Intranasal Midazolam vs Intravenous methods for prehospital paediatric sedation

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CAT Question
Is Intranasal Midazolam better for Sedation in Children than Intravenous methods?

Clinical Scenario
Paramedics are called code one to an eight-year-old child who has been seizing for ten minutes. The paramedics are greeted by a distressed mother who says there were no warning signs and the patient has never had a seizure before. The child is having active tonic-clonic seizures on a carpeted floor and appears cyanosed. It is clear that this child needs sedation to stabilize their ventilation, however, gaining IV access would be difficult given the seizure. The paramedics must find an alternate route to deliver the medication.

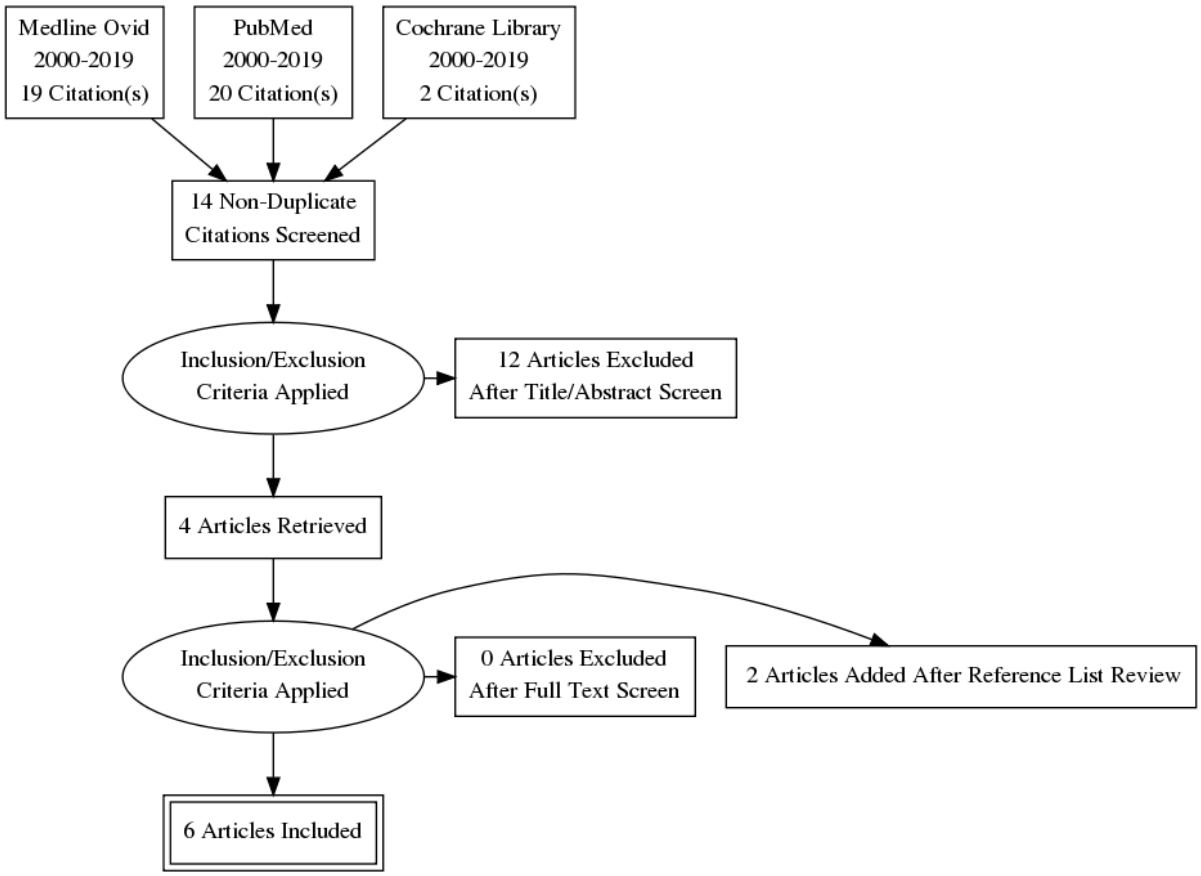
PICO
In paediatric patients (<12 years), is intranasal midazolam a better than midazolam or other drugs delivered by the intravenous route for prehospital sedation?

Search Strategy

(paediatric* OR infant OR child*) AND (sedat* OR "conscious sedation" OR hypno*) AND (midazolam OR benzodiazepine* OR ketamine OR fentanyl) AND (prehospital OR "out of hospital" OR "out-of-hospital" OR paramedic)
Limits: English Language, Humans
Publication Year: 2000- 2019

Inclusion Criteria:
- Primary Study
- Contains data describing intranasal administration midazolam or intravenous medication for seizures in paediatric patients.
- Prehospital or emergency department setting
- Paediatric Patients

Exclusion Criteria:
- Administration via route other than IV or IN
- IN Midazolam administration combined with another drug
- Case Studies
- Studies focussed on analgesia without sedation



Author	Population	Design	Oxford rating	Outcome	Results	Strengths/ Weaknesses

			of Evidence Level & Journal Impact Factor			
Javadzadeh, M., Sheibani, K., Hashemieh, M., Saneifard, H. (2012)	60 patients aged 2 months to 15 years. Presenting to hospital with active seizure.	Prospective Randomised Clinical Trial. -Single blind	1b 0.587	IN Midazolam vs IV Diazapam. Time needed to control seizure. O_2 Saturation Pulse Rate	Time to control seizure: IN M- 3.16 ± 1.24 IV D- 2.16 ± 1.02 With IV setup- 6.42 ± 2.59 All treatment attempts of both methods successful. No statistical difference between HR or O_2 saturation between methods.	(-) Low impact journal (-) End of seizure time decided by individual clinician (-) Single Blind (-) Small population (60) (-) Single centre study (-) In hospital (-) Only 2 vital signs recorded after treatment. No mention of consciousness levels. (-) Only applicable to seizures (-) Only compared to Diazepam (+) Randomization (+) Generalisability /applicable to PICO
Holsti, M., Sill, B., Firth, S., Filloux., F., Joyce., S. & Furnival, R. (2007)	124 patients (<18y) presenting to EMS with seizures. 67 patients no treatment. 39 patients IN Midazolam. 18 patients PR diazepam. Treatment given prehospitally.	Retrospective Cohort Study. Data taken from 18months before/after implementation of IN-M protocol for seizure.	II 1.119	Presence of seizure in ED. Total seizure time. EMS seizure duration. Respiratory complications. Additional anticonvulsant administration.	Seizure Duration: IN-M 11 mins R-D 30 mins R-D associated with more: ED seizure, additional anticonvulsants. No difference in adverse effects associated with either.	(-) Low Impact Journal (-) More recent, better designed studies. (-) Small sample size (-) Only applicable to seizures in presence of EMS (-) Single Centre (-) Retrospective (-) Not Randomized (-) Not blinded (-) Estimated length of seizure (-) Missing documentation from EMS (-) Co-morbidities not controlled (-) Compared with Rectal route (+) Prehospital administration

						(+) Generalizability (+) No significant difference in success between IN-M & R-D groups
Thakker, A. & Shanbag, P. (2012)	50 patients (1 month-12 years) presenting to ED department with acute seizures (> 10 mins duration)	Randomised Clinical Trial. Single Blind	1b 4.204	Duration of seizure. Arrival at hospital to initiation of treatment duration. Time taken to secure IV. Time taken for cessation of seizure. Recurrence of seizure after 60 mins.	Both drugs (equally) effective in stopping seizures. Duration of arrival at hospital to treatment shorter with IN-M (3.37min, 2.46 SD) than IV-M (14.13min, SD 3.39) Arrival at hospital to seizure cessation: IN-M 6.67mins (SD 3.12) IV-D 17.18 mins (SD 5.09) Interval between administration and seizure cessation: IN-M: 3.01 (SD 2.79) IV-D: 2.67 (SD 2.31) No recurrence of seizure <60m in either drug or respiratory compromise.	(-) Small sample (-) Single Centre (-) ED setting (-) Only Seizures (-) Used Nasal drips rather than atomiser (-) Older Article (+) Moderate impact journal (+) Randomised (+) Generalisable to Prehospital (+) Controlled samples
Mittal, P., Monhar, R., & Rawat, A. (2006)	125 patients. Ages 6 days- 12 years. Patient presenting with seizure or needing	Prospective Randomised Control Trial. No mention of blinding	1b 1.136	Time to seizure cessation after hospital arrival. Time to seizure cessation after drug	Seizure cessation after arriving in hospital: IN-M: 5.25 $\pm$0.86 IV-D: 6.41 $\pm$1.06 P<0.001 both	(-) Low impact Journal (-) Article states randomisation but no method how. (-) No mention of blinding (-) Hospital-based (-) Nasal drip

	sedation for minor procedure.			administration. Level of sedation before & after drug. Heart Rate & O_2 Saturation before & 10 mins post drug administration.	Seizure cessation after drug admin: IN-M: 2.97±0.53 IV-D: 1.92±0.45 Time to drug administration after arriving in hospital: IN-M: 2.34±0.9 IV-D: 4.61±1.08 Behaviour during Invasive/Non-invasive procedure: Both minimal Heart Rate & O_2: No compromise found in either group.	instead of atomiser (-) Single Centre (-) Old Study (-) Article full of grammatical errors, journal quality questioned. (-) No mention of limitations (-) No mention of exclusion criteria (-) Measurement of sedation post-treatment limited to 1 measurement at 10 mins. (-) No mention of exclusion criteria (i.e prehospital admin of drugs) (+) Larger sample size than other studies (125) (+) Generalizable to prehospital setting due to similarity in treatment method. (+) Level of sedation post drug administration measured. (+) Included data for pre-procedural sedation (not limited to seizure).
Silbergleit, R., et al. (2012)	893 patients with bodyweight >13kg. Active seizures >5mins requiring sedation prehospital. Adults were also included.	Randomised Control Trial. Prospective Double-blind Noninferiority trial Multi-centre	1b 70.670	Termination of seizure before ED arrival. Time from box opening to termination of seizure. Time from medication administration to seizure cessation. Frequency of rescue care required. Seizure recurrence within 12 hours.	Results of fields of interest for this CAT: IV-Lorazepam Seizure Cessation: 63.4% Treatment failed: 36.6% Time from box opening to treatment: 4.36 (±1.2) mins Time from box opening to seizure cessation: 6.50 (±1.6)	(-) Comparisons not generalizable: IV Lorazepam vs IM Midazolam (not IN) (-) No placebo (unethical) (-) No description of why IV access unachievable (-) Older article (2012) (-) Data for paediatrics extrapolated from data including adults (-) Only measures sedation for seizures

					mins Treatments not given due to IV access failure: 9.4% of attempted.	(+) High impact journal (+) Randomised (+) Controlled (+) Double-Blind (+) Multicentre (+) Large sample size (+) IV results similar to other studies with similar drugs but with better validity. (+) Breakdown of inclusions/exclusions (+) Uses different Benzodiazepine (lorazepam)
Kunusoth, R., et al. (2019)	60 patients undergoing dental surgery requiring conscious sedation.	Randomised control trial. Single blinded	1b 0.421	Physiologic parameters, anxiety level, sedation rating, patient cooperation	Both IN & IV decreased BP & HR during sedation. No significant difference. Neither group required rescue intervention. IN was as effective IV in producing anxiolytic response during procedure.	(-) Low impact journal (-) Dental setting rather than prehospital emergency (-) Only basic statistical analysis (-) Poorly written (-) Single-blind (+) Recent study (+) Randomised (+) Controlled (+) Compares IV & IN midazolam directly (+) Studies for procedural sedation which may be generalisable to prehospital.

Conclusion

This literature review has found that intranasal midazolam (IN-M) is quicker to administer and reduces total seizure time when compared to intravenous methods. IV administration did lead to faster cessation of seizures, however, this was negated by the much quicker administration of IN. IN-M was at least as effective in stopping seizures as IV diazepam or lorazepam with some studies finding IN-M superior. IN-M was as safe as IV methods with no studies finding any increase in respiratory compromise or other sedation related side effects.

One study found that clinicians were unable to gain IV access in 9.4% of seizure patients which highlights the benefits of IN administration.

Several ambulance service clinical practice guidelines recognise the need for non-IV administration sedation methods. These guidelines generally permit the use of intramuscular (IM) administration instead of IN. Further research should be carried out to compare IM and IN midazolam as IN-M as IN-M could potentially reduce the risk of needlestick injury. Also, further research should be conducted comparing midazolam to other non-benzodiazepine medications as few studies currently exist. The safety and efficacy described by these articles may encourage increased scope of use for IN-M in procedural sedation as well as seizure cessation for advanced care paramedics.

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