Mini Review Article

Comparison of diazepam and lorazepam for the emergency treatment of adult status epilepticus: a systemic review and meta-analysis

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Status epilepticus (SE) is a life-threatening medical and neurological emergency. Prompt recognition and treatment are essential to stop the seizure and improve patient outcomes. To elucidate which benzodiazepine should be used as the first-line treatment, a systemic search of the PubMed, Cochrane Central Register of Controlled Trials, and Igaku Chuo Zasshi databases was carried out to identify randomized controlled trials (RCTs) comparing i.v. administration of lorazepam and diazepam used for adult SE. The certainty of evidence was assessed using the Grading of Recommendations, Assessment, Development, and Evaluation approach. Only two RCTs were finally analyzed among 2182 papers extracted. The SE definitions, inclusion criteria, and doses of the drugs differed in the two studies. Of 204 patients included, 103 and 101 patients were allocated to the lorazepam and diazepam groups, respectively. The pooled risk ratio (RR) and confidence interval (CI) for lorazepam treatment on seizure cessation (two RCTs, n = 204) showed a significantly superior effect of lorazepam over diazepam (RR, 1.24; 95% CI, 1.03–1.49). No statistically significant relationship was found for mortality (two RCTs, n = 204) (RR 0.43; 95% CI, 0.43–6.90), poor neurological outcome (one RCT, n = 134) (RR, 1.10; 95% CI, 0.59–2.04), hypotension (one RCT, n = 70) (RR, 2.68; 95% CI, 0.11–63.61), and respiratory depression (two RCTs, n = 204) (RR, 1.07; 95% CI, 0.48–2.48). The certainty of the evidence was rated as very low. The results of this meta-analysis of RCTs showed that i.v. lorazepam was better than i.v. diazepam for the cessation of adult SE.

Key words: Convulsion, diazepam, lorazepam, seizure, status epilepticus

INTRODUCTION

STATUS EPILEPTICUS (SE) is a life-threatening medical and neurological emergency. The current definition of SE is 5 min or more of continuous clinical and/or electrographic seizure activity or recurrent seizure activity without recovery between seizures.[1–3] Prolonged seizures are associated with higher mortality and worse clinical outcomes. The adverse effects of SE include both indirect systemic problems arising from the convulsive state and direct neuronal cellular injury.[3] Prompt recognition and treatment are essential to stop the seizure and improve patient outcomes. For this purpose, benzodiazepines are chosen as first-line therapy.[1–5] The Japanese "Clinical Practice Guideline for Epilepsy 2018" recommends the i.v. administration of diazepam or lorazepam as the initial treatment;[6] however, lorazepam was not authorized at the time of publication. In February 2019, lorazepam was released in Japan and both

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diazepam and lorazepam became available for use. Therefore, the clinical question of which benzodiazepine should be used is of great importance. Although lorazepam is recommended as class I, level A and diazepam as class IIa, level A,[1] recent meta-analyses did not provide evidence to strongly support the preferential use of i.v. lorazepam over diazepam for the first-line treatment of convulsive SE. These studies included randomized controlled trials (RCTs) involving child cases and were not restricted to adult SE.[7,8] We aimed to assess all available studies to resolve the following research question: which benzodiazepine—diazepam or lorazepam—should be used in adult patients with SE?

P (Patients): Adult patients with SE.

I (Interventions): Lorazepam.

C (Comparisons, Controls): Diazepam.

O (Outcomes): Mortality, seizure cessation, poor neurological outcome (defined as modified Rankin Scale 3–6), hypotension, respiratory depression.

METHODS

THE JAPAN RESUSCITATION Council (JRC) Neuroresuscitation Task Force and the Guidelines Editorial Committee were established in 2020, and were organized by the Japan Society of Neuroemergencies and Critical Care, the Japanese Society of Intensive Care Medicine, and the Japan Society of Neurosurgical Emergency. The JRC Neuroresuscitation Task Force set six clinically relevant questions and this systematic review was carried out. Following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA),[9,10] we undertook a systemic review and meta-analysis. This study was registered with the University Hospital Medical Information Network (UMIN-CTR, No. R000046716) in Japan.

Search strategies

A systematic search of published reports was carried out in the MEDLINE (through PubMed), Cochrane Central Register of Controlled Trials (CENTRAL), and Igaku Chuo Zasshi (ICHUSHI) databases to retrieve relevant articles for the review. We searched for full-text RCTs in humans published before September 2019. We used a combination of key terms and established a full search strategy (Figure S1).

Study selection and inclusion criteria

Our study population of interest was adult SE patients in an emergency setting, including prehospital care. We did not restrict our analysis by country but only included studies written in English or Japanese. We sought to determine whether lorazepam is more effective or safer to use for SE compared to diazepam. The following outcomes were compared between the i.v. use of lorazepam and diazepam.

The critical outcomes for this study were: (i) mortality at discharge, (ii) seizure cessation, (iii) poor neurological outcomes at discharge, (iv) hypotension, (v) respiratory depression.

Assessment of the risk of bias

The risk of bias was evaluated according to the Cochrane Handbook version 5.1.0,[11] including: A, random sequence generation (selection bias); B, allocation concealment (selection bias); C, blinding of participants and personnel (performance bias); D, blinding of related outcome assessment (detection bias); E, incomplete outcome data (attrition bias); F, selective reporting (reporting bias); G, other biases.

Studies were categorized as having a "low," "unclear," or "high" risk of bias in each domain. The risk of bias for each element was considered "high" when bias was present and likely to affect the outcomes and "low" when bias was not present or present but unlikely to affect the outcomes.[12]

Data extraction and management

The following data were extracted: author(s), title, journal name, year of publication, website (URL), and abstract. After removal of duplicates, two independent reviewers (KN and MS) screened the abstracts and titles of the studies and subsequently reviewed the full-text articles. Disagreements were reconsidered and discussed until a consensus was reached. The full texts of the articles included in the final selection were independently reviewed by the other two reviewers (KN and MS). Disagreements were resolved by a third reviewer (TH).

Rating the certainty of evidence

We used the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) tool to rate the certainty of the evidence on effects of lorazepam and diazepam in adult patients with SE.[13–16] The certainty of the evidence was assessed as "high," "moderate," "low," or "very low" by evaluating risk of bias, inconsistency, indirectness, imprecision, and publication bias.

Statistical analysis

The results were summarized using a random effects model to facilitate the pooling of estimates of the treatment effects. Risk ratios (RRs) and 95% confidence intervals (CIs) were used for dichotomous outcomes. Heterogeneity between trials for each outcome was evaluated using the I^2 statistic to quantify inconsistency,[17] and was considered significant if the reason for heterogeneity could not be explained and if the I^2-value was 50% or higher.

We generated a funnel plot to investigate the potential for publication bias. The estimates were pooled using a random effects model. The meta-analysis was carried out based on all published data and data made available to us. All analyses were undertaken using Review Manager software (RevMan 5.3; The Nordic Cochrane Center, the Cochrane Collaboration, Copenhagen, Denmark).

RESULTS

Literature search

FIGURE 1 hows A flow diagram of our study adapted from the PRISMA statement (2009).[10] A search of the PubMed, CENTRAL, and ICHUSHI databases returned 2,182 articles. We eliminated 11 duplicates and excluded 2,168 articles because their designs did not meet the inclusion criteria. Of the three included articles, one was excluded because it was not an RCT. Thus, we retained two articles[18,19] for review in the final analysis.

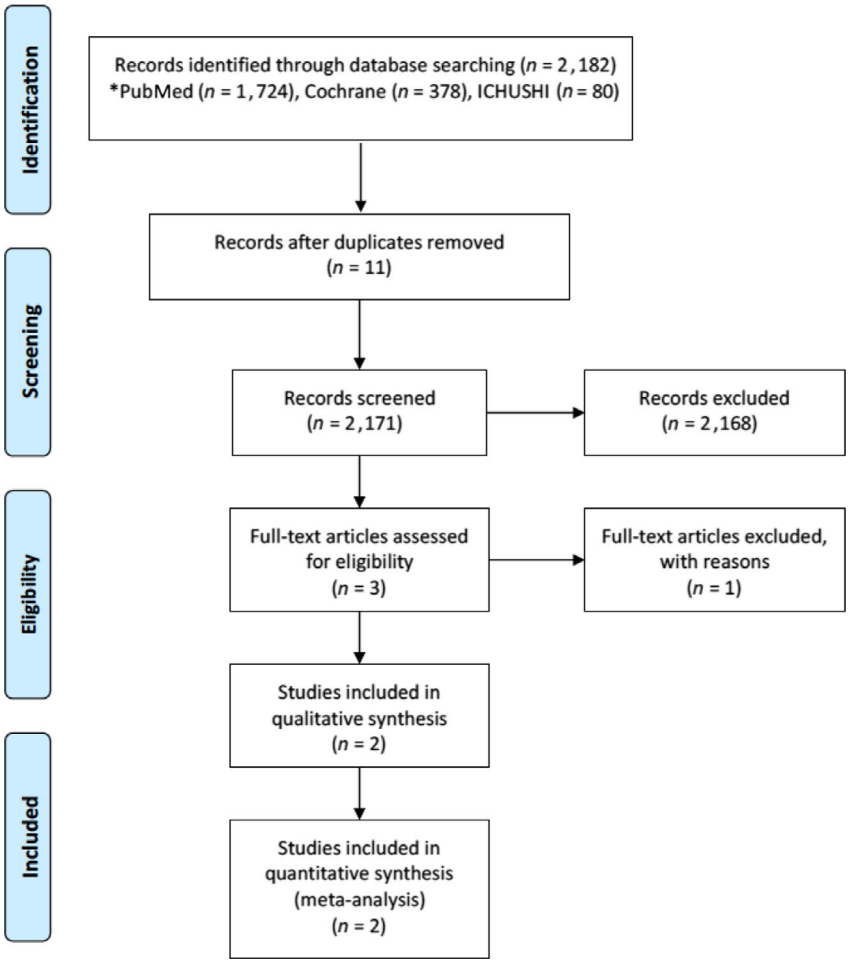

Fig. 1. Flow diagram for the identification of relevant studies. A total of 2,182 articles were identified by searching three biomedical research databases. We excluded 11 duplicate articles and 2,168 articles that did not satisfy the selection criteria. We reviewed the full texts of the remaining three articles and excluded one article. After reviewing the full texts, this study included two articles.

Study characteristics

One RCT compared i.v. diazepam (5 mg) to lorazepam (2 mg)[19]; the other RCT compared i.v. diazepam (10 mg) to lorazepam (4 mg).[18] In total, 204 patients were included, 103 and 101 in the lorazepam and diazepam groups, respectively. The detailed characteristics of the individual trials are shown in Table 1. Both RCTs were carried out in a prehospital setting and, if the seizures did not terminate or recurred, second injections of identical doses of the same benzodiazepines were given.

Of note, the study populations differed: one study included convulsive and non-convulsive SE,[18] whereas the other included only generalized tonic-clonic seizure.[19] In addition, one study described the etiology and duration of SE before treatment,[19] but the other did not.[18]

Outcomes

The risks of bias were evaluated in each of the studies and are summarized in Figure 2. Two RCTs evaluated mortality (two RCTs, $n = 204$).[18,19] The RR and CI for lorazepam treatment on mortality were not significantly better than those for diazepam (RR 0.43; 95% CI, 0.43–6.90). (Fig. 2A). The pooled RR for seizure cessation (two RCTs, $n = 204$)[18,19] was statistically significant (RR, 1.24; 95% CI, 1.03–1.49) (Fig. 2B), showing the superior effect of lorazepam over diazepam. No statistically significant relation was found for poor neurological outcome (one RCT, $n = 134$)[19] (RR, 1.10; 95% CI, 0.59–2.04) (Fig. 2C), hypotension (one RCT, $n = 70$)[18] (RR, 2.68; 95% CI, 0.11–63.61) (Fig. 2D), or respiratory depression (two RCTs, $n = 204$)[18,19] (RR, 1.07; 95% CI, 0.48–2.48) (Fig. 2E).

Certainty of evidence

We assessed the certainty of evidence for each outcome and present a summary in the evidence profile table (Table 2). We rated the risk of bias as serious in hypotension. The imprecision was assessed as serious in seizure cessation and very serious in mortality, poor neurological outcomes, hypotension, and respiratory depression. Thus, the certainty of the evidence was downgraded by one to three levels in each outcome. The overall certainty of the evidence was rated very low. No statistically significant heterogeneity was observed between the lorazepam and diazepam groups for mortality, seizure cessation, or respiratory depression, (not applicable, $I^2 = 0\%$; $\chi^2 = 0.78$; $P = 0.03$, $I^2 = 0\%$;

Table 1. Baseline characteristics of eligible studies

First author, year	Definition of SE and inclusion criteria	Underlying etiology	No. of patients	Age (years)	Duration of SE before treatment (min)	Interventions	Outcomes	Notes
Leppik, 1983[18]	Convulsive SE (defined as ≥3 GTC seizures in 1 h or ≥2 in rapid succession), absence SE, or complex partial SE	NR	LZP 37 DZP 33	LZP 50 DZP 56	NR	LZP 4 mg IV, DZP 10 mg i.v., prehospital (repeated if needed)	Seizure control Adverse effects	Phenytoin given after 30 min
Alldredge, 2001[19]	Continuous or repeated seizure activity >5 min without recovery of consciousness	Reported	LZP 66 DZP 68	LZP 49.9 DZP 50.4	LZP 34.0 ± 17.8 DZP 31.3 ± 14.5	LZP 2 mg i.v., DZP 5 mg i.v., prehospital (repeated if needed)	Mortality Seizure control Adverse effects	Multicentric (three centers), cause of SE described

DZP, diazepam; GTC, generalized tonic-clonic; LZP, lorazepam; NR, not reported; SE, status epilepticus.

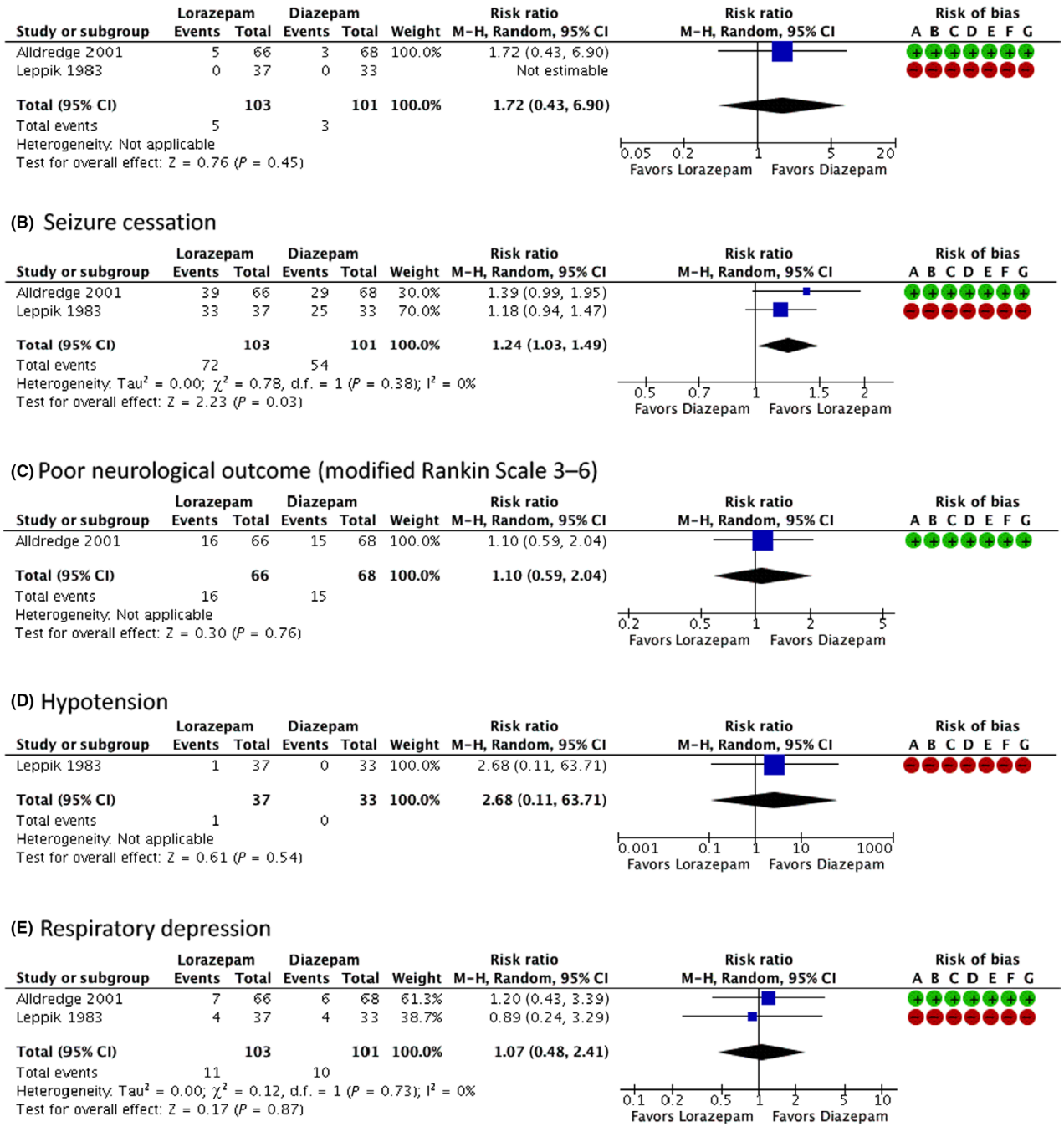

Fig. 2. Forest plot comparing lorazepam and diazepam with risk of bias summary A, Mortality. B, Seizure resolution. C, Poor neurological outcome (modified Rankin Scale 3–6). D, Hypotension. E, Respiratory depression. Risk of bias (green [+], low risk; red [–], high risk) categories: A, random sequence generation (selection bias); B, allocation concealment (selection bias); C, blinding of participants and personnel (performance bias); D, blinding of outcome assessment (detection bias); E, incomplete outcome data (attrition bias); F, selective reporting (reporting bias); and G, other bias. CI, confidence interval; M–H, Mantel–Haenszel method.

Table 2. Evidence profile of two published reports comparing lorazepam and diazepam for emergency treatment of adult status epilepticus

Certainty assessment							No. of patients		Effect		Certainty	Importance
No. of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Lorazepam	Diazepam	Relative (95% CI)	Absolute (95% CI)		
Mortality at discharge												
2	RCT	Not serious	Not serious	Not serious	Very serious[†]	None	5/103 (4.9%)	3/101 (3.0%)	RR 1.72 (0.43 to 6.90)	32 more per 1,000 (from 25 fewer to 260 more)	Low ⊕⊕◯◯	Critical
Seizure cessation												
2	RCT	Not serious	Not serious	Not serious	Serious[‡]	None	72/103 (69.9%)	54/101 (53.5%)	RR 1.24 (1.03 to 1.49)	128 more per 1,000 (from 16 more to 262 more)	Moderate ⊕⊕⊕◯	Critical
Poor neurological outcomes (modified Rankin Scale 3–6)												
1	RCT	Not serious	Not serious	Not serious	Very serious[†]	None	16/66 (24.2%)	15/68 (22.1%)	RR 1.10 (0.59 to 20.4)	22 more per 1,000 (from 90 fewer to 229 more)	Low ⊕⊕◯◯	Critical
Hypotension												
1	RCT	Serious[§]	Not serious	Not serious	Very serious[†]	None	1/37 (2.7%)	0/33 (0%)	RR 2.68 (0.11 to 63.71)	0 fewer per 1000 (from 0 fewer to 0 more)	Very low ⊕◯◯◯	Critical
Respiratory depression												
2	RCT	Not serious	Not serious	Not serious	Very serious[†]	None	11/103 (10.7%)	10/101 (9.9%)	RR 1.07 (0.48 to 2.41)	7 more per 1000 (from 51 fewer to 140 more)	Low ⊕⊕◯◯	Critical

RCT, randomized controlled trial; RR, risk ratio.
[†]Sample size is smaller than optimal information size and 95% confidence interval (CI) is wide.
[‡]Sample size is smaller than optimal information size.
[§]Risk of bias is serious. In addition, sample size is smaller than optimal information size and 95% CI is wide.

$\chi^2 = 0.12$; $P = 0.87$, respectively). Only one study assessed poor neurological outcome and hypotension. A visual inspection of the funnel plots suggested no existence of publication bias (Figure S2).

DISCUSSION

OUR findings IN this systemic review suggested that lorazepam was superior to i.v. diazepam in treating adult SE as first-line treatment, with no significant differences in undesirable effects. However, the certainty of evidence was rated very low. Although the number of deaths was slightly higher in the lorazepam group compared to the diazepam group, a direct association between death and lorazepam use seemed unlikely, considering the higher rate of seizure termination and the similar incidence of hypotension and respiratory depression in the lorazepam group.

The two RCTs retrieved in this study were reported in 1983[18] and 2001[19] in the prehospital settings by paramedics. The definition of SE and the dosage of benzodiazepines differed between these RCTs. In one study, the underlying etiology and the duration of SE before benzodiazepine treatment were not clarified.[18] Subsequently, no RCTs for adult SE have compared lorazepam and diazepam. In one meta-analysis including an RCT comparing lorazepam with diazepam plus phenytoin,[20] diazepam and lorazepam had equal efficacy and side-effects for the treatment of SE. Recently published meta-analyses including child SE reported conflicting results: one concluded that lorazepam was more effective than diazepam; the other did not. This disparity resulted from differences in the included RCTs.[7,21] The RCTs comparing lorazepam and diazepam for child SE also reported inconsistent results.[22–24]

Lorazepam is less lipophilic than diazepam; it has a smaller volume of distribution and a longer intracerebral half-life (12 h) than diazepam (15–30 min),[25] which enables a longer-lasting antiepileptic effect. This pharmacokinetic profile is deemed to support the preferable use of lorazepam over diazepam. Benzodiazepines are given more quickly and the seizure control is more effective in patients with SE. One RCT reported that intramuscular midazolam is at least as safe and effective as i.v. lorazepam for prehospital seizure cessation.[26]

We found no RCTs in Japan comparing the effect of lorazepam and diazepam. Recently, a multicenter, open-label, uncontrolled study was undertaken in Japan to evaluate the efficacy and safety of lorazepam in 25 Japanese patients with SE or repetitive seizures. In 10 adults aged 16 years and older, 4 mg i.v. lorazepam resolved epilepsy in 66.7% of patients and in 77.8% of patients who received a repeated dose. There have been no reports of serious adverse events.[27] In Japan, lorazepam is priced at ¥2,229 per 2 mg and diazepam costs ¥88 per 5 mg (as at 1 April, 2020). The cost and benefits could be balanced in selecting which benzodiazepine should be used.

This review revealed a lack of uniform definitions of SE and insufficient data on the underlying disease and seizure duration before benzodiazepine treatment. Future research with a standardized protocol and more detailed information is necessary to provide a resolution regarding which benzodiazepine should be used for SE.

CONCLUSION

THE RESULTS OF this meta-analysis showed very low evidence to support the i.v. use of lorazepam over diazepam as first-line treatment for the cessation of adult SE.

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DISCLOSURE

Approval of the research protocol: N/A.
Informed consent: N/A.
Registry and the registration no. of the study/trial: University Hospital Medical Information Network (UMIN-CTR, No. R000046716).
Animal studies: N/A.
Conflict of interest: Hitoshi Kobata: received speakers' honoraria from Eisai.

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SUPPORTING INFORMATION

Additional Supporting Information may be found in the online version of this article at the publisher's web-site:

Figure S1. Search strategies.
Figure S2. Funnel plot of respiratory depression.