A Comparison of Midazolam, Lorazepam, and Diazepam for the Treatment of Status Epilepticus in Children: A Network Meta-analysis

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Abstract

Midazolam, lorazepam, and diazepam were recommended as emergent initial therapy for status epilepticus. However, there are no current studies to confirm the best agent for pediatric status epilepticus. We compared the efficacy of midazolam, lorazepam, and diazepam in treating pediatric status epilepticus using a network meta-analysis method. In total, 16 randomized controlled trials containing 1821 patients were included. Nonintravenous midazolam, intravenous lorazepam, and intravenous diazepam were more successful in achieving seizure cessation when compared with nonintravenous diazepam (odds ratio = 2.23, 95% credibility interval: 1.62, 3.10; odds ratio = 2.71, 95% credibility interval: 1.25, 5.89; odds ratio = 2.65, 95% credibility interval: 1.12, 6.29; respectively). Among lorazepam, midazolam, and diazepam, midazolam had the highest probability (surface under the cumulative ranking area [SUCRA] = 0.792) of achieving seizure cessation, and lorazepam had the largest probability (surface under the cumulative ranking area = 0.4346) of being the best treatment in reduction of respiratory depression. In conclusion, nonintravenous midazolam and intravenous lorazepam were superior to intravenous or nonintravenous diazepam, and intravenous lorazepam was at least as effective as nonintravenous midazolam in treating pediatric status epilepticus.

Keywords

Background

The most recent Neurocritical Care Society guideline for status epilepticus management in children and adults defined status epilepticus as "5 minutes or longer continuous clinical and/or electrographic seizure activity or recurrent seizure activity without recovery between seizures."[1] Approximately 10 000 status epilepticus episodes occur in children annually in the United States and 4 to 8 children per 1000 have an episode of status epilepticus before age 15.[2,3] Convulsive status epilepticus with undertreatment or inappropriate treatment may result in death or significant morbidity.[4]

Current guidelines and protocols for the treatment of status epilepticus recommended a rapid administration of antiepileptic drugs based on results from basic and clinical research.[5] Rapid administration of status epilepticus was associated with better outcomes.[2] Benzodiazepines have been widely used as first-line therapy for status epilepticus, achieving lasting seizure control in up to 80% of patients.[6,7] Evidence supported and experts agreed that benzodiazepines should be a better choice when compared with other antiepileptic drugs.[1]

The most recent Neurocritical Care Society guideline for pediatric status epilepticus management strongly recommended that intravenous lorazepam, intramuscular midazolam, and rectal diazepam should be given as emergent initial therapy for pediatric status epilepticus.[1] The results of previous studies showed that intravenous lorazepam, intravenous midazolam, intramuscular midazolam, and intravenous diazepam have demonstrated similar efficacy, with lorazepam being slightly superior in some studies and with intramuscular midazolam

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being non-inferior to intravenous lorazepam in the initial treatment of status epilepticus in adults.[5,8] Moreover, various meta-analyses showed that intravenous lorazepam was at least as effective as intravenous diazepam and was associated with fewer adverse events for acute tonic-clonic convulsions,[4] and nonintravenous midazolam was safe and effective when compared with any-route diazepam for status epilepticus in children and young adults.[9] However meta-analysis by Prasad et al[10] concluded that intravenous lorazepam was better than intravenous diazepam or intravenous phenytoin alone for cessation of seizures. These studies have produced inconsistent conclusions.

Only 1 recent randomized controlled trial compared lorazepam with midazolam for treating status epilepticus in children,[11] but the statistical power to evaluate the effectiveness and safety of the 2 drugs was inadequate. Moreover, the number of studies was limited for the treatment of status epilepticus in children. Most importantly, status epilepticus is a medical emergency with a significant mortality, like many other acute medical emergencies, status epilepticus is a challenging topic for randomized controlled trials.[10] Whereas the efficacy of lorazepam, midazolam, and diazepam can be comprehensively compared using the method of network meta-analysis, which enhances the statistical power and indirectly compares all therapeutic regimens despite the lack of head-to-head randomized controlled trials. That is, an indirect estimate of the effect of treatment A over B can be obtained by comparing trials of A vs C and B vs C.

The current network meta-analysis aims to comprehensively compare the efficacy and the incidences of respiratory depression between lorazepam, midazolam, and diazepam for pediatric status epilepticus and to determine the optimal routes of administration by subgroup analyses.

Methods

Literature search, literature selection, data extraction, and quality assessment were performed independently by 2 trained reviewers; disagreements between reviewers were resolved through consensus or by consulting a third expert adjudicator. The reporting of this network meta-analysis adhered to the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) statement.[12] It is not necessary to obtain ethical approval and patient consent because this is a meta-analysis based on published studies.

Definition of Bayesian Network Meta-analysis

Network meta-analysis can be performed by Bayesian and traditional frequentist statistical methods. Bayesian network meta-analysis is based on Bayes theorem, is defined as the explicit quantitative use of external evidence in the design, monitoring, analysis, interpretation, and reporting.[13]

Search Strategy

A systematical literature search was conducted on PubMed, EMBASE.com, Web of Science (via ISI Web of Knowledge), and the Cochrane Library from inception to February 1, 2015, using status

epilepticus, lorazepam (Ativan, Durazolam, Duralozam, Idalprem, Laubeel, Temesta), midazolam (Dormicum, Versed), diazepam (Diazemuls, Faustan, Valium, Seduxen, Sibazon, Stesolid, Apaurin, Relanium), random* and other search terms. The references of included articles and systematic reviews/meta-analyses were tracked to identify potential relevant studies. Full detail of the search strategy for PubMed was as following: (((((((("Status Epilepticus"[Mesh]) OR status epilepticus[Title/Abstract])) AND ((((("Midazolam"[Mesh]) OR "Lorazepam"[Mesh]) OR "Diazepam"[Mesh])) OR ((Dormicum[Title/Abstract] OR Versed[Title/Abstract] OR Ativan[Title/Abstract] OR Duralozam[Title/Abstract] OR Durazolam[Title/Abstract] OR Idalprem[Title/Abstract] OR Laubeel[Title/Abstract] OR Temesta[Title/Abstract] OR Lorazepam[Title/Abstract] OR Diazemuls[Title/Abstract] OR Faustan[Title/Abstract] OR Valium[Title/Abstract] OR Seduxen[Title/Abstract] OR Sibazon[Title/Abstract] OR Stesolid[Title/Abstract] OR Apaurin[Title/Abstract] OR Relanium[Title/Abstract]))))))) AND (Random* OR randomized controlled trial* OR randomized trial* OR Randomized Controlled Trial[ptyp] OR "Randomized Controlled Trials as Topic"[Mesh]).

Inclusion and Exclusion Criteria

Randomized controlled trials meeting the following eligibility criteria were included:

1. Type of studies: randomized controlled trials, systematic reviews or meta-analyses were also included to track their references.
2. Type of participants: children younger than 18 years of age; status epilepticus was defined in accordance with the most recent Neurocritical Care Society guideline[1]; and both convulsive status epilepticus (convulsions that are associated with rhythmic jerking of the extremities) and nonconvulsive status epilepticus (seizure activity seen on electroencephalogram without the clinical findings associated with convulsive status epilepticus) were considered for eligibility criteria.
3. Type of interventions: studies comparing any of lorazepam, midazolam, or diazepam against placebo or other antiepileptic drugs, no matter the routes of administration.
4. Type of outcome measures: the primary outcome was cessation of status epilepticus and secondary outcome was respiratory depression.
5. Other criteria: we included randomized controlled trials reported in the English languages. There were no limitations on year of publication, publication status, duration of study follow-up, or period of study conduct.

Studies were excluded if they were animal studies, reviews, abstracts, letters, comments, or studies of intervened group and controlled group that did not contain any of lorazepam, midazolam, or diazepam.

### Data Extraction and Risk of Bias of Individual Studies

After examining the title, abstract, and full text of search records according to inclusion and exclusion criteria, data of interest were extracted from included studies using a standard form including authors, journals, year of publications, study arms, study sample, median age, routes and doses of administration, definition of status epilepticus, status epilepticus controlled time, respiratory depression, and absolute number of patients in different groups that had seizure

activity terminated. The risk of bias was evaluated according to the Cochrane Handbook version 5.1.0,[14] including method of random sequence generation (selection bias), allocation concealment (selection bias), blinding (performance bias and detection bias), incomplete outcome data (detection bias), selective reporting (detection bias), and other bias. We evaluated methodological quality as low, high, or unclear risk of bias.

Data Analysis

Data analysis was performed by 2 reviewers (FK, FJC). When head-to-head randomized controlled trials between different interventions were available, we performed pairwise meta-analysis by using Stata 12.0 software (Stata Corporation, College Station, TX). The pooled odds ratios and 95% confidence interval were calculated. Heterogeneity of treatment effects across trials was assessed by c^2 statistic and the I^2 statistic. If P value $\geq .1$, and I^2 was $\leq 50\%$, it suggested that there was no statistical heterogeneity and the Mantel-Haenszel fixed effects model was used for meta-analysis; otherwise the Mantel-Haenszel random effects model was used.[14] Publication bias was examined with the Begg and Egger funnel plot method.[15,16]

In order to indirectly compares all therapeutic regimens despite the lack of head to head randomized controlled trials, an indirect estimate of the effect of treatment A over B could be obtained by comparing trials of A vs C and B vs C. The odds ratio of A vs B was calculated as follows: $\ln(OR_{A \, vs \, B}) = \ln(OR_{A \, vs \, C}) - \ln(OR_{B \, vs \, C})$. Network meta-analysis provided effect estimates for all possible pairwise comparisons within the network. To do this, the available direct and indirect evidence was combined simultaneously for every pairwise analysis. Data analysis could be performed using either a frequentist or a Bayesian approach. We performed a Bayesian network meta-analysis using WinBUGS 1.4.3 software (MRC Biostatistics Unit, Cambridge, UK) and NetMetaXL 1-6-1 software.[17] This code for this model was adapted from WinBUGS code from the multi-parameter Evidence Synthesis Research Group at the University of Bristol (website: www.bris.ac.uk/cobm/research/mpes) (see Appendix A). The choice between fixed and random effects model was fitted by comparing the deviance information criteria for each model.[18,19] The model with the lowest deviance information criteria was preferred (differences >3 are considered meaningful). The pooled estimates and the probability of which treatment was the best were obtained using the Markov Chains Monte Carlo method. We used vague priors for all trial baselines, basic parameters, and random effects standard deviation (Appendix B). The surface under the cumulative ranking area (SUCRA) was calculated to obtain the results of ranking of treatments. The surface under the cumulative ranking area values were expressed as percentages; if a treatment was certainly the best, its surface under the cumulative ranking area value would be 100%, and if a treatment was certainly the worst, its surface under the cumulative ranking area value would be 0%.[20] Clinical decisions about the choice of treatments can be recommended based on the probability results of ranking when the differences in effect size of different treatments were small.[21] We generated 60 000 simulations for initial values, and we discarded the first 10 000 simulations as the burn-in period. The inconsistency between direct and indirect comparisons was evaluated by using Stata 12.0 software when a loop existed.[22] We assessed model convergence on the basis of inspection of Brooks-Gelman-Rubin plots.[23] In addition, we conducted subgroup analyses based on different routes of administration (intravenous vs nonintravenous) to determine the optimal therapeutic regimens.
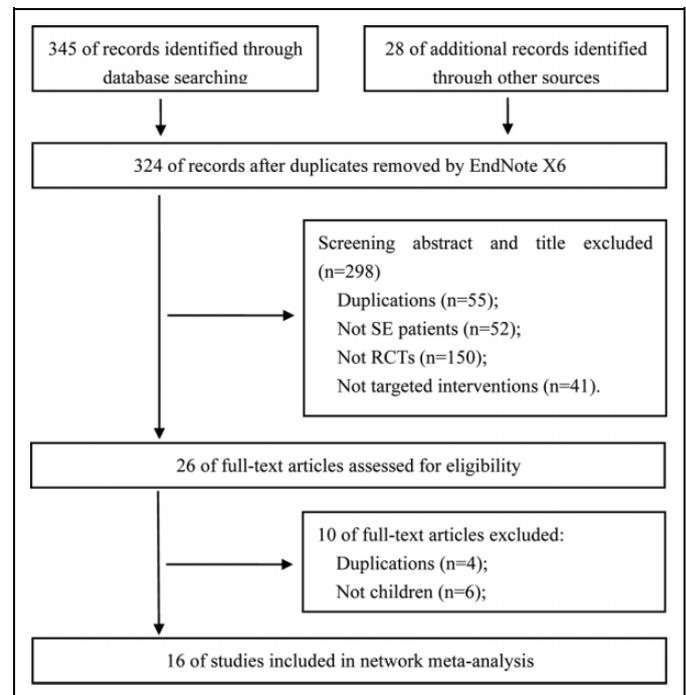
Figure 1. The search results and selection details.

All results of pairwise meta-analysis were reported with 95% confidence interval, and network meta-analyses were reported with 95% credibility interval, as well as the probability of ranking by treatments. There was no statistical significance for specific comparison groups if the confidence interval or credibility interval of odds ratio value contained 1. Statistical significance was defined as $P \leq .05$.

Results

Study Selection

A total of 345 records were identified from electronic databases, and 28 references included in 3 systematic reviews[4,9,10] were tracked. Finally, 16 randomized controlled trials[2,11,24-37] involving 1821 patients were included. The search results and selection details are shown in Figure 1.

Patient Characteristics and Study Characteristics

A total of 1821 patients were included. The definition of status epilepticus of the included studies was at least 5 minutes of seizure activity, and the success of seizure cessation was defined based on time until seizure cessation and/or absence of seizure recurrence. The median age of included patients and status epilepticus controlled time could be found in Table 1.

Sixteen included studies evaluated 7 different antiepileptic drug treatment regimens, which were based on common lorazepam, midazolam, or diazepam. Two studies[2,36] compared diazepam with lorazepam. Eight studies[26,27,29-34] compared diazepam with midazolam. The number of study for other comparison groups was 1, respectively. Routes of medication administration included intravenous, rectal, and infusion

Table 1. The Characteristics of Included Studies.

Study	Arm	Sample	Median age (y)	Dose/route	SE controlled time (median/min)	Outcomes[a]	Study design
Chamberlain JM 2014[2]	Diazepam	140	3.2 (0.3-28.0)	0.2 mg/kg IV	2.5 (1.0-12.5)	ab	RCT
	Lorazepam	133	3.1 (0.3-17.8)	0.1 mg/kg IV	2.0 (1.0-11.0)		
Fallah R 2007[24]	Lidocaine	10	3.4 ± 2.9	1 mg/kg IV	NR	ab	RCT
	Midazolam	10	4.2 ± 4.4	0.15 mg/kg IF	NR		
Mehta V 2007[25]	Sodium valproate	20	27	30 mg/kg IV	5 (2-25)	ab	RCT
	Diazepam	20	27	10 μg/kg/min IF	17 (5-117)		
Momen AA 2015[26]	Midazolam	50	2 ± 1.1	0.3 mg/kg IM	1.1 (0.4-4.1)	ab	RCT
	Diazepam	50	2.5 ± 1.4	0.5 mg/kg PR	2.2 (0.8-10)		
Singhi S 2002[27]	Midazolam	21	0.17-11.5	0.2 mg/kg IV	15 (3-30)	ab	RCT
	Diazepam	19	0.17-11.0	0.01 mg/kg/min IF	15 (5-40)		
Sreenath TG 2010[28]	Lorazepam	90	A7.0	0.1 mg/kg IV	0.33 (0.25-0.38)	ab	RCT
	Diazepam + phenytoin	88	A6.6	0.2+18 mg/kg IV	0.33 (0.26-0.40)		
Welch RD 2015[11]	Midazolam	60	6.4 ± 4.8	5-10 mg IM	16.5 (13.8-25.1)	a	RCT
	Lorazepam	60	6.9 ± 4.6	2-4 mg IV	19.6 (15.0-27.1)		
Chamberlain JM 1997[29]	Diazepam	11	3.25 (0.25-9.33)	0.3 mg/kg IV	A3.4 ± 2.0	a	RCT
	Midazolam	13	3.50 (0.75-13.75)	0.2 mg/kg IM	A4.5 ± 3.0		
Lahat E 2000[30]	Diazepam	23	1.5 (0.5-3.3)	0.3 mg/kg IV	2.5 (2.4-2.6)	a	RCT
	Midazolam	21	1.3 (0.5-3.2)	0.2 mg/kg IN	3.1 (2.9-3.3)		
Mahmoudian T 2004[31]	Diazepam	35	NR	0.2 mg/kg IV	A2.94 ± 2.62	a	RCT
	Midazolam	35	NR	0.2 mg/kg IN	A3.58 ± 1.68		
McIntyre J 2005[32]	Diazepam	110	3 (1-6)	0.5 mg/kg PR	15 (5-31)	ab	RCT
	Midazolam	109	2 (1-5)	0.5 mg/kg buccal	8 (5-20)		
Mpimbaza A 2008[33]	Diazepam	165	1.5 (0.96-3.0)	0.5 mg/kg PR	4.35 (2.72-6.58)	ab	RCT
	Midazolam	165	1.42 (0.88-2.5)	0.5 mg/kg buccal	4.75 (3.02-6.52)		
Scott RC 1999[34]	Diazepam	39	NR	10 mg PR	8 (4-12)	a	RCT
	Midazolam	40	NR	10 mg buccal	6 (4-10)		
Ahmad S 2006[35]	Lorazepam	80	1.54 (0.75-2.75)	100 mg/kg IN	7.5 (4.5-11.5)	a	RCT
	Paraldehyde	80	1.58 (0.88-3.00)	0.2 mL/kg IM	8 (5-21)		
Appleton R 1995[36]	Diazepam	53	5.2	0.3-0.4 mg/kg IV/PR	IV: 26 (20-51)s/PR: 38 (35-49)s	b	RCT
	Lorazepam	33	6.6	0.05-0.1 mg/kg IV/PR	IV: 29 (25-60)s/PR :37 (31-48)s		
Mahmoudian T 2006n[17]	Midazolam	19	0.17-18	400 μg/kg IV	A16.5 ± 0.8	a	RCT
	Sodium valproate	19		20 mg/kg PR	A4.5 ± 0.5		

Abbreviations: A, average; IF, infusion; IM, intramuscular; IN, intranasal; IV, intravenous; NR, not report; PR, per rectum; RCT, randomized controlled trial; SE, status epilepticus.
[a]*Note:* a = seizure cessation; b = respiratory depression.

diazepam; intravenous, intramuscular, rectal, infusion, buccal, and intranasal midazolam; and intranasal, intravenous, and rectal lorazepam.

Risk of Bias of Individual Studies

Risk of bias evaluation showed that inadequate random sequence generation and allocation concealment, as well as lack of blinding of participants and personnel, could lead to potential bias (see Table 2).
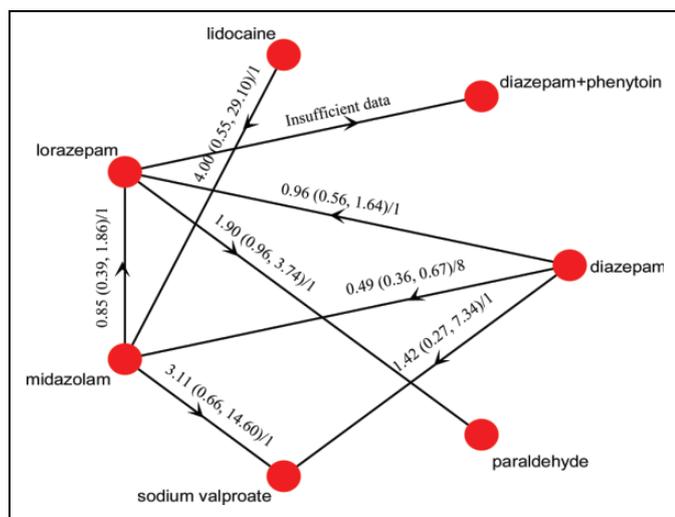
Pairwise Meta-analysis

Seizure cessation and respiratory depression were evaluated regardless of the routes of medication administration. Figure 2 summarizes the results of pairwise meta-analysis regarding seizure cessation.

Eight studies reported the number of success of seizure cessation in diazepam vs midazolam group. There was no significant statistical heterogeneity in pooled analysis of all included studies ($I^2 = 10.8\%$, $P = .347$). Compared with midazolam, diazepam was less successful in achieving seizure

Table 2. The Results of Risk of Bias Assessment.

Studies	Adequate sequence generation	Adequate allocation concealment	Blinding	Incomplete outcome data addressed	Free of selective reporting	Other bias
Chamberlain JM 2014[2]	Low risk	Low risk	Double-blind	Low risk	Low risk	Low risk
Fallah R 2007[24]	Low risk	Unclear	Unclear	Low risk	Low risk	Low risk
Mehta V 2007[25]	Unclear	Unclear	Unclear	Low risk	Low risk	Low risk
Momen AA 2015[26]	Low risk	Low risk	High risk	Low risk	Low risk	Low risk
Singhi S 2002[27]	Low risk	Low risk	Unclear	Low risk	Low risk	Low risk
Sreenath TG 2010[28]	Low risk	Low risk	Unclear	Low risk	Low risk	Low risk
Welch RD 2015[11]	Low risk	Low risk	Double-blind	Low risk	Low risk	Low risk
Chamberlain JM 1997[29]	Low risk	Unclear	Unclear	Low risk	Low risk	Low risk
Lahat E 2000[30]	Low risk	Low risk	Double-blind	Low risk	Low risk	Low risk
Mahmoudian T 2004[31]	Low risk	Low risk	Double-blind	Low risk	Low risk	Low risk
McIntyre J 2005[32]	Low risk	Low risk	Unclear	Low risk	Low risk	Low risk
Mpimbaza A 2008[33]	Low risk	Low risk	Single-blind	Low risk	Low risk	Low risk
Scott RC 1999[34]	Low risk	Low risk	Unclear	Low risk	Low risk	Low risk
Ahmad 2006[35]	Low risk	Low risk	Single-blind	Low risk	Low risk	Low risk
Appleton 1995[36]	High risk	High risk	Unclear	Low risk	Low risk	Low risk
Mahmoudian T 2006[17]	Unclear	Unclear	Unclear	Low risk	Low risk	Low risk

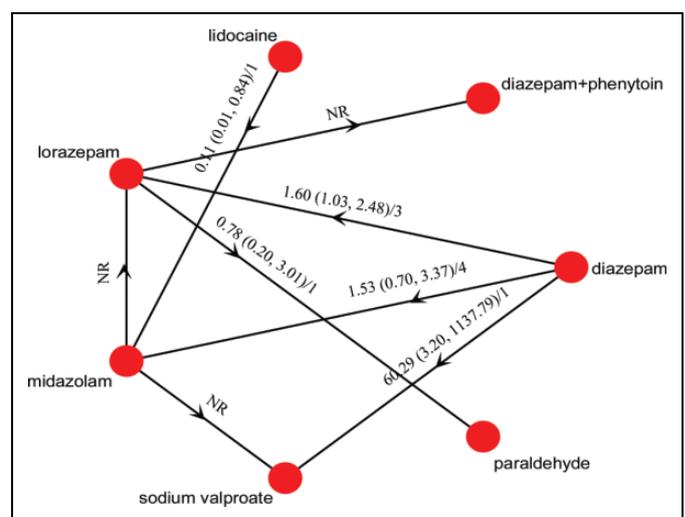**Figure 2.** The results of pairwise meta-analysis regarding seizure cessation.

Figure 3. The results of pairwise meta-analysis regarding respiratory depression.

cessation (odds ratio = 0.49, 95% confidence interval: 0.36, 0.67). The differences of other comparison groups were not statistically significant in the success of seizure cessation (Figure 2).

There was no statistically significant difference in reducing the incidences of respiratory depression for all comparison groups except for lidocaine vs midazolam and diazepam vs sodium valproate (Figure 3). However, the statistical power of 2 groups was inadequate because of limited patient numbers (20 for lidocaine vs midazolam and 40 patients for diazepam vs sodium valproate).

No publication bias was identified among those pairwise comparisons of different regimens.

Network Meta-analysis

The results of convergence assessment could be found in Appendix B.

The deviance information criteria of random and fixed effects models for seizure cessation were 140.508 and 140.744, respectively. Fixed effect model was used to perform network meta-analysis. According to the results of network meta-analysis, midazolam was more successful in achieving seizure cessation when compared with diazepam (odds ratio = 1.91, 95% confidence interval: 1.42, 2.57) and paraldehyde (odds ratio = 2.76, 95% credibility interval: 1.20, 6.43). There were no statistically significant differences for lorazepam vs diazepam (odds ratio = 1.32, 95% credibility interval: 0.84,
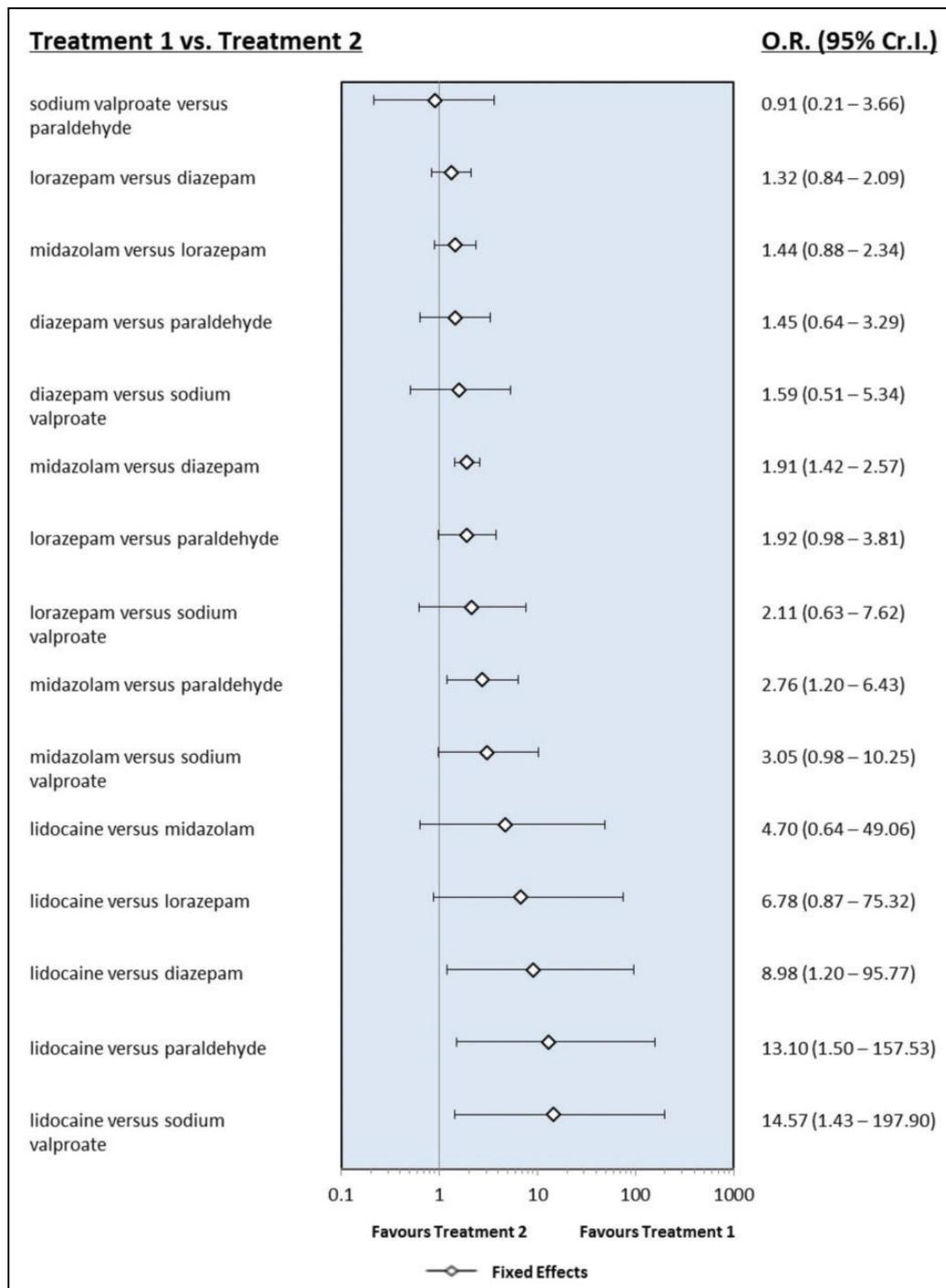
Figure 4. The results of network meta-analysis regarding seizure cessation.

2.09) and midazolam vs lorazepam (odds ratio = 1.44, 95% credibility interval: 0.88, 2.34).

The deviance information criteria of random and fixed effects models for respiratory depression were 92.417 and 91.86, respectively. The fixed effect model was used to perform network meta-analysis. Lorazepam could reduce the incidences of respiratory depression when compared with diazepam (odds ratio = 0.61, 95% credibility interval: 0.39, 0.95); however, the difference was not statistically significant when compared with midazolam (odds ratio = 0.98, 95% credibility interval: 0.39, 2.53). Sodium valproate and lidocaine could significantly reduce the incidences of respiratory depression, but there was no statistically significant difference for sodium valproate vs lidocaine (odds ratio = 0.13, 95% credibility interval: 0.00, 6.18) (Figures 4 and 5).
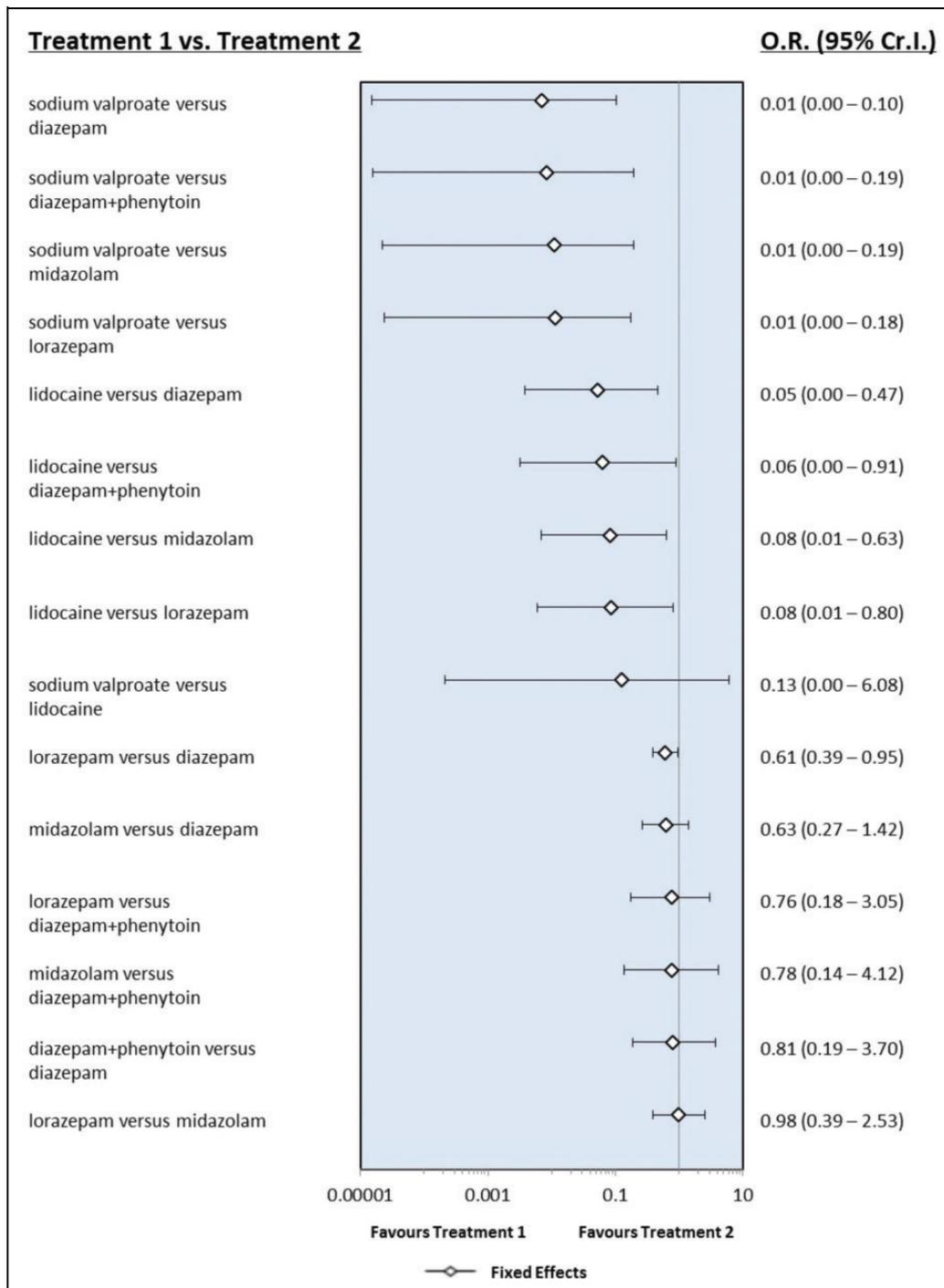
Figure 5. The results of network meta-analysis regarding respiratory depression.

Inconsistency Between Direct and Indirect Comparisons

Inconsistency analyses (Supplementary Figure S1) did not detect any inconsistency among pairwise meta-analysis and network meta-analysis for seizure cessation (*P* > .01). There were no triangular or quadratic loops found for respiratory depression, so the inconsistency was not detected.

Rank Probability

From the ranking probability results (Figure 6), lidocaine had the highest probability (surface under the cumulative ranking area = 0.9727) of achieving seizure cessation, followed by midazolam (surface under the cumulative ranking area = 0.792) and lorazepam (surface under the cumulative ranking area = 0.5699). Sodium valproate had the largest probability
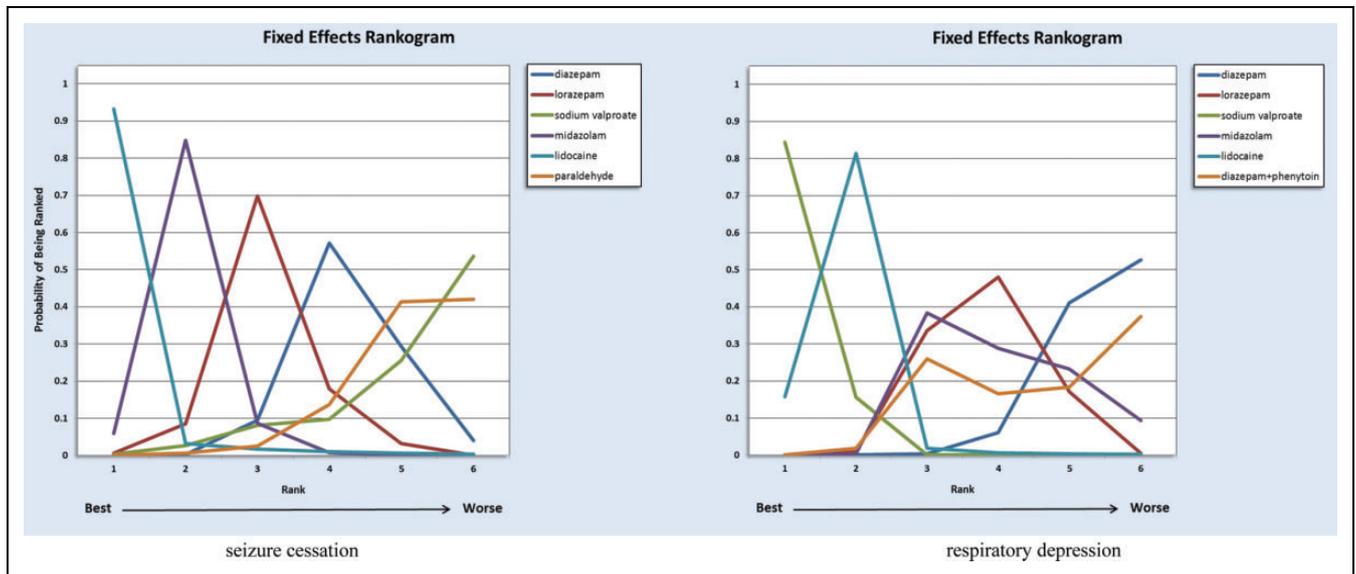
Figure 6. Rank probability.

(surface under the cumulative ranking area = 0.9686) of being the best treatment in reduction of respiratory depression, followed by lidocaine (surface under the cumulative ranking area = 0.8218), lorazepam (surface under the cumulative ranking area = 0.4346), and midazolam (surface under the cumulative ranking area = 0.3943).

Subgroup Analysis

Five different routes of administration were identified. Subgroup analysis was performed to compare intravenous and nonintravenous routes for all included treatment regimens. The results showed that regarding seizure cessation, the differences were statistical significance for nonintravenous midazolam, intravenous lorazepam, and intravenous diazepam vs nonintravenous diazepam (odds ratio = 2.23, 95% credibility interval: 1.62, 3.10; odds ratio = 2.71, 95% credibility interval: 1.25, 5.89; odds ratio = 2.65, 95% credibility interval: 1.12, 6.29, respectively). However, there were no statistically significant differences for intravenous lorazepam vs intravenous diazepam (odds ratio = 1.03, 95% credibility interval: 0.62, 1.70), intravenous diazepam vs nonintravenous midazolam (odds ratio = 1.18, 95% credibility interval: 0.54, 2.63), intravenous lorazepam vs nonintravenous midazolam (odds ratio = 1.22, 95% credibility interval: 0.60, 2.46), nonintravenous diazepam vs intravenous midazolam (odds ratio = 1.52, 95% credibility interval: 0.20, 14.23), nonintravenous midazolam vs intravenous midazolam (odds ratio = 3.38, 95% credibility interval: 0.45, 32.64), and intravenous diazepam vs intravenous midazolam (odds ratio = 4.02, 95% credibility interval: 0.46, 44.18).

In addition, there were no statistically significant differences for all comparison groups except for intravenous lorazepam vs intravenous diazepam (odds ratio = 0.62, 95% credibility interval: 0.39, 0.96) in the reduction of incidences

of respiratory depression. The subgroup results of seizure cessation and respiratory depression for lorazepam, midazolam, and diazepam can be found in Supplementary Tables S1 and S2.

Sensitivity Analysis

Welch et al[11] performed a secondary analysis of a larger randomized controlled trial that included only the pediatric age group. Therefore, a sensitivity analysis of excluding the Welch et al study was performed to observe the stability of network meta-analysis. Only seizure cessation was reported in Welch et al, so we only performed a sensitivity analysis for seizure cessation. The results showed that the differences were light before and after excluding the Welch et al study (Supplementary Table S3).

Publications Bias

The comparison-adjusted funnel plot for seizure cessation and respiratory depression can be found in Supplementary Figures S2 and S3. Different colors correspond to different comparisons. The results showed that the probability of bias of small-study effects was medium for 2 interesting outcomes.

Discussion
Summary of Evidence

It was difficult to conduct randomized controlled trials in the emergency situation for status epilepticus, particularly when the patient is unconscious. Our review identified 8 randomized controlled trials comparing diazepam with midazolam, 2 randomized controlled trials for diazepam vs lorazepam, and only 1 randomized controlled trial for midazolam vs lorazepam in pediatric patients with status epilepticus. Current evidence was

inadequate for lorazepam, midazolam, and diazepam in the treatment of pediatric status epilepticus, although recent guideline has strongly recommended that they should be given as emergent initial therapy for pediatric status epilepticus.[1] This study was the first comprehensive comparison for the treatment of status epilepticus in children, and indirect comparisons were used for the first time to compare the efficacy between lorazepam and midazolam because of the limited available head-to-head randomized controlled trials.

The current study demonstrated that compared to intravenous or nonintravenous diazepam, midazolam by any route achieved seizure cessation more often. The results of direct comparisons and network meta-analysis were consistent. Subgroup analyses showed that nonintravenous midazolam was superior to nonintravenous diazepam and was at least as effective as intravenous diazepam. Our results combining direct and indirect evidence were similar to previous meta-analysis in children and adults.[9]

The study by Prasad et al[10] has demonstrated that intravenous lorazepam was better than intravenous diazepam alone for cessation of seizures in adults. Appleton et al also demonstrated that intravenous lorazepam was at least as effective as intravenous diazepam and was associated with fewer adverse events for the treatment of acute tonic-clonic convulsions in children.[4] Our direct comparisons showed that the difference of lorazepam and diazepam in achieving seizure cessation was not statistically significant; however, lower incidences of respiratory depression were found in the lorazepam group. Similar results could be found in our network meta-analysis.

Our subgroup analyses demonstrated that intravenous lorazepam was better than intravenous or nonintravenous diazepam. A recent multicenter randomized controlled trial comparing lorazepam with midazolam in pediatric status epilepticus[11] concluded that intravenous lorazepam was similar to intramuscular midazolam in achieving successful seizure cessation. However, the statistical power was limited because only 120 patients were included. We conducted this network meta-analysis to increase the statistical power and demonstrated similar results for lorazepam and midazolam, by any routes. Moreover, comparisons between other antiepileptic drugs and lorazepam, midazolam, or diazepam were also included. The results showed that lidocaine and sodium valproate were effective alternatives in controlling status epilepticus in children and were free of respiratory depression. However, the statistical power was inadequate because of only a single trial with 10 patients for lidocaine. Moreover, our study mainly aimed to compare the seizure cessation and respiratory depression of lorazepam, midazolam, and diazepam.

Previous studies demonstrated that midazolam and lorazepam were better than diazepam for the treatment of status epilepticus in children and adults; however, data were limited in children, and it was unclear which one was better for midazolam and lorazepam. In our study, the efficacy of lorazepam, midazolam, and diazepam were comprehensively compared using network meta-analysis. We also calculated the inconsistency of direct and indirect evidences, and the results of direct and indirect comparisons were consistent. We conducted subgroup analyses according to different routes of administration to determine the optimal therapeutic regimens, and the methodological quality of included studies was good. Moreover, to ensure the similarity, we only included truly random or quasi-random controlled trials, meanwhile, the definition of status epilepticus of the included studies was at least 5 minutes of seizure activity, and the success of seizure cessation was defined based on time until seizure cessation and/or absence of seizure recurrence.

Limitations

Some limitations were found in our network meta-analysis. Firstly, the number of included studies was small and bias of small-study effects existed although a systematic literature search was performed. Then, only 2 outcomes were analyzed because most of the studies did not report other outcomes such as recurrent, death, or other measures. Thirdly, many antiepileptic drugs were not compared for the treatment of status epilepticus in children. Finally, we included both convulsive and nonconvulsive status epilepticus. However, the differences between convulsive and nonconvulsive status epilepticus were not compared in our study because of the limited number of studies. Moreover, the location of first treatment for status epilepticus and other characteristics were not considered in our study because of inadequate reporting of included randomized controlled trials, although there was no significant statistical heterogeneity in pooled analysis of all included studies.

Conclusions

Overall, the quality of included randomized controlled trials was good. Nonintravenous midazolam and intravenous lorazepam were superior to intravenous or nonintravenous diazepam; intravenous lorazepam was at least as effective as nonintravenous midazolam. Nonintravenous midazolam should be recommended for the prehospital treatment of status epilepticus in the pediatric population. The results of ranking probability showed that midazolam had the largest probability of being the best treatment in achieving seizure cessation, and lorazepam had the largest probability of being the best treatment in reduction of respiratory depression. More head-to-head randomized controlled trials should be needed to compare the efficacy of intravenous lorazepam and nonintravenous midazolam in future studies.

Appendix A

The Code of Fixed and Random Effect Models Used

```
model{          # fixed effect model
  for(i in 1:NS)
    {

        mu[i] ~ dnorm(0,.0001)                                                    #
vague priors for baselines          # vague priors for all trial baselines
        for (k in 1:na[i])          # LOOP THROUGH ARMS
    {
    r[i,k] ~ dbin(p[i,k],n[i,k])                                                  #
binomial likelihood
                    logit(p[i,k]) <- mu[i] + d[t[i,k]] - d[t[i,1]]          # model for linear predictor
    rhat[i,k] <- p[i,k] * n[i,k]          # expected value of the numerators
    #Deviance contribution
    dev[i,k] <- 2 * (r[i,k] * (log(r[i,k])-log(rhat[i,k])) + (n[i,k]-r[i,k]) * (log(n[i,k]-r[i,k]) - log(n[i,k]-rhat[i,k])))
    }
  resdev[i] <- sum(dev[i,1:na[i]])          # summed residual deviance contribution for this trial
  }
  totresdev <- sum(resdev[])          # Total Residual Deviance

  d[1]<-0

  for (k in 2:NT)
  {
    d[k] ~ dnorm(0,.0001) #      vague priors for basic parameters
  }


  # ranking best and probability
  for (k in 1:NT)
  {
        #events good
  rk[k]<- rank(d[],k)      #events bad
    best[k]<-equals(rk[k],1)

  for (h in 1:NT)
  {
    prob[k,h]<-equals(rk[k],h)
  }
}
for (k in 1:NT)
  {
    for (h in 1:NT)
    {
      cumeffectiveness[k,h]<-sum(prob[k,1:h])      # The cumulative ranking probability of treatment i to be among the j best
  treatments.
    }
  }
  for(i in 1:NT)
  {
        SUCRA[i]<-sum(cumeffectiveness[i,1:(NT-1)])/(NT-1) # The surface under the cumulative rankings for treatment i.
  }
```

```
   # pairwise ORs
   for (c in 1:(NT-1))
   {
     for (k in (c+1):NT)
     {
       OR[c,k] <- exp(d[k] - d[c] )
       lOR[c,k]<-d[k]-d[c]
     }
   }

} #END Program
```

model   # random effect model

```
{
  for(i in 1:NS)
  {
        w[i,1] <-0          # adjustment for multi-arm trials is zero for control arm
        delta[i,1]<-0       # treatment effect is zero for control arm
        mu[i]                              ~                              dnorm(0,.0001)
# vague priors for all trial baselines
        for (k in 1:na[i])          # LOOP THROUGH ARMS
    {
        r[i,k] ~ dbin(p[i,k],n[i,k])           # binomial likelihood
            logit(p[i,k]) <- mu[i] + delta[i,k]           # model for linear predictor
          rhat[i,k] <- p[i,k] * n[i,k]           # expected value of the numerators
        #Deviance contribution
      dev[i,k] <- 2 * (r[i,k] * (log(r[i,k])-log(rhat[i,k])) + (n[i,k]-r[i,k]) * (log(n[i,k]-r[i,k]) - log(n[i,k]-rhat[i,k])))
  }
  resdev[i] <- sum(dev[i,1:na[i]])        # summed residual deviance contribution for this trial
    for (k in 2:na[i]) # LOOP THROUGH ARMS
    {
        delta[i,k] ~ dnorm(md[i,k],taud[i,k])           # trial-specific LOR distributions
        md[i,k] <- d[t[i,k]] - d[t[i,1]] + sw[i,k]           # mean of LOR distributions (with multi-arm trial correction)
          taud[i,k] <- tau *2*(k-1)/k           # precision of LOR distributions (with multi-arm trial correction)
          w[i,k] <- (delta[i,k] - d[t[i,k]] + d[t[i,1]])           # adjustment for multi-arm RCTs
          sw[i,k] <- sum(w[i,1:k-1])/(k-1) # cumulative adjustment for multi-arm trials
    }
  }
  totresdev <- sum(resdev[])        # Total Residual Deviance

  d[1]<-0
  for (k in 2:NT)
  {
    d[k] ~ dnorm(0,.0001) # vague priors for basic parameters
  }
  sd ~ dunif(0,2)          # vague prior for random effects standard deviation
  tau<-1/pow(sd,2)         # vague prior for random effects standard deviation
                    # Informative log-normal prior for heterogeneity variance parameter tau - Turner 2012
                    # Informative log-normal prior for heterogeneity variance parameter tau - Turner 2012
                    # Informative log-normal prior for heterogeneity variance parameter tau - Turner 2012


  # Treatment 1 baseline, based on average of NP trials including it.

  # ranking
  for (k in 1:NT)
```

```
{
        # events good
    rk[k]<- rank(d[],k)          # events bad
    best[k]<-equals(rk[k],1)
    for (h in 1:NT)
    {
        prob[k,h]<-equals(rk[k],h)
    }
}
for (k in 1:NT)
{
    for (h in 1:NT)
    {
        cumeffectiveness[k,h]<-sum(prob[k,1:h]) # The cumulative ranking probability of treatment i to be among the j best
 treatments.
    }
}
for(i in 1:NT)
{
        SUCRA[i]<-sum(cumeffectiveness[i,1:(NT-1)])/(NT-1) # The surface under the cumulative rankings for treatment i.
}
# pairwise ORs
for (c in 1:(NT-1))
{
    for (k in (c+1):NT)
    {
        OR[c,k] <- exp(d[k] - d[c] )
        lOR[c,k]<-d[k]-d[c]
    }
}

} #END Program
```

Appendix B

The Results of Convergence Assessment
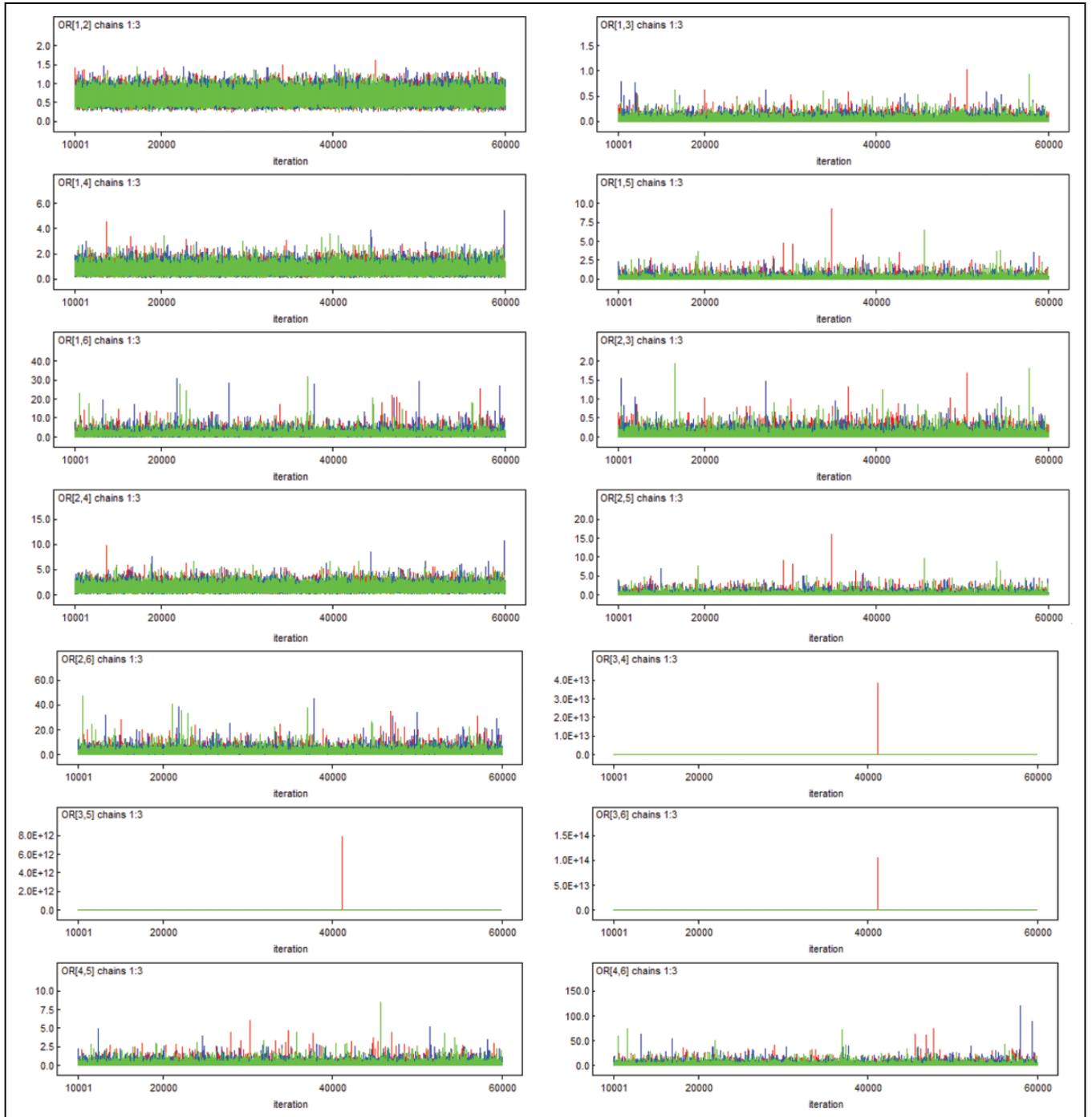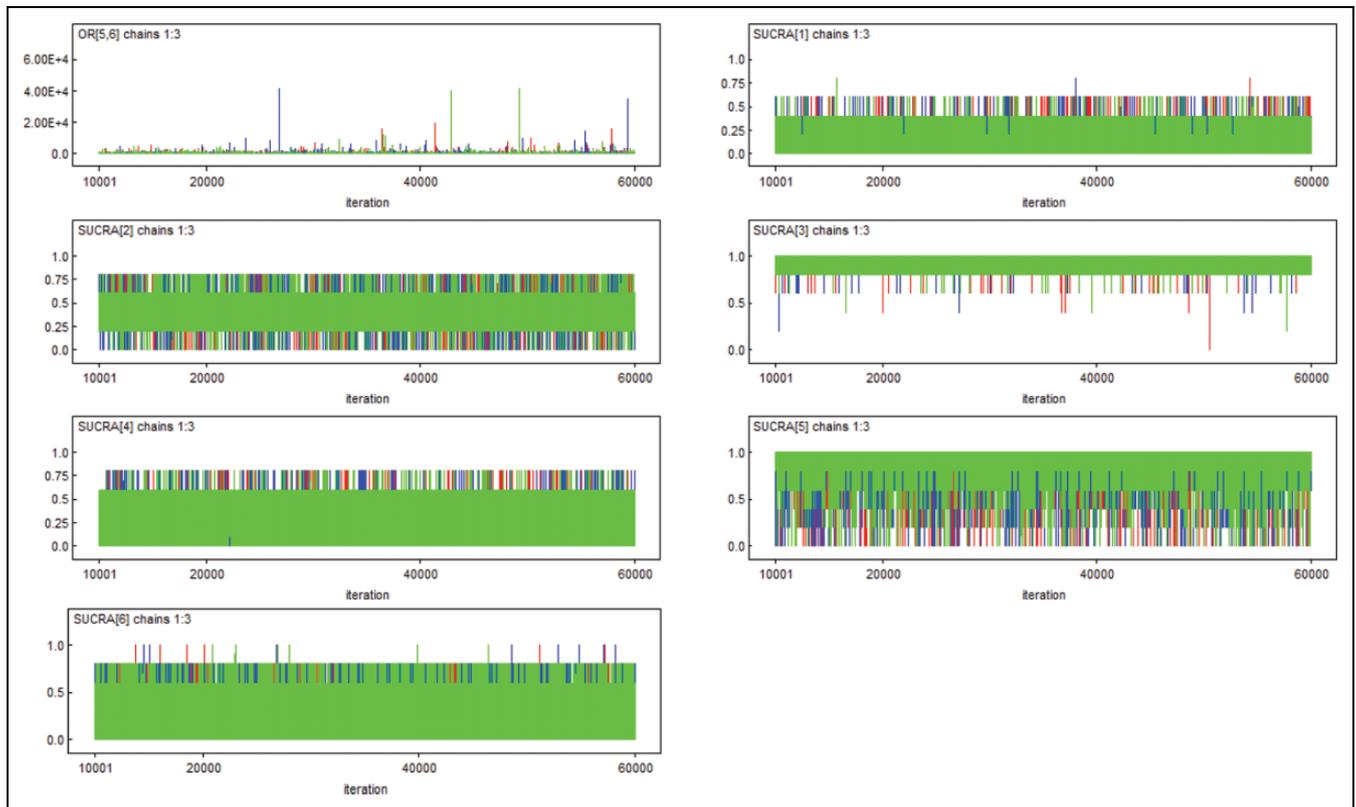
Appendix B (Continued)

Authors Contributions

ZZY conceived and designed the research; ZZY, WHY, WB, and YZB performed the research; FK and FJC analyzed the data; ZZY and WHY wrote the manuscript. All authors read and approved the final manuscript.

Declaration of Conflicting Interests

The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Funding

The authors received no financial support for the research, authorship, and/or publication of this article.

Supplementary Material

The online [appendices/data supplements/etc] are available at http://jcn.sagepub.com/supplemental.

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