Supplementary File of

Efficacy, Safety, Route of Administration of Midazolam and Diazepam for Pediatric Status Epilepticus: Systematic Review, Meta-Analysis, and Trial Sequential Analysis

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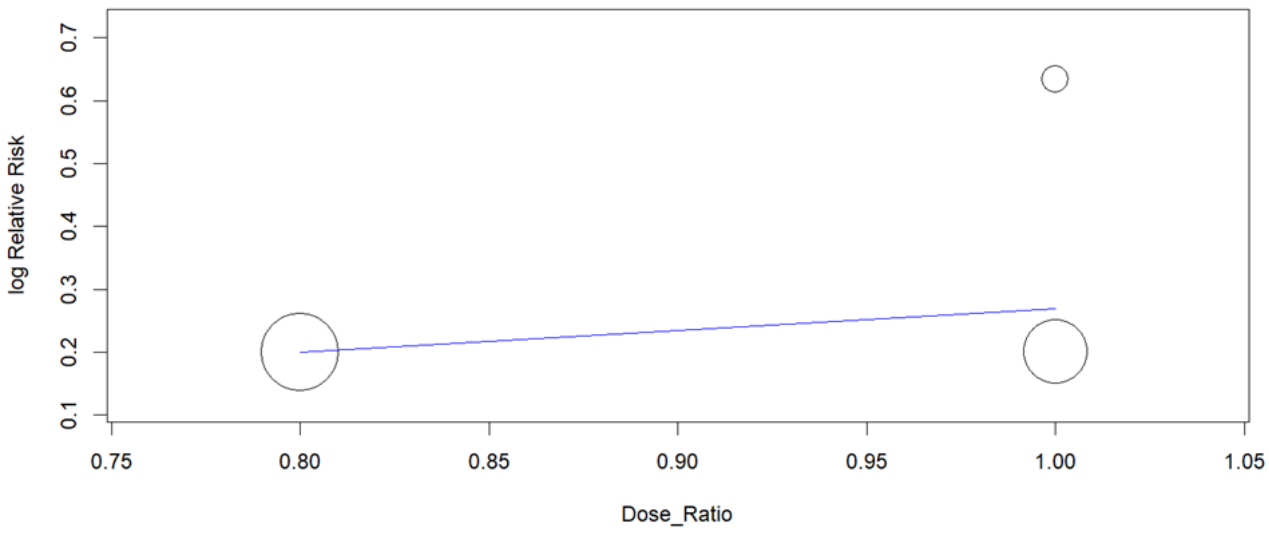
Figure S8: Trial sequential analysis of seizure relapse event rates comparing midazolam and diazepam

Figure S9: Trial sequential analysis of respiratory depression comparing midazolam and diazepam.

Table S1: GRADE assessment results.

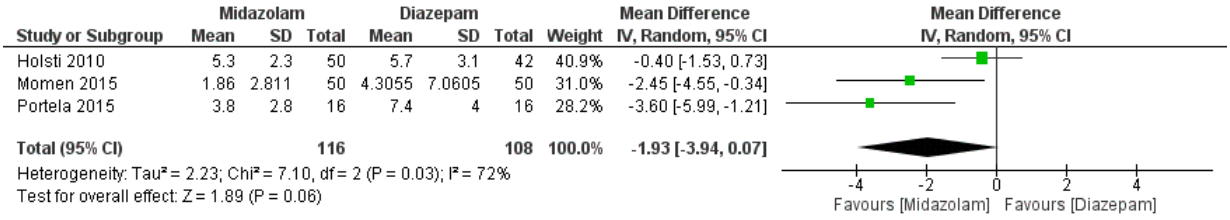
Figure S1: random-effects meta-regression of the dose ratio for the buccal midazolam vs. rectal diazepam subgroup



The plot displays the log relative risk (y-axis) against the dose ratio (x-axis). The size of each circle is proportional to the study's weight. The relationship was not statistically significant (p=0.517), indicating that the dose ratio does not explain the residual heterogeneity (I^2=55%) identified in Subgroup 1.2.2 of Figure 3.

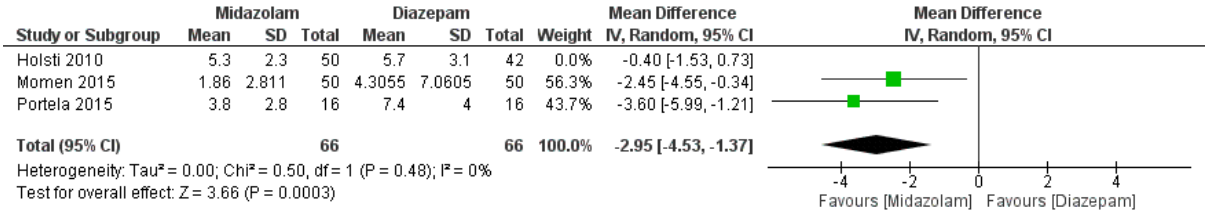
Statistical Note: To investigate potential sources of variability in this subgroup, we performed a random-effects meta-regression (REML estimator). We selected the midazolam: diazepam dose ratio as a continuous covariate to test the hypothesis that the relative efficacy (log Relative Risk) is linearly dependent on the dose ratio. A random-effects model was chosen to maintain consistency with the primary subgroup analysis and to account for the observed between-study variance.

Figure S2: Comparison of the time from admission to active treatment (minutes) between midazolam and diazepam.



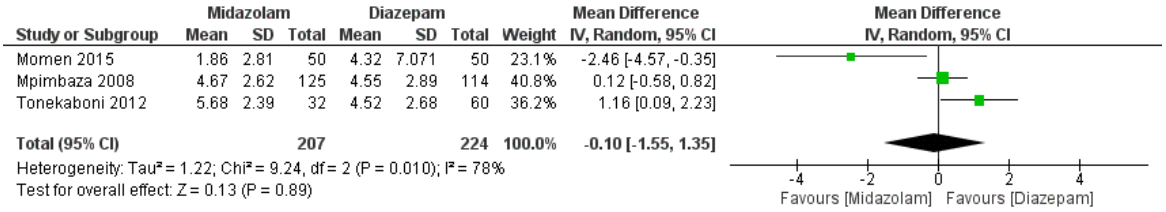
Meta-analysis of time from admission to active treatment (all studies). The overall analysis revealed no significant difference between midazolam and diazepam (mean difference (MD): -1.93 min; 95% CI: [-3.94, 0.07], p=0.06), with substantial heterogeneity (I2=72%).

Figure S3: Time since admission to treatment (sensitivity analysis) forest plot comparing midazolam and diazepam



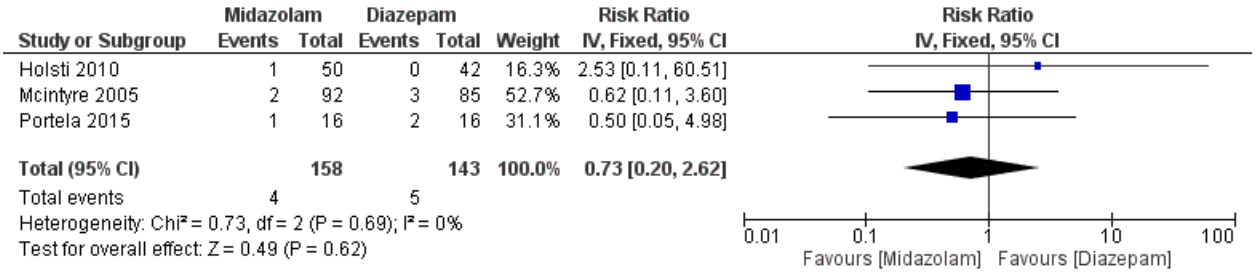
This analysis excludes Holsti et al. 2010 to investigate the substantial heterogeneity (I^2=72%) observed in the primary analysis. Holsti et al. was identified as the primary source of statistical heterogeneity; its removal reduced the I^2 from 72% to 0%. In this homogeneous subset, midazolam significantly reduced the time to treatment compared to diazepam (MD: -2.95 min; 95% CI: [-4.53, -1.37], p=0.0003).

Figure S4: Seizures stopped within a 10-minute period compared with midazolam and diazepam



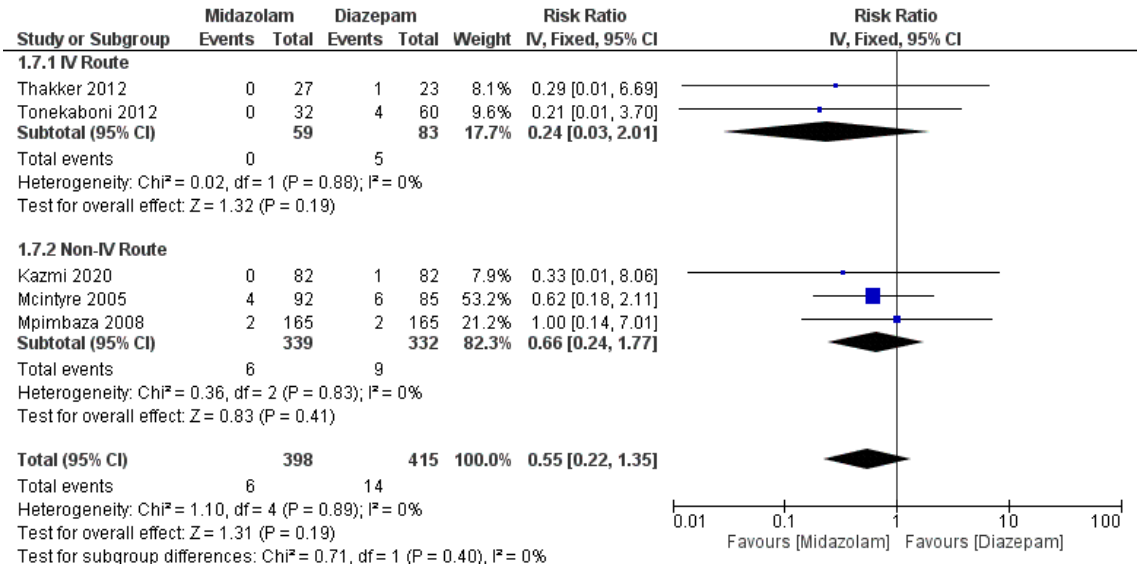
The meta-analysis for seizures stopped within 10 minutes included three studies with a total of 207 children in the midazolam group and 224 in the diazepam group. The overall pooled analysis, performed via a random-effects model, revealed no statistically significant difference between midazolam and diazepam. The pooled mean difference was -0.10 minutes (95% CI: -1.55, 1.35; p=0.89), indicating no clear advantage for either drug in achieving seizure cessation within this timeframe. The analysis revealed substantial heterogeneity among the studies (I2=78%; p=0.010). This suggests that the study results were inconsistent, which is visually apparent in the forest plot, where the individual study findings point in different directions.

Figure S5: Intubation rate forest plot of midazolam and diazepam



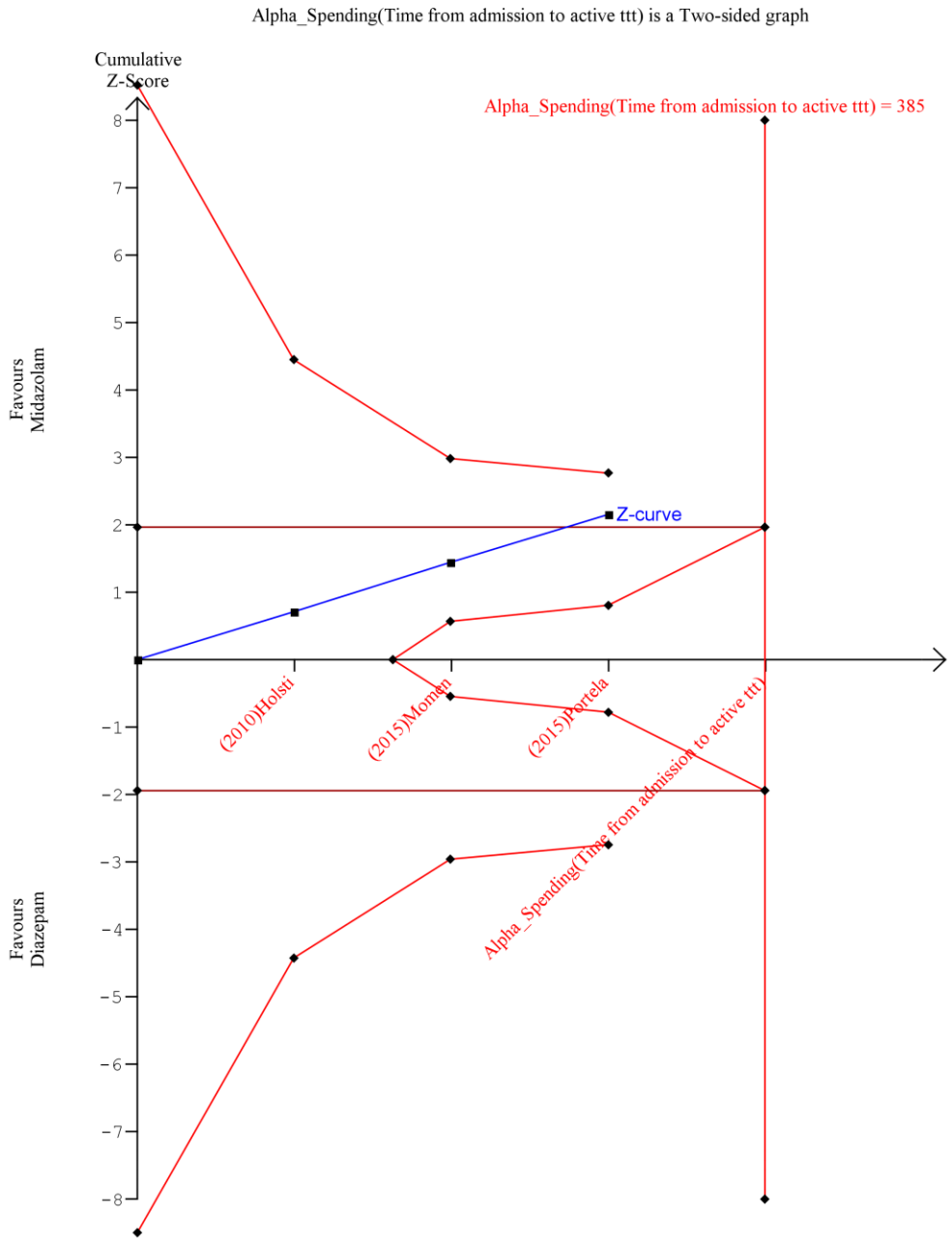
The meta-analysis for the intubation rate included three studies with a total of 158 children in the midazolam group and 143 in the diazepam group. With a very small number of events (4 in the midazolam group and 5 in the diazepam group), the pooled analysis revealed no statistically significant difference between the two drugs. The pooled risk ratio was 0.73 (95% CI: 0.20, 2.62; p=0.62). There was no heterogeneity among the included studies (I2=0%; p=0.69), indicating that the results across the trials were consistent.

Figure S6: Respiratory depression forest plot comparing midazolam and diazepam



The meta-analysis for respiratory depression included five studies. The overall pooled analysis revealed no statistically significant difference between midazolam and diazepam (RR = 0.55, 95% CI: 0.22, 1.35; p=0.19). To further investigate this outcome, a subgroup analysis was performed. In the subgroup of studies that used the IV route or non-IV route, no significant difference was found. The pooled risk ratio for the non-IV route subgroup was 0.66 (95% CI: 0.24, 1.77; p=0.41). Similarly, in the intravenous (IV) route subgroup, there was no significant difference between the two drugs, with a risk ratio of 0.24 (95% CI: 0.03, 2.01; p=0.19). The results of the test for subgroup differences were not statistically significant (p=0.40). These findings indicate that the risk of respiratory depression was not significantly different between the subgroups. Notably, there was no heterogeneity among the included studies (I2=0%), suggesting a consistent nonsignificant finding across all trials.

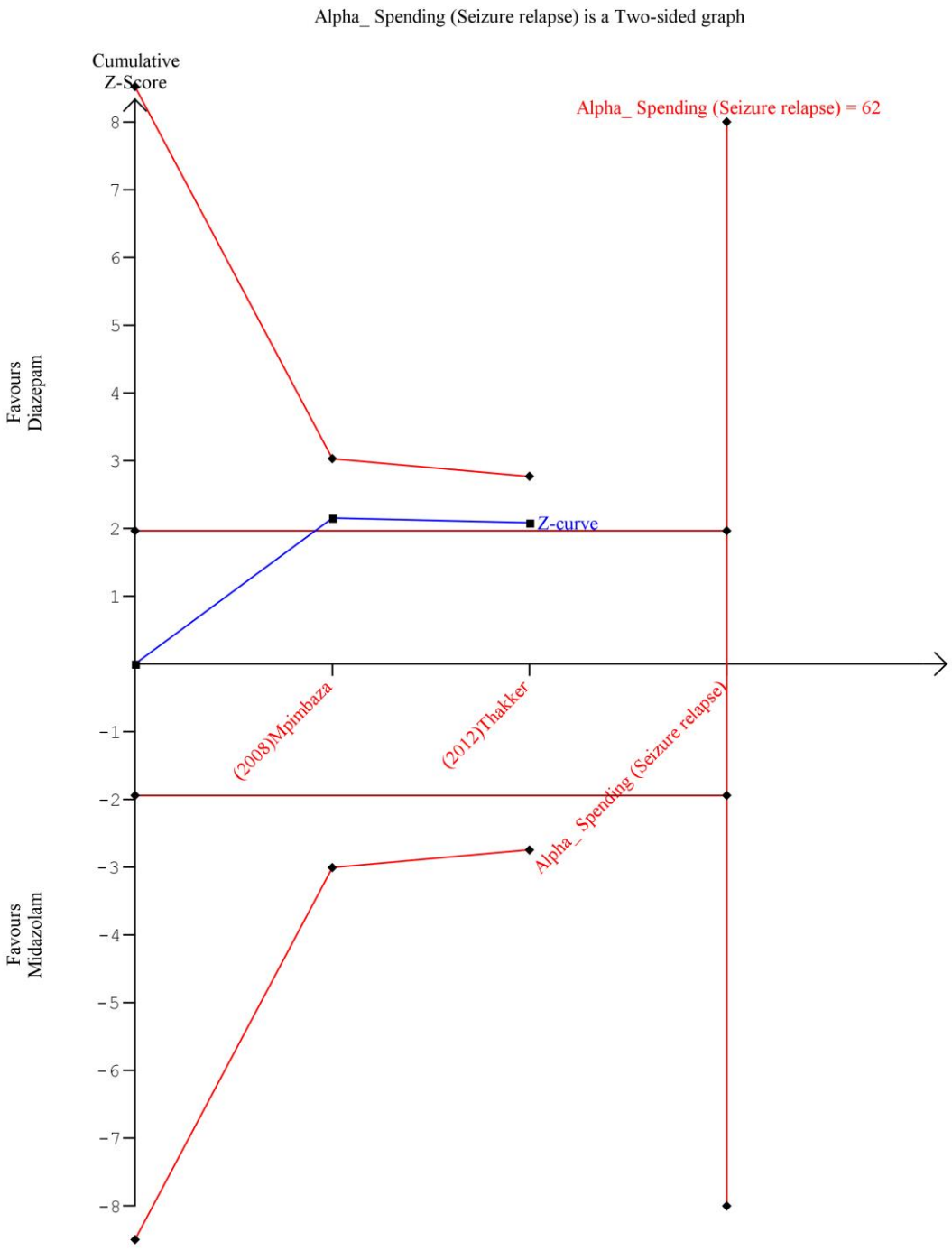
Figure S7: Trial sequential analysis of the time to seizure termination (minutes) of midazolam and diazepam



TSA of the time to seizure termination was conducted via a random-effects model (BT). The conventional meta-analysis for this outcome revealed a significant pooled effect (MD=−1.45 minutes, 95% CI: −2.78--−0.12; P value: 0.0323), confirming that midazolam is faster. The analysis revealed substantial heterogeneity (I2=0.71, Q=7.0, P

value: 0.0302) and diversity (D2=0.52). The TSA was based on a double-sided alpha of 0.05 and a power of 80%. As shown in the TSA plot (Figure S7), the cumulative blue Z-curve (blue line) crossed the conventional statistical significance boundary but did not cross the superiority boundary (the outer red line). With a required information size (RIS) of 385 patients, the cumulative evidence is considered insufficient and inconclusive. The Z-curve's failure to cross the boundaries indicates that although the conventional analysis suggests significance, the result is prone to a Type I error, and further trials are needed to confirm or refute a difference between midazolam and diazepam for time to seizure termination.

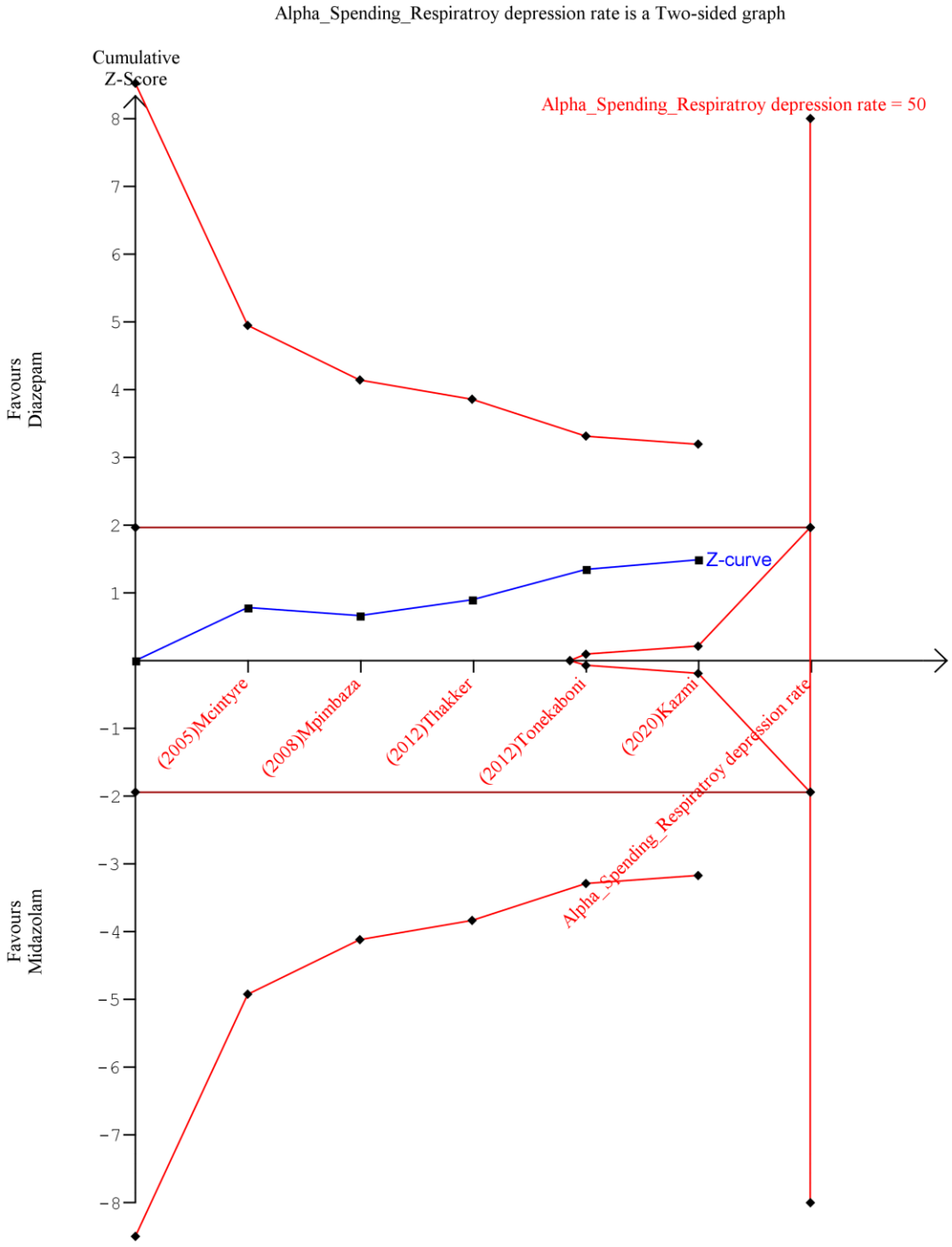
Figure S8: Trial sequential analysis of seizure relapse event rates comparing midazolam and diazepam



TSA of the seizure relapse event rates was conducted via a fixed effects model. The conventional meta-analysis revealed a significant pooled effect (RR=0.51, 95% CI: 0.27--0.97; P value: 0.0391), with no observed heterogeneity

(I2=0.0, Q=0.54, P value: 0.4611) or diversity (D2=0.0). The TSA was based on a double-sided alpha of 0.05 and a power of 80%. The cumulative Z-curve (blue line) crossed the conventional statistical significance boundary but did not cross the superiority boundary (the outer red line). With a required information size (RIS) of 62 patients, the cumulative evidence is considered insufficient and inconclusive, which means that further trials are needed to confirm or refute a difference in seizure relapse event rates between midazolam and diazepam.

Figure S9: Trial sequential analysis of respiratory depression comparing midazolam and diazepam



TSA of the respiratory depression rate was conducted via a fixed effects model. The conventional meta-analysis revealed a nonsignificant pooled effect (RR=0.51, 95% CI: 0.21--1.24; P value: 0.1374), with no observed heterogeneity (I2=0.0, Q=1.12, P value: 0.8906). The TSA was based on a double-sided alpha of 0.05 and a power of 80%. The cumulative Z-curve (blue line) did not cross either the conventional statistical significance boundary or the superiority boundary (the outer red line). With a required information size (RIS) of 50 patients, the cumulative evidence is considered insufficient and inconclusive, which means that further trials are needed to confirm or refute a difference between midazolam and diazepam for the risk of respiratory depression.

Table S1: GRADE assessment table

Summary of findings:

Midazolam compared to Diazepam for Pediatric patients with status epilepticus

Patient or population: Pediatric patients with status epilepticus

Setting: Studies whose population included pediatric patients with status epilepticus, whether these patients were children, infants, adolescents, or neonates.

Intervention: Midazolam

Comparison: Diazepam

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with Diazepam	**Risk with Midazolam**				
Therapeutic Success (Non-IV Route)	62 per 100	**74 per 100** (65 to 82)	**RR 1.18** (1.04 to 1.32)	961 (6 RCTs)	⨁⨁⨁◯ Moderate[a]	Effect driven by non-IV subgroup; pooled estimate in footnote.[b]
Therapeutic Success (IV Route)	72 per 100	**72 per 100** (60 to 85)	**RR 1.00** (0.84 to 1.19)	174 (3 RCTs)	⨁⨁◯◯ Low[c,d]	Effect driven by IV subgroup; pooled estimate in footnote.[b]
Time to Seizure Termination (Non-IV Route) assessed with: Minutes		MD **1.4 minutes lower** (2.67 lower to 0.13 lower)	-	772 (5 RCTs)	⨁⨁◯◯ Low[a,e]	Effect driven by non-IV subgroup; pooled estimate in footnote.[f]
Time to Seizure Termination (IV Route) assessed with: Minutes		**0.88 minutes higher** (0.03 higher to 1.73 higher)	-	174 (3 RCTs)	⨁⨁◯◯ Low[c,d]	Effect driven by IV subgroup; pooled estimate in footnote.[f]

Summary of findings:

Midazolam compared to Diazepam for Pediatric patients with status epilepticus

Patient or population: Pediatric patients with status epilepticus

Setting: Studies whose population included pediatric patients with status epilepticus, whether these patients were children, infants, adolescents, or neonates.

Intervention: Midazolam

Comparison: Diazepam

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with Diazepam	**Risk with Midazolam**				
Respiratory Depression	3 per 100	**2 per 100** (1 to 5)	**RR 0.55** (0.22 to 1.35)	813 (5 RCTs)	⨁⨁⨁◯ Moderate[g]	Subgroup analysis by route (IV vs non-IV) showed no meaningful differences; results presented pooled.
Seizure Relapse	17 per 100	**8 per 100** (4 to 16)	**RR 0.47** (0.22 to 0.97)	289 (2 RCTs)	⨁⨁◯◯ Low[d]	Based on limited data from two small trials.
Intubation Rate	3 per 100	**3 per 100** (1 to 10)	**RR 0.72** (0.19 to 2.75)	301 (3 RCTs)	⨁⨁◯◯ Low[h]	Rare events across few small studies.
Time since admission to treatment assessed with: Minutes		MD **1.93 minutes lower** (3.94 lower to 0.07 higher)	-	224 (3 RCTs)	⨁⨁◯◯ Low[a,d]	Reported in only three small trials.[i]

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: confidence interval; **MD:** mean difference; **RR:** risk ratio

Summary of findings:

Midazolam compared to Diazepam for Pediatric patients with status epilepticus

Patient or population: Pediatric patients with status epilepticus

Setting: Studies whose population included pediatric patients with status epilepticus, whether these patients were children, infants, adolescents, or neonates.

Intervention: Midazolam

Comparison: Diazepam

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with Diazepam	**Risk with Midazolam**				

GRADE Working Group grades of evidence

High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.

Moderate certainty: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.

Low certainty: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.

Very low certainty: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

Explanations

a. Downgraded for inconsistency due to heterogeneity.

b. Across all 9 RCTs (1,135 children), pooled RR = 1.13 (95% CI 1.03–1.25); certainty moderately decreased for inconsistency (I^2=55%). Subgroup analysis revealed that the benefit was restricted to non-IV administration.

c. Downgraded for risk of bias due to study limitations.

d. Imprecision: wide CI/small sample size.

e. Imprecision: wide CI.

f. Overall pooled estimate (8 RCTs, 946 children): MD –0.62 min (95% CI –1.70 to 0.46); CI includes no effect, certainty low (downgraded for heterogeneity and imprecision). Subgroup effects differed (non-IV: 5 RCTs, 772 children, favored midazolam; IV: 3 RCTs, 174 children, favored diazepam).

g. Imprecision: wide CI/few events.

h. Two levels of imprecision were downgraded due to wide confidence intervals, few events, and a small sample size.

i. No publication bias was detected; assessment was limited because each outcome included <10 studies.