beneficial to the patient in this case report	Clinical practice consideration of proposed treatment
McTague et al., 2018 [33]	🟢	🟢	🟢	🟡
Zhao et al., 2016 [34]	🟡	🟡	🟢	🟡
Wu et al., 2015 [35]	🔴	🟡	🟢	🟡

Abbreviation: EBCR: an evidence-based case report. **Notes:** Yes, clearly stated in the study (🟢); Unclear (🟡); No, definitely not matched with the criteria (🔴). Heterogeneity interpretation follows the criteria: 0–40% (not important); 30–60% (moderate heterogeneity); 50–90% (substantial heterogeneity); and 75–100% (considerable heterogeneity) [32].

and the corresponding free drug was lower in lorazepam than in diazepam, with the value being 0.7–1.6 vs 0.32–2.0 and 12.0 vs 132.7, respectively [39].

A consequence of the smaller volume distribution of lorazepam is a longer intracerebral half-life (12 hours) than diazepam (15–30 minutes), which enables a longer-lasting anti-epileptic effect [39,42]. Intravenous diazepam might be faster to enter the brain since more excellent volume distribution of a drug, but its effective duration of action is short. In contrast, the half-life of intravenous lorazepam, which has a significantly smaller volume of unbound drug distribution, is at least several hours after a single intravenous administration [39]. These pharmacological attributes imply that lorazepam concentrations in the central compartment to stop SE remain within the therapeutic range longer than diazepam concentrations [39]. Lorazepam had a prolonged duration of action, up to 24 hours, compared to diazepam, with only an hour [15].

Thus, although in our results, the efficacy of intravenous lorazepam and the overall route is similar to diazepam, based on the pharmacokinetic profile, lorazepam is superior to diazepam [39,43]. For this reason, lorazepam is preferable for the initial management of CSE [39,42,43].

Safety Comparison

Three systematic reviews and meta-analyses assessed respiratory depression as the most common side effect after giving a benzodiazepine among children with SE [33–35]. Respiratory depression episodes may indirectly lead to ICU admission due to respiratory failure or the need for advanced anti-epileptic treatment to maintain seizure cessation.

Table 2 shows a significant difference between intravenous lorazepam and diazepam in the risk of respiratory depression noted by Zhao et al. [34] and McTague et al. [33]. In 2016, Zhao et al. [34] found that intravenous lorazepam is less likely to cause respiratory depression (OR 0.62, 95%CI: 0.39–0.96) [34]. Recently, in 2018, McTague et al. [33] agreed on similar results to Zhao et al. [34], who demonstrated that the incidence of respiratory depression in patients who received intravenous lorazepam was less risky than those who received intravenous diazepam (RR 0.71, 95%CI: 0.55–0.92, I^2=12.76%) [33]. Meanwhile, participants who received rectal therapy had no significant difference in their risk of respiratory depression between the two benzodiazepines (RR 0.95, 95%CI: 0.04–20.78) [33].

On the other hand, a different conclusion has been drawn in a study by Wu et al. [35], who found no difference in respiratory depression incidence between diazepam and lorazepam, although diazepam tended to cause respiratory depression (OR 1.35 95%CI: 0.92–1.99). These conflicting findings could be due to the differences in selection and the number of studies between the three SRs-MAs used in this EBCR, where Wu et al. [35] include the least RCT number discussing the comparison between the two benzodiazepines. Conversely, McTague et al. [33] and Zhao et al. [34] included a more significant number of studies and participants.

Furthermore, we also noted that rectal administration had no significant result, possibly because only one study [20] was included by McTague et al. [33]. Appleton et al. [20] assigned an unequal and small proportion of participants in the two groups of lorazepam and diazepam. This discrepancy might result in a nonsignificant comparison statistically. Despite the inconsistent findings, the risk of respiratory depression was lower in the lorazepam groups compared to their counterparts without distinguishing routes (RR 0.72, 95%CI: 0.55–0.93, I^2=0%) [33].

In terms of ICU admission, McTague A et al. [33] reported no significant difference between children with CSE who were given lorazepam compared to diazepam through intravenous routes (RR 0.07, 95%CI: 0.00–1.22) and rectal routes (RR 0.57, 95%CI: 0.03–10.51), respectively. However, when not taking into account the administration route, a greater number of children who received diazepam were admitted to the ICU (10

vs 0 for lorazepam). The RR was 0.15, 95%CI: 0.02–0.98, and no substantial heterogeneity was found [33].

The protective effect of lorazepam over diazepam in respiratory depression and ICU admission can be attributed to a higher clearance rate of lorazepam which might make this drug less toxic and hazardous than diazepam [39]. Its smaller volume distribution and low threshold of minimal effective concentration also allow this drug to lower the risk of respiratory depression related to the repeated dose of benzodiazepines [39]. Since the complication presented before admission to the ICU related to the seizures was respiratory depression [33,44], thus by lowering the risk of this side effect will also lower the ICU admission.

As highlighted in the applicability aspect (Table 3), our study is limited to the current clinical practice of applying lorazepam for epilepsy indication (both in adults and children). Worldwide, diazepam is available in the form of rectal (5mg/mL) [22], tablets (2 mg, 5 mg, and 10 mg), injection (5mg/mL), and nasal (10 mg/dose, 15 mg/dose, 20 mg/dose, and 5 mg/dose) [33], while lorazepam is available in rectal (2 mg/mL and 4 mg/mL) [21,38], oral (0.5 mg, 1 mg, and 2 mg), injection (2mg/mL and 4 mg/mL) [38], and nasal (7.5 mg/dose and 10 mg/dose) [38]. Meanwhile, in Indonesia, diazepam has various preparations, yet lorazepam is very limited. Diazepam is available in tablets (2 mg and 5 mg), intravenous injections (5mg/mL), and suppositories (5mg) [36,37], whereas lorazepam is only available in tablet (0.5 mg, 1 mg, 2 mg) and intravenous injections (2mg/mL) [36,37]. Nevertheless, current approval in Indonesia for lorazepam is only for premedication of surgery and sleep problems, such as insomnia [36,37].

The high price gap between lorazepam and diazepam may explain why lorazepam is not commonly available in Indonesia for epilepsy (~37 USD/1 mL lorazepam and ~1 USD/2.5 mL diazepam [45,46]. Therefore, more study is required to analyse the cost-benefit of lorazepam in terms of SE treatment for children. Since few studies supported the superiority of rectal lorazepam for CSE [20,33,40], multidisciplinary clinical studies should be further conducted to compare rectal lorazepam and diazepam in proving the efficacy of lorazepam rectal. In the research setting, parenteral lorazepam can be modified through rectal, as done in three prior studies [20,22,40].

CONCLUSION

Plenty of evidence is provided with three high-level quality SR-MAs with low-risk biases. They were reliable and generated significant clinical findings comparing the efficacy and safety of lorazepam and diazepam in treating CSE in children. Without addressing the route of administration and focusing on the intravenous route, both lorazepam and diazepam have equal efficacy and can be used as the first line of treatment. Meanwhile, when it comes to rectal preparation, lorazepam outperforms diazepam in halting seizures and might thus be utilised to prevent a refractory episode of CSE. Lorazepam is also considered safer than diazepam regarding respiratory depression and ICU admission risk, mainly when administered intravenously.

Nevertheless, the superiority of lorazepam is still constrained in clinical practice due to its limited drug preparation. Therefore, we recommended that clinicians, pharmacists, and policymakers might procure intravenous and rectal lorazepam as one alternative for treating CSE in a hospital setting. The recommended dose for intravenous lorazepam was 0.07–0.1 mg/kgBW (up to 4 mg/dose) IV bolus with a maximum rate of 2 mg/kg (could be repeated after 10 minutes) [47,48]. Rectal lorazepam is also prescribed at 0.05–0.1/kgBW [20].

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CONFLICT OF INTEREST

The authors declare there is no conflict of interest.

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