Efficacy and safety of intramuscular midazolam versus other non-intravenous benzodiazepine formulations in children with convulsive status epilepticus: a systematic review

Drugs and Therapy Perspectives

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Online supplementary material

1. Search strategy (MEDLINE)

1. exp Epilepsy, Tonic-Clonic/
2. (tonic adj2 clonic).tw
3. exp Seizures/
4. epilep$.tw
5. seizure$.tw
6. convuls$.tw
7. exp Status Epilepticus/
8. (status adj2 epilepticus).tw
9. 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8
10. randomized controlled trial.pt
11. controlled clinical trial.pt
12. pragmatic clinical trial.pt
13. clinical trial.pt
14. (clin$ adj2 (study or trial)).tw
15. ((singl$ OR doubl$ or trebl$ or trip$) adj (blind$ or mask$)).tw
16. (control$ adj2 (study or trial)).tw
17. randomi$.tw
18. (randomi$ adj (allocate$ or assign$)).tw
19. exp Random Allocation/
20. exp Double-Blind Method/
21. exp Single-Blind Method/
22. exp Clinical Trial/
23. 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22
24. 9 and 23
25. exp Infant/
26. exp Child/
27. exp Adolescent/
28. (pediatr$ or paediat$ or child$ or adolesc$).tw
29. 25 or 26 or 27 or 28
30. 24 and 29
31. ((intramuscul$ or IM) adj2 (midazolam)).tw
32. 30 and 31
33. (1980:3000/12/12).pdat
34. 32 and 33

35. (animals not human).sh

36. 34 not 35

2. Figure S1. Number of individuals with cessation of seizure within 5-10 minutes of medication administration (excl. Muchohi et al.[1])

Figure S1a. Emergency room and home data

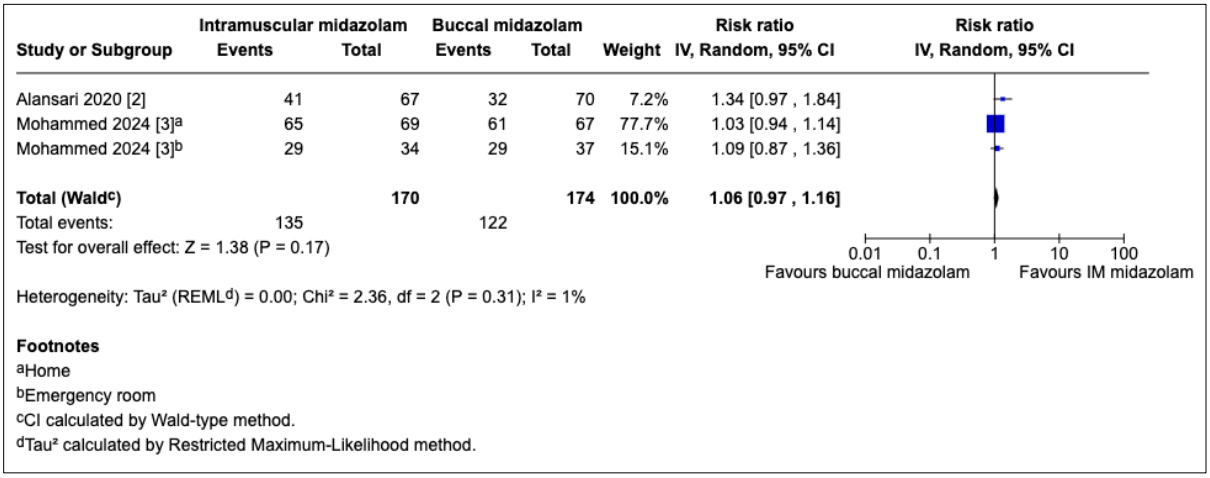
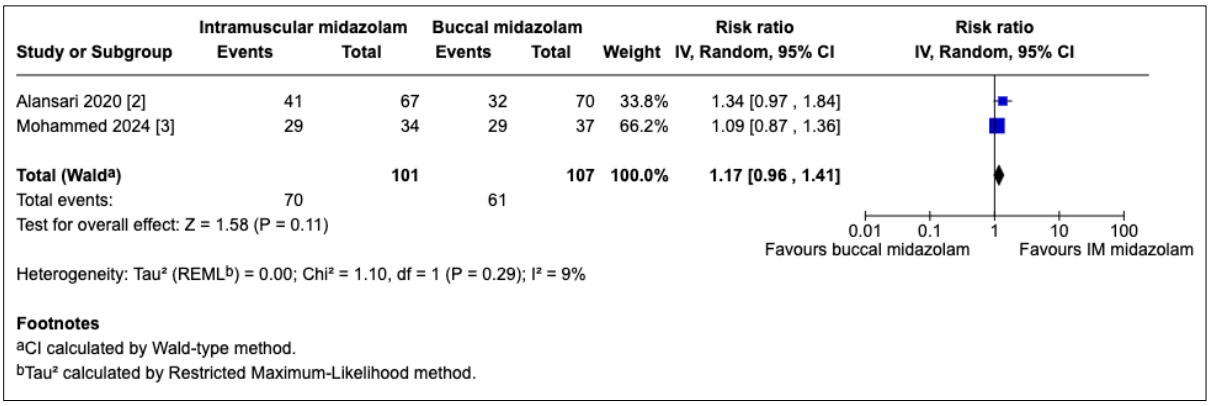


Figure S1b. Emergency room data only



3. Table S1

Intramuscular midazolam compared to buccal midazolam for acute seizures or convulsive status epilepticus in children and young people

Patient or population: acute seizures or convulsive status epilepticus in children and young people

Setting: Out of hospital, pre-hospital or hospital emergency department

Intervention: intramuscular midazolam

Comparison: buccal midazolam

Outcome № of participants (studies)	Relative effect (95% CI)	Anticipated absolute effects (95% CI)			Certainty	What happens
		buccal midazolam	**intramuscular midazolam**	**Difference**		
Cessation of seizure within 5-10 minutes of medication administration (Seizure cessation within 5-10 mins) № of participants: 364 (3 RCTs)	**RR 1.07** (0.97 to 1.17)	68.7%	**73.5%** (80.4 to 66.6)	**4.8% more** (2.1 fewer to 11.7 more)	⨁⨁◯◯ Low[a,b]	The evidence suggests that intramuscular midazolam results in little to no difference in cessation of seizures within 5-10 minutes of medication administration compared with buccal midazolam.

***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; **RR:** risk ratio

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. Two of three studies included in analysis accounting for > 90% of weighting considered to have high risk of bias

b. Limited data for outcome from small, pooled sample size (< 380) and small total number of events (< 300)

4. Table S2

Intramuscular midazolam compared to intranasal midazolam for acute seizures or convulsive status epilepticus in young people

Patient or population: acute seizures or convulsive status epilepticus in young people

Setting: out of hospital, pre-hospital or hospital emergency department

Intervention: intramuscular midazolam

Comparison: intranasal midazolam

Outcome № of participants (studies)	Relative effect (95% CI)	Anticipated absolute effects (95% CI)			Certainty	What happens
		intranasal midazolam	**intramuscular midazolam**	**Difference**		
Seizure cessation within 5-10 minutes of medication administration (Seizure cessation within 5-10 mins) № of participants: 197 (1 RCT)	**RR 1.03** (0.41 to 2.55)	91.5%	**94.2%** (100 to 37.5)	**2.7% more** (54 fewer to 141.8 more)	⊕◯◯◯ Very low[a,b]	Very limited evidence suggests that intramuscular midazolam results in little to no difference in cessation of seizures within 5-10 minutes of medication administration compared with intranasal midazolam.

***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; **RR:** risk ratio

GRADE Working Group grades of evidence
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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. Single study judged to be at high risk of bias

b. Single study with small sample size (< 200) and small number of events (< 200)

5. References

1. Muchohi SN, Kokwaro GO, Ogutu BR, Edwards G, Ward SA, Newton CR. Pharmacokinetics and clinical efficacy of midazolam in children with severe malaria and convulsions. Br J Clin Pharmacol. 2008;66(4):529-38. doi:10.1111/j.1365-2125.2008.03239.x.

2. Alansari K, Barkat M, Mohamed AH, Al Jawala SA, Othman SA. Intramuscular versus buccal midazolam for pediatric seizures: A randomized double-blinded trial. Pediatr Neurol. 2020;109:28-34. doi:10.1016/j.pediatrneurol.2020.03.011.

3. Mohammed MZ, Elagouza I, El Gaafary M, El-Garhy R, El-Rashidy O. Intranasal versus buccal versus intramuscular midazolam for the home and emergency treatment of acute seizures in pediatric patients: A randomized controlled trial. Pediatr Neurol. 2024;158:135-43. doi:10.1016/j.pediatrneurol.2024.06.014.