[Updated 2015]

EPI 1: Antiepileptic medications for management of acute convulsive seizures when no intravenous access is available [Updated 2015]

SCOPING QUESTION: In adults with acute convulsive seizures in first-level care or in the community (when no IV access is available), which antiepileptic medications produce benefits and/or harm when compared to comparator?

BACKGROUND

The treatment for acute convulsive seizures is aimed at earliest cessation of seizures in order to prevent progression to status epilepticus, cardiorespiratory compromise and cerebral damage. Absence of timely intervention may lead to a protracted seizure episode that is more difficult to control with significant subsequent neurological morbidity and mortality (Chen et al., 2014). Rapid and sustained control of seizure status may obviate the need for multiple anti-epileptics and prolonged hospitalization and drastically reduces the chances of adverse outcomes (Chen et al., 2014).

It is generally accepted that brief tonic-clonic seizures do not require medication treatment, as they are usually self-limiting. However, seizures of more than five minutes duration, recurrent seizures, delayed recovery of consciousness and a compromised cardio-respiratory system warrant emergency medication treatment. The ideal anti-epileptic medication is one that can be given safely and easily, is rapidly acting, has minimum cardiorespiratory adverse effects, has a long-lasting effect and is inexpensive (Shorvon, 2012).

Dispensing antiepileptic medications intravenously is the fastest route of administration; however, achieving peripheral venous access may be difficult in a convulsing patient. This situation is compounded by resource constraints, lack of trained personnel and pre-hospital settings, resulting in the frequent use of non-intravenous routes as the first line for administration of anti-epileptic medications in resource-limited settings (Anderson and Saneto, 2012). Similarly, intravenous (IV) access is not possible in home settings by caregivers.

Intramuscular routes enable an exact quantity of the medicine to be delivered with absorption rate of > 90%. However, the rate of absorption varies depending on the vascularity of the site of injection, volume and osmolarity of the injection and physio-chemical medication properties. The injection is also more painful and administration requires expertise. Buccal and sublingual routes have variable bioavailability because of combination of buccal absorption and swallowing with subsequent first pass metabolism. The intranasal route also bypasses gastric and hepatic first pass metabolism. Pre-treatment suctioning of the nasal cavity may improve the medication retention and absorption during a seizure episode. Using both nostrils for administration also increases absorption surface area. Per-rectal route administration enables partial avoidance of hepatic first pass metabolism, however there is significant variability in absorption from this route. Other issues include rectal migration of medicines into more

proximal areas and problem with rectal retention (Anderson and Saneto, 2012). Strapping the buttocks together after rectal administration is advisable.

However, the optimal agent and route of administration for resource constrained or pre-hospital treatment of acute convulsive seizures (including in status epilepticus) is unknown (Shorvon, 2012). Rectal diazepam is commonly used to control convulsive seizures in pre-hospital settings, but concerns over social acceptability and convenience have stimulated a search for better alternatives. This review explores the existing evidence for the most commonly used, first-line anti-epileptic medications (including benzodiazipines and paraldehyde) and the routes of administration in treating acute seizures in patients when IV access is not available.

PART 1: EVIDENCE REVIEW

Population/ Intervention / Comparison / Outcome (PICO)

- **Population:** Adults with acute convulsive seizures where no IV access is available
- **Interventions:**
  - Anti-epileptic medication by non-IV route:
    - Diazepam [rectal, intramuscular (IM)]
    - Midazolam [intranasal (IN), IM, buccal]
    - Lorazepam [IN, buccal, rectal, IM]
    - Paraldehyde [IM, rectal]
- **Comparison:** Intravenous benzodiazepines (diazepam IV, lorazepam IV)**,** benzodiazepines by other routes
- **Outcomes:**
  - **Critical** – Seizure cessation (within 10 minutes), adverse effects (respiratory complications requiring ventilation/intubation)

Search strategy

In order to identify relevant systematic reviews, the following databases were searched: Medline, Embase, The Cochrane Library, BMJ Clinical Evidence and PsychINFO up to October 2014. The following search strategy developed by the McMaster University[i] was used to identify systematic reviews:

- (meta=analysis [Publication Type] OR meta analysis [Title/Abstract] OR meta analysis [MeSH Terms] OR review[Publication Type] OR search*[Title/Abstract]).

The following additional terms were used: *(status epilepticus OR acute seizures) AND (midazolam OR diazepam OR lorazepam OR paraldehyde)*. See the Appendix for details.

In order to identify additional primary studies, the search strategy used in the Appleton 2008 Cochrane review was replicated (see the Appendix for details). This was supplemented by the following search strategy developed by the McMaster University to identify primary studies:

- (randomized controlled trial [Publication Type] OR randomized [Title/Abstract] OR placebo [Title/Abstract]).

The following additional terms were used: *(status epilepticus OR acute seizures) AND (midazolam OR diazepam OR lorazepam OR paraldehyde)* and the search included studies from 2008 to October 2014.

Inclusion and exclusion criteria for new systematic review

A new systematic review and meta-analysis was conducted after recent primary studies were identified but no systematic reviews published in the last two years including non-IV treatment of acute seizures were available. The inclusion and exclusion criteria for this review were as follows:

Type of studies

- Randomized controlled trials, quasi-randomized controlled trials, irrespective of blinding.

Types of participants

- Adults or children presenting with an acute seizure (hospital or community setting) and who received treatment with an anti-epileptic medication, irrespective of the duration of the presenting convulsion;
- Children including those presenting *de novo* with a first convulsion and those with an established diagnosis of epilepsy; and
- Any and all causes of the convulsion (including convulsive status epilepticus) were included in the review.

Types of interventions

- In adults or children presenting with an acute seizure including status epilepticus, trials were included if they compared one treatment with another;
- Specific medicines included the benzodiazepines (diazepam, lorazepam and midazolam), and paraldehyde; and

- Different routes of medication administration were also included, these included IV, intra-nasal, buccal, sublingual, rectal and intra-muscular administration.

Types of outcome measures

- *Efficacy*: Cessation of seizure within 10 minutes of medication administration.
- *Safety*: Incidence of Respiratory depression requiring intubation/ventilation.

Data collection and analysis

Two members of the research team independently assessed trials for inclusion. Outcome data and information on study properties was extracted during this process. Any disagreements over inclusion were resolved by discussion among the members of the research team. Those deemed to have sufficient quality were included in the review. Study quality was determined by availability of the following information:

Methodological/trial design

- Method of randomization
- Method of double-blinding
- Allocation concealment
- Whether any participants had been excluded from the reported analyses.
- Where data were missing, the original authors were contacted for this information.

Participant/demographic information

- Total number of participants allocated to each treatment group/audited in any protocol
- Age and sex
- Whether any pre-hospital emergency anti-epileptic treatment was given
- Duration of presenting seizure/episode of convulsive status.
- Cause of acute seizure/episode of convulsive status

Data analysis including meta-analysis methodology

The primary analysis was by 'intention-to-treat' and included all randomized participants analyzed in the treatment group to which they were allocated, irrespective of which treatment they actually received. Clinical heterogeneity was assessed by reviewing the differences across trials in characteristics of recruited participants and treatment protocols, as well as being assessed statistically using a chi-squared test and I^2 for heterogeneity. Dichotomous outcomes were expressed as relative risks (RR) with 95% confidence intervals (CIs).

Included in GRADE tables or footnotes (Systematic Reviews and Individual studies)

Systematic reviews

- Appleton R, Macleod S, Martland T (2008). Drug management for acute tonic-clonic convulsions including convulsive status epilepticus in children. Cochrane Database of Systematic Reviews.3:CD001905.

- McMullan J, Sasson C, Pancioli A, Silbergleit R (2010). Midazolam versus diazepam for the treatment of status epilepticus in children and young adults: a meta-analysis. Academic Emergency Medecine. 17(6):575-582. doi:10.1111/j.1553-2712.2010.00751.x.

- Prasad K, Al-Roomi K, Krishnan PR, Sequiera R (2005). Anticonvulsant therapy for status epilepticus. Cochrane Database of Systematic Reviews.4:CD003723**.**

- Prasad M, Krishnan PR, Sequeira R, Al-Roomi K (2014). Anticonvulsant therapy for status epilepticus. Cochrane Database of Systematic Reviews.9:CD003723. doi:10.1002/14651858.CD003723.pub3

Primary studies included in the systematic reviews

- Ahmad S, Ellis JC, Kamwendo H, Molyneux E (2006). Efficacy and safety of intranasal lorazepam versus intramuscular paraldehyde for protracted convulsions in children: an open randomized trial. Lancet. 367(9522):1591–1597. doi:10.1016/S0140-6736(06)68696-0.

- Appleton R, Sweeney A, Choonara I, Robson J, Molyneux E (1995). Lorazepam versus diazepam in the acute treatment of epileptic seizures and status epilepticus. Developmental Medicine & Child Neurology. 37(8):682–688.

- Chamberlain JM, Altiere MA, Futterman C, Young CM, Ochsenschlager DW, Waisman Y (1997). A prospective, randomized study comparing IM midazolamwith IV diazepam for the treatment of seizures in children. Pediatric Emergency Care.13(2):92–94.

- Lahat E, Goldman M, Barr J, Bistritzer T, Berkovitch M (2000). Comparison of intranasal midazolam with IV diazepam for treating febrile seizures in children: prospective randomized study. British Medical Journal.321:83–86. doi:10.1136/bmj.321.7253.83.

- Mahmoudian T and Zadeh MM (2004). Comparison of intranasal midazolam with IV diazepam for treating acute seizures in children. Epilepsy & Behavior. 5(2):253–255.

- McIntyre J, Robertson S, Norris E, Appleton R, Whitehouse WP, Phillips B, Martland T, Berry K, Collier J, Smith S, Choonara I (2005). Safety and efficacy of buccal midazolam versus rectal diazepam for emergency treatment of seizures in children: a randomized controlled trial. Lancet. 366(9481):205–210.

- Mpimbaza A, Ndeezi G, Staedke S, Rosenthal PJ, Byarugaba J (2008). Comparison of buccal midazolam with rectal diazepam in the treatment of prolonged seizures in Ugandan children: a randomized clinical trial. Pediatrics. 121(1):e58–64. doi:10.1542/peds.2007-0930.

- Scott RC, Besag FM, Neville BG (1999). Buccal midazolam and rectal diazepam for treatment of prolonged seizures in childhood and adolescence: a randomized trial. Lancet. 353(9153):623–626.

Additional Individual Studies

- Arya R, Gulati S, Kabra M, Sahu JK, Kalra V (2011). Intranasal versus intravenous lorazepam for control of acute seizures in children: a randomized open-label study. Epilepsia. 52(4):788–793. doi:10.1111/j.1528-1167.2010.02949.x.
- Ashrafi MR, Khosroshahi N, Karimi P, Malamiri RA, Bavarian B, Zarch AV, Mirzaei M, Kompani F (2010). Efficacy and usability of buccal midazolam in controlling acute prolonged convulsive seizures in children. European Journal of Paediatric Neurology. 14(5):434–438. doi:10.1016/j.ejpn.2010.05.009.

- Holsti M, Dudley N, Schunk J, Adelgais K, Greenberg R, Olsen C, Healy A, Firth S, Filloux F (2010). Intranasal midazolam vs. rectal diazepam for the home treatment of acute seizures in pediatric patients with epilepsy. Archives of Pediatrics & Adolescent Medicine. 164(8):747–753. doi:10.1001/archpediatrics.2010.130.

- Malu CK, Kahamba DM, Walker TD, Mukampunga C, Musalu EM, Kokolomani J, Mayamba RM, Wilmshurst JM, Dubru JM, MIsson JP (2014). Efficacy of Sublingual Lorazepam versus Intrarectal Diazepam for Prolonged Convulsions in Sub-Saharan Africa. Journal of Child Neurology. 29(7):895–902. doi:10.1177/0883073813493501.

- Nakken KO and Lossius MI (2011). Buccal midazolam or rectal diazepam for treatment of residential adult patients with serial seizures or status epilepticus. Acta Neurologica Scandinavica. 124(2):99–103. doi:10.1111/j.1600-0404.2010.01474.x.

- Portela JL, Garcia PC, Piva JP, Barcelos A, Bruno F, Branco R, Tasker RC (2014). IM midazolamversus intravenous diazepam for treatment of seizures in the pediatric emergency department: A randomized clinical trial. Medicina Intensiva.39(3):160-166. doi:10.1016/j.medin.2014.04.003.

- Shah I and Deshmukh CT (2005). IM midazolamvs. Intravenous diazepam for acute seizures. Indian Journal of Pediatrics. 72(8):667–670.

- Silbergleit R, Durkalski V, Lowenstein D, Conwitt R, Pancioli A, Plaesch Y, Barsan W (2012). Intramuscular versus intravenous therapy for prehospital status epilepticus. New England Journal of Medicine. 366(7):591–600. doi:10.1056/NEJMoa1107494.

- Talukdar B and Chakrabarty B (2009). Efficacy of buccal midazolam compared to intravenous diazepam in controlling convulsions in children: a randomized controlled trial. Brain & Development. 31(10):744–749. doi:10.1016/j.braindev.2008.11.006.

- Thakker A and Shanbag P (2013). A randomized controlled trial of intranasal-midazolam versus intravenous-diazepam for acute childhood seizures. Journal of Neurology. 260(2):470–474. doi:10.1007/s00415-012-6659-3.

Excluded from GRADE tables and footnotes (Comparator was placebo)

Abou-Khalil B, Wheless J, Rogin J, Wolter KD, Pixton GC, Shukla RB, Sherman NA, Sommerville K, Goli V, Roland CL (2013). Epilepsia. 54(11):1968–1976. doi:10.1111/epi.12373.

REASON FOR EXLUSION: A double-blind, randomized, placebo-controlled trial of a diazepam auto-injector administered by caregivers to patients with epilepsy who require intermittent intervention for acute repetitive seizures.

[Updated 2015]

PICO Table

Population: Adults with acute convulsive seizures where no IV access is available				
Non-IV route compared to IV route*				
Intervention	**Comparison**	**Outcome**	**Systematic review selected and justification for use**	**Relevant GRADE Table**
Buccal midazolam	IV diazepam	Stopping seizure	Talukdar and Chakrabarty (2009)	Table 1
		Adverse effects	No evidence	
Intramuscular (IM) midazolam	IV diazepam	Stopping seizure	New meta-analysis of the following studies: Chamberlain et al. (1997) Shah and Deshmukh (2005) Portela et al. (2014)	Table 2 (with forest plot)
		Adverse effects	No evidence	
	IV lorazepam	Stopping seizure	Prasad et al.'s (2014) Cochrane Review (Analysis 18.1 - Silbergleit et al. [2012])	Table 3
		Adverse effects	Prasad et al.'s (2014) Cochrane Review (Analysis 18.2 - Silbergleit et al. [2012])	
Intranasal (IN) midazolam	IV diazepam	Stopping seizure	New meta-analysis of the following studies: Lahat et al. (2000) Mahmoudian and Zadeh (2004) Thakker and Shanbag (2013)	Table 4 (with forest plot)
		Adverse effects	Lahat et al. (2000) Mahmoudian and Zadeh (2004) Thakker and Shanbag (2013)	Table 4
IN lorazepam	IV lorazepam	Stopping seizure	Arya et al. (2011)	Table 5
		Adverse effects	Arya et al. (2011)	
Non-IV midazolam	IV diazepam	Stopping seizure	New meta-analysis of the following studies:	Table 6 (with forest plot)

			Chamberlain et al. (1997) Lahat et al. (2000) Mahmoudian and Zadeh (2004) Shah and Deshmukh (2005) Talukdar and Chakrabarty (2009) Thakker and Shanbag (2013) Portela et al. (2014)	
		Adverse effects	Chamberlain et al. (1997) Lahat et al. (2000) Mahmoudian and Zadeh (2004) Shah and Deshmukh (2005) Talukdar and Chakrabarty (2009) Thakker and Shanbag (2013) Portela et al. (2014)	Table 6
Non-IV route compared to each other*				
Intervention	**Comparison**	**Outcome**	**Systematic review/study selected**	**Relevant GRADE Table(s)**
Rectal diazepam	Rectal lorazepam	Stopping seizure	Appleton et al. (2008) Cochrane Review (Analysis 1.1)	Table 7
		Adverse effects	Appleton et al. (1995)	
Rectal diazepam	Sublingual lorazepam	Stopping seizure	Malu et al. (2014)	Table 8
		Adverse effects	No evidence	
Buccal midazolam	Rectal diazepam	Stopping seizure	New meta-analysis of the following studies: Scott et al. 1999 McIntyre et al. 2005 Mpimbaza et al. 2008 Ashrafi et al. 2010 Nakken et al. 2011	Table 9 (with forest plots)
		Adverse effects (Respiratory depression)	New meta-analysis of the following studies: Scott et al. 1999 McIntyre et al. 2005 Mpimbaza et al. 2008	

			Ashrafi et al. 2010 Nakken et al. 2011	
IN midazolam	Rectal diazepam	Stopping seizure	Holsti et al. 2010	Table 10
		Adverse effects	Holsti et al. 2010	
IM paraldehyde	IN lorazepam	Stopping seizure	Appleton Cochrane Review 2008 (Analysis 4 - Ahmad et al. 2006)	Table 11
		Adverse effects	No evidence	

** If there is no intervention, comparison or outcome combination entered into the table then the combination in question does not have any evidence base.*

Narrative description of the studies that went into analysis

Systematic reviews

Prasad et al. (2005): Review includes randomized controlled trials (RCTs) of participants with premonitory, early, established or refractory status epilepticus using a truly random or quasi-random allocation of treatments. There were 11 studies (including Chamberlain et al.,1997) with a total of 2017 participants. Authors concluded that lorazepam is better than diazepam or phenytoin alone for cessation of seizures and carries a lower risk of continuation of status epilepticus requiring a different medication or general anaesthesia. Both lorazepam and diazepam are better than placebo for the same outcomes. In the treatment of premonitory seizures, diazepam 30 mg in an intrarectal gel is better than 20 mg for cessation of seizures, without a statistically significant increase in adverse effects. Universally accepted definitions of premonitory, early, established and refractory status epilepticus are required.

Appleton et al. (2008): Review comprised of randomized and quasi-randomized controlled trials comparing any anti-epileptic medications used for the treatment of an acute tonic-clonic convulsion, including convulsive status epilepticus in children. The review included four trials (Appleton et al., 1995; Lahat et al., 2000; McIntyre et al., 2005; Ahmad et al., 2006) involving 383 participants. The authors concluded that IV lorazepam is at least as effective as IV diazepam and is associated with fewer adverse events in the treatment of acute tonic-clonic convulsions. Where IV access is unavailable, there is evidence from one trial that buccal midazolam is the treatment of choice.

McMullan et al. (2010): Review identified randomized and quasi-randomized controlled trials comparing non-IV midazolam to IV or non-IV diazepam for treatment of status epilepticus in pediatric and adult patients. There were six trials included (Chamberlain et al., 1997; Lahat et al., 2000; Mahmoudian and Zadeh, 2004; McIntyre et al., 2005; Mpimbaza et al., 2008; Scott et al.,1999) involving 774 participants in total. The authors

concluded that non-IV midazolam, compared to non-IV or IV diazepam, is safe and effective in treating status epilepticus. Comparison to lorazepam, evaluation in adults and prospective confirmation of safety and efficacy is needed.

Prasad et al. (2014): Review comprised of RCTs of participants with premonitory, early, established or refractory status epilepticus, using a truly random or quasi-random allocation of treatments. There were 18 studies (including Silbergleit et al., 2012) with 2755 total participants. The authors concluded that IV lorazepam is better than IV diazepam or IV phenytoin alone for cessation of seizures. IV lorazepam also carries a lower risk of continuation of status epilepticus requiring a different medication or general anaesthesia, compared with IV diazepam. Both IV lorazepam and diazepam are better than placebo for the same outcomes. For pre-hospital management, midazolam IM seemed more effective than lorazepam IV for cessation of seizures, frequency of hospitalisation and ICU admissions; however, it was unclear whether the risk of recurrence of seizures differed between treatments. The results of other comparisons of anti-epileptic therapies vs. each other were also uncertain. Universally accepted definitions of premonitory, early, established and refractory status epilepticus are required. Diazepam gel was better than placebo gel in reducing the risk of non-cessation of seizures. Results for other comparisons of anti-epileptic therapies were uncertain due to single studies with few participants.

Individual studies

Lahat et al. (2000): Included children aged 6 months to 5 years presenting with febrile seizures (≥ 10 min, tonic, clonic, tonic-clonic) in a pediatric emergency department. There were 44 children (52 episodes) randomized into intranasal midazolam (0.2 mg/kg; midazolam solution dripped by syringe into both the nostrils) and IV diazepam (0.3 mg/kg) groups.

Mahmoudian and Zadeh (2004): Included children aged 2 months to 15 years presenting with acute seizures (Generalized, focal, myoclonic) in a pediatric emergency department. There were 70 children quasi-randomized into intranasal midazolam (0.2 mg/kg; midazolam [5mg/ml] solution dripped by syringe into both the nostrils) and IV diazepam (0.2 mg/kg) groups.

Thakker and Shanbag (**2013)**: Included children aged 1 month to 12 years presenting with seizures (≥ 10 min, Generalized, focal, subtle) in a pediatric emergency department. There were 50 children randomized into intranasal midazolam (0.2 mg/kg; midazolam [5mg/ml] solution dripped by syringe into both the nostrils) and IV diazepam (0.3 mg/kg) groups.

Shah and Deshmukh (2005): Included children aged 1 month to 12 years presenting with acute seizures (Generalized, focal) in a pediatric emergency department and wards. There were 81 children without IV access randomized into IM midazolam(50) [0.2 mg/kg) and IV diazepam (0.2 mg/kg) groups (31).

Chamberlain et al. (1997): Included children up to 18 years of age presenting with seizures (≥ 10 min, Generalized, focal) in an emergency department. There were 24 children randomized into IM midazolam(13) [0.2 mg/kg] and IV diazepam groups (11) [0.3 mg/kg].

Portela et al. (2014): Included children aged 2 months to 14 years presenting with acute seizures in a pediatric emergency department were included. There were 32 children randomized into IM midazolam(0.5 mg/kg) and IV diazepam (0.5 mg/kg) groups.

Talukdar and Chakrabarty (**2009)**: Included children up to 12 years of age presenting with acute seizures (gen, focal) in a pediatric emergency department. There were 120 children randomized into buccal midazolam (0.2 mg/kg midazolam IV solution [1 mg/ml] squirted into the buccal mucosa by syringe) and IV diazepam (0.3 mg/kg) groups.

Silbergleit et al. (2012): Included children (> 13 kg) and adults presenting with acute seizures (> 5 min) in a pre-hospital setting. There were a total of 893 participants (majority > 20 years of age) randomized into IM midazolam(auto-injector) [> 40 kg – 10 mg; < 40 kg- 5 mg] and IV lorazepam (> 40 kg – 4 mg; < 40 kg – 2 mg) groups.

Arya et al. (2011): Included children aged 6-14 years presenting with acute seizures in a pediatric emergency department. There were 141 children randomized into intranasal lorazepam (0.1 mg/kg; solution instilled in one nostril drop by drop over 30-60 seconds) and IV lorazepam (0.1 mg/kg) groups.

Ahmad et al. (2006): Included children aged 2 months to 12 years presenting with seizures (> 5 min) in a pediatric emergency department. There were 160 children randomized into intranasal lorazepam (100 µg/kg [4mg/ml] squirted into a nostril through mucosal atomization device) and intramuscular paraldehyde (0.2 ml/kg) groups.

Appleton et al. (1995): Included children (age not disclosed) presenting with acute seizures in a pediatric emergency department. There were 86 children quasi-randomized into diazepam (0.3-0.4 mg/kg) and lorazepam (0.05-0.1 mg/kg) groups. The medications were given IV (lorazepam-27, Diazepam-34). If IV access was not possible, the same dose was given rectally (lorazepam (IV solution) -6, Diazepam (Rectal tube-Stesolid)-19).

Holsti et al. (2010): Included children up to 18 years of age presenting with seizures (> 5 min). The trial involved the children's caretakers, with a total of 358 caretakers randomized to use either intranasal midazolam (0.2 mg/kg) or rectal diazepam (0.3-0.5 mg/kg) at home. Among these, 92 caretakers gave study medication to their child (midazolam-50, diazepam-42).

McIntyre et al. (2005): Included children aged > 6 months presenting with acute seizures in a pediatric emergency department. There were 219 children randomized into buccal midazolam (IV preparation administered between gums and cheeks) and rectal diazepam groups (2.5 mg – 6 to 12 months; 5 mg – 1 to 4 years; 7.5 mg – 5 to 9 years; 10 mg – 10 years or older).

Mpimbaza et al. (2008): Included children aged 3 months to 12 years with acute seizures (> 5 min) in a pediatric emergency department. There were 330 children randomized into buccal midazolam (the solution was administered between teeth and cheek by syringe followed by cheek massage) and rectal diazepam (the solution administered by a tube inserted into the rectum followed by air flush) groups (0.5 mg/kg).

Nakken et al. (2011): The trial enrolled adults aged 25-82 years residing in a residential institution in Norway with convulsive or non-convulsive status epilepticus (not defined) or prolonged/serial seizures (> 5 min). They were alternatively given buccal midazolam (buccal solution-epistatus-10 mg/ml) and rectal diazepam (stesolid prefill actavis- 5mg/ml).

Scott et al. (1999): The trial enrolled students aged 5-22 years from a residential centre with seizures > 3 min. There were 79 episodes randomized into buccal midazolam (2 ml squirted around the buccal mucosa by syringe) and rectal diazepam (pre-packed rectal tube) groups.

Ashrafi et al. (2010): Included children aged > 3 months with seizures > 5 min presenting to an emergency room. There were 98 children randomized into buccal midazolam (epistatus buccal solution – 0.3-0.5 mg/kg; syringe placed between teeth and cheek) and rectal diazepam (0.5 mg/kg; administered by a tube inserted into the rectum) groups.

Malu et al. (2014): Children aged 5 months to 10 years presenting with acute seizures (> 5 min) in a pediatric emergency department were included. There were 436 children quasi-randomized into sublingual lorazepam (234) [0.1 mg/kg, tablet placed under the tongue or between cheek and gum) and rectal diazepam (202) [0.5 mg/kg reconstituted solution] groups.

[Updated 2015]

GRADE Tables

Table 1. Buccal misazolam vs. IV diazepam for treatment of acute seizures

Author: P Jain
Question: Should buccal midazolam vs. IV diazepam be used for treatment of acute seizures in adults?
Bibliography: Talukdar B and Chakrabarty B (2009). Efficacy of buccal midazolam compared to intravenous diazepam in controlling convulsions in children: a randomized controlled trial. Brain & Development.31(10):744–749. doi:10.1016/j.braindev.2008.11.006.

Quality assessment							No. of patients		Effect		Quality	Importance
No. of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Buccal midazolam	IV diazepam	Relative (95% CI)	Absolute		
Seizure cessation within 10 minutes (assessed with clinical Observation)												
1	Randomized trials	Serious[1]	No serious inconsistency	Serious[2]	Serious[3]	None	51/60 (85%)	56/60 (93.3%)	RR 0.91 (0.8 to 1.03)	84 fewer per 1000 (from 187 fewer to 28 more)	⊕OOO VERY LOW	CRITICAL
								0%		-		
Respiratory depression requiring intubation (assessed with clinical observation)												
1	Randomized trials					None	0/60 (0%)	0/60 (0%)	-	-		CRITICAL
								0%		-		

[1] No mention of allocation concealment.
[2] Study done exclusively in children.
[3] CI crossing line of no effect.

[Updated 2015]

Table 2. IM midazolam vs. IV diazepam for treatment of acute seizures

Author: P Jain
Question: Should IM midazolam vs. IV diazepam be used for treatment of acute seizures in adults?
Bibliography:

- Chamberlain JM, Altiere MA, Futterman C, Young CM, Ochsenschlager DW, Waisman Y (1997). A prospective, randomized study comparing intramuscular midazolam with IV diazepam for the treatment of seizures in children. Pediatric Emergency Care.13(2):92–94.
- Shah I and Deshmukh CT (2005). Intramuscular midazolamvs. intravenous diazepam for acute seizures. Indian Journal of Pediatrics.72(8):667–670.
- Portela JL, Garcia PC, Piva JP, Barcelos A, Bruno F, Branco R, Tasker RC (2014). Intramuscular midazolam versus intravenous diazepam for treatment of seizures in the pediatric emergency department: A randomized clinical trial. Medicina Intensiva.39(3):160-166. doi:10.1016/j.medin.2014.04.003.

Quality assessment							No. of patients		Effect		Quality	Importance
No. of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	IM midazolam	IV diazepam	Relative (95% CI)	Absolute		
Seizure Cessation within 10 minutes (assessed with clinical observation)												
3	Randomized trials	Very serious[1]	No serious inconsistency	Serious[2]	Serious[3]	None	71/79 (89.9%)	68/73 (93.2%)	RR 0.96 (0.87 to 1.07)	37 fewer per 1000 (from 121 fewer to 65 more)	⊕OOO VERY LOW	CRITICAL
								0%		-		
Respiratory depression requiring intubation (assessed with clinical observation)												
3	Randomized trials					None	0/79 (0%)	0/73 (0%)	-	-		CRITICAL
								0%		-		

[1] Randomization process not described in any study
[2] Studies done exclusively in children
[3] N < 100 in each group

Figure 1. Results of a new meta-analysis: Outcome 1 – Seizure cessation within 10 minutes with IM midazolam vs. IV diazepam

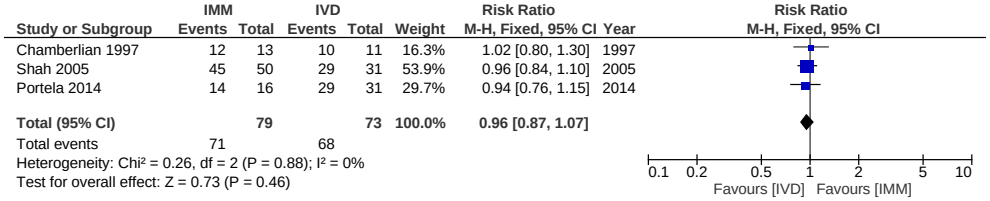

Table 3. IM midazolam vs. IV lorazepam for treatment of acute seizures

Author: P Jain

Question: Should IM midazolamvs. IV lorazepam be used for treatment of acute seizures in adults?

Bibliography:

- Prasad M, Krishnan PR, Sequeira R, Al-Roomi K (2014). Anticonvulsant therapy for status epilepticus. Cochrane Database of Systematic Reviews.9:CD003723. doi:10.1002/14651858.CD003723.pub3.
- Silbergleit R, Durkalski V, Lowenstein D, Conwitt R, Pancioli A, Plaesch Y, Barsan W (2012). Intramuscular versus intravenous therapy for prehospital status epilepticus. New England Journal of Medicine.366(7):591–600. doi:10.1056/NEJMoa1107494.

Quality assessment							No. of patients		Effect		Quality	Importance
No. of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	IM midazolam	IV lorazepam	Relative (95% CI)	Absolute		
Seizure cessation at arrival in emergency department (assessed with clinical observation)												
1	Randomized trials	No serious risk of bias	No serious inconsistency	Serious[1]	No serious imprecision	None	329/448 (73.4%)	282/445 (63.4%)	RR 1.16 (1.06 to 1.27)	1011 more per 1000 (from 38 more to 171 more)	⊕⊕⊕O MODERATE	CRITICAL
								0%		-		
Respiratory depression requiring Intubation (assessed with clinical observation)												
1	Randomized trials	No serious risk of bias	No serious inconsistency	Serious[1]	Serious[2]	None	64/445 (14.4%)	63/448 (14.1%)	RR 1.02 (0.74 to 1.41)	3 more per 1000 (from 37 fewer to 58 more)	⊕⊕OO LOW	CRITICAL
								0%		-		

[1] Indirect as Silbergleit et al. (2012) paper includes adults and children.

[2]Wide CI.

[Updated 2015]

Table 4. IN midazolam vs. IV diazepam for treatment of acute seizures

Author: P Jain
Question: Should IN midazolam vs. IV diazepam be used for treatment of acute seizures in adults?
Bibliography:

- Lahat E, Goldman M, Barr J, Bistritzer T, Berkovitch M (2000). Comparison of intranasal midazolam with IV diazepam for treating febrile seizures in children: prospective randomized study. British Medical Journal.321:83–86. doi:10.1136/bmj.321.7253.83.
- Mahmoudian T and Zadeh MM (2004). Comparison of intranasal midazolam with IV diazepam for treating acute seizures in children. Epilepsy & Behavior. 5(2):253–255.
- Thakker A and Shanbag P (2013). A randomized controlled trial of intranasal-midazolam versus intravenous-diazepam for acute childhood seizures. Journal of Neurology. 260(2):470–474. doi:10.1007/s00415-012-6659-3.
- Appleton R, Macleod S, Martland T (2008). Drug management for acute tonic-clonic convulsions including convulsive status epilepticus in children. Cochrane Database of Systematic Reviews.3:CD001905.

Quality assessment							No. of patients		Effect		Quality	Importance
No. of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	IN midazolam	IV diazepam	Relative (95% CI)	Absolute		
Seizure cessation within 10 minutes (assessed with clinical observation)												
3	Randomized trials	Serious[1]	No serious inconsistency	Serious[2]	Serious[3]	None	81/88 (92%)	78/84 (92.9%)	RR 1.00 (0.91 to 1.08)	0 fewer per 1000 (from 444 fewer to 848 more)	⊕OOO VERY LOW	CRITICAL
								0%		-		
Respiratory depression requiring intubation (assessed with clinical observation)												
3	Randomized trials					None	0/88 (0%)	0/84 (0%)	-	-		CRITICAL
								0%		-		

[1] Mahmoudian and Zadeh (2004) was a quasi-randomized (odd and even number table) trial. All three studies are open-label.
[2] Studies done in children.
[3] N=<100 in each group.

Figure 2. Results of a new meta-analysis: Outcome 1 – Seizure cessation within 10 minutes with IN midazolam vs. IV diazepam

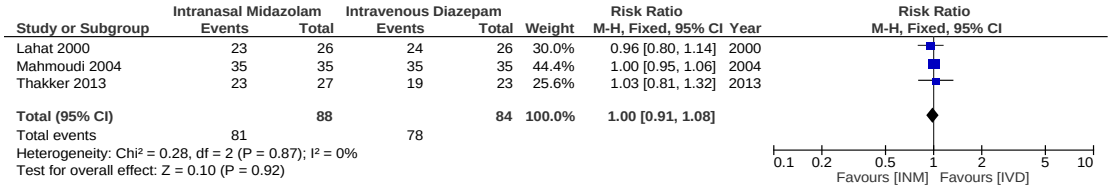

Table 5. IN lorazepam vs. IV lorazepam for treatment of acute seizures

Author: P Jain

Question: Should IN lorazepam vs. IV lorazepam be used for treatment of acute seizures in adults?

Bibliography: Arya R, Gulati S, Kabra M, Sahu JK, Kalra V (2011). Intranasal versus intravenous lorazepam for control of acute seizures in children: a randomized open-label study. Epilepsia.52(4):788–793. doi:10.1111/j.1528-1167.2010.02949.x.

Quality assessment							No. of patients		Effect		Quality	Importance
No. of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	IN lorazepam	IV lorazepam	Relative (95% CI)	Absolute		
Seizure cessation within 10 minutes (assessed with clinical observation)												
1	Randomized trials	No serious risk of bias	No serious inconsistency	Serious[1]	Serious[2]	None	59/71 (83.1%)	56/70 (80%)	RR 1.04 (0.89 to 1.22)	32 more per 1000 (from 88 fewer to 176 more)	⊕⊕OO LOW	CRITICAL
								0%		-		
Respiratory depression requiring intubation (assessed with clinical observation)												
1	Randomized trials	No serious risk of bias	No serious inconsistency	Serious[1]	Serious[3]	None	1/71 (1.4%)	0/70 (0%)	-	-	⊕⊕OO LOW	CRITICAL
								0%		-		

[1] Study done in children.
[2] CI crossing line of no effect.
[3] Very small number of events.

[Updated 2015]

Table 6. Non-IV midazolam vs. IV diazepam for treatment of acute seizures

Author: P Jain
Question: Should Non-IV midazolam vs. IV diazepam be used for treatment of acute seizures in adults?
Bibliography:

- Lahat E, Goldman M, Barr J, Bistritzer T, Berkovitch M (2000). Comparison of intranasal midazolam with IV diazepam for treating febrile seizures in children: prospective randomized study. British Medical Journal.321:83–86. doi:10.1136/bmj.321.7253.83.
- Mahmoudian T and Zadeh MM (2004). Comparison of intranasal midazolam with intravenous diazepam for treating acute seizures in children. Epilepsy & Behavior. 5(2):253–255.
- Thakker A and Shanbag P (2013). A randomized controlled trial of intranasal-midazolam versus intravenous-diazepam for acute childhood seizures. Journal of Neurology. 260(2):470–474. doi:10.1007/s00415-012-6659-3.
- Shah I and Deshmukh CT (2005). Intramuscular midazolam vs. intravenous diazepam for acute seizures. Indian Journal of Pediatrics.72(8):667–670.
- Chamberlain JM, Altiere MA, Futterman C, Young CM, Ochsenschlager DW, Waisman Y (1997). A prospective, randomized study comparing intramuscular midazolam with intravenous diazepam for the treatment of seizures in children. Pediatric Emergency Care.13(2):92–94.
- Portela JL, Garcia PC, Piva JP, Barcelos A, Bruno F, Branco R, Tasker RC (2014). Intramuscular midazolam versus intravenous diazepam for treatment of seizures in the pediatric emergency department: A randomized clinical trial. Medicina Intensiva.39(3):160-166. doi:10.1016/j.medin.2014.04.003.
- Talukdar B and Chakrabarty B (2009). Efficacy of buccal midazolam compared to intravenous diazepam in controlling convulsions in children: a randomized controlled trial. Brain & Development.31(10):744–749. doi:10.1016/j.braindev.2008.11.006.

Quality assessment							No. of patients		Effect		Quality	Importance
No. of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Non-IV midazolam	IV diazepam	Relative (95% CI)	Absolute		
Seizure cessation within 10 minutes (assessed with clinical observation)												
7	Randomized trials	Very serious[1]	No serious inconsistency	Serious[2]	Serious[3]	None	203/227 (89.4%)	187/202 (92.6%)	RR 0.97 (0.91 to 1.03)	28 fewer per 1000 (from 83 fewer to 28 more)	⊕OOO VERY LOW	CRITICAL
								0%		-		
Respiratory depression requiring intubation (assessed with clinical observation)												
7	Randomized trials					None	0/227 (0%)	0/202 (0%)	-	-		CRITICAL
								0%		-		

[1] All studies are open label. Mahmoudian and Zadeh (2004) is quasi-randomized (odd and even number table) study; Randomization process not described in Chamberlain et al. (1997); Shah and Deshmukh (2005) or Portela et al. (2014); No mention of allocation concealment in Talukdar and Chakrabarty (2009).
[2] Studies done in children.
[3] CI crossing line of no effect.

Figure 3. Results of a new meta-analysis: Outcome 1 – Seizure cessation within 10 minutes with Non-IV midazolam vs. IV diazepam

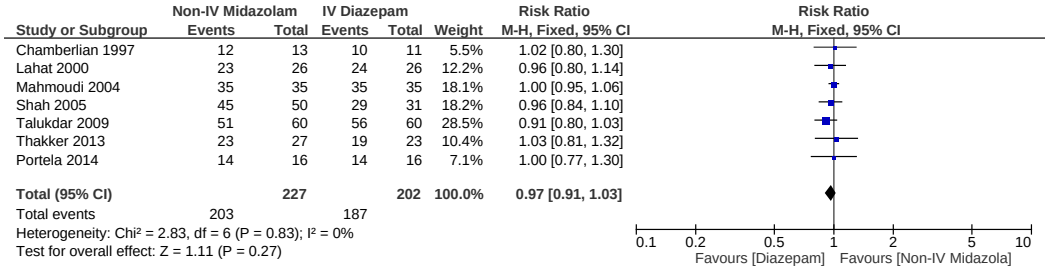

Table 7. Rectal diazepam vs. rectal lorazepam for treatment of acute seizures

Author: P Jain
Question: Should rectal diazepam vs. rectal lorazepam be used for treatment of acute seizures in adults?
Bibliography:

- Appleton R, Sweeney A, Choonara I, Robson J, Molyneux E (1995). Lorazepam versus diazepam in the acute treatment of epileptic seizures and status epilepticus. Developmental Medicine & Child Neurology. 37(8):682–688.
- Appleton R, Macleod S, Martland T (2008). Drug management for acute tonic-clonic convulsions including convulsive status epilepticus in children. Cochrane Database of Systematic Reviews.3:CD001905.

Quality assessment							No. of patients		Effect		Quality	Importance
No. of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Rectal diazepam	Rectal lorazepam	Relative (95% CI)	Absolute		
Successful seizure cessation (assessed with clinical observation)												
1	Randomized trials	Very serious[1]	No serious inconsistency[2]	Serious[3]	Serious[4]	None	6/19 (31.6%)	6/6 (100%)	RR 0.32 (0.16 to 0.61)	680 fewer per 1000 (from 390 fewer to 840 fewer)	⊕OOO VERY LOW	CRITICAL
								0%		-		
Respiratory depression requiring intubation (assessed with clinical observation)												
1	Randomized	Very	No serious	No serious	Serious[4]	None	1/19	0/6	-	-	⊕OOO	CRITICAL

	trials	serious[1]	inconsistency	indirectness			(5.3%)	(0%)			VERY LOW	
								0%		-		

[1] Groups assigned on 'odd and even dates' basis, no mention of allocation concealment, no blinding, Rectal route used as second alternative (after IV route failed) in both the arms
[2] Single study.
[3] Study done in children.
[4] Small number of patients in each group; difference in number of patients; single study.

Table 8. Sublingual lorazepam vs. rectal diazepam for treatment of acute seizures

Author: P Jain
Question: Should sublingual lorazepam vs. rectal diazepam be used for treatment of acute seizures in adults?
Bibliography: Malu CK, Kahamba DM, Walker TD, Mukampunga C, Musalu EM, Kokolomani J, Mayamba RM, Wilmshurst JM, Dubru JM, MIsson JP (2014). Efficacy of Sublingual Lorazepam Versus Intrarectal Diazepam for Prolonged Convulsions in Sub-Saharan Africa. Journal of Child Neurology. 29(7):895–902. doi:10.1177/0883073813493501.

Quality assessment							No. of patients		Effect		Quality	Importance
No. of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Sublingual lorazepam**	**Rectal diazepam**	**Relative (95% CI)**	**Absolute**		
Seizure Cessation within 10 minutes (assessed with clinical Observation)												
1	Randomized trials	Very serious[1]	No serious inconsistency[2]	Serious[3,4]	No serious imprecision	None	131/234 (56%)	160/202 (79.2%)	RR 0.71 (0.62 to 0.81)	230 fewer per 1000 (from 150 fewer to 301 fewer)	⊕OOO VERY LOW	CRITICAL
								0%		-		
Respiratory depression requiring intubation (assessed with clinical observation)												
1	Randomized trials					None	-	-	-	-		CRITICAL
								0%		-		

[1] It was a single blinded study with no mention of allocation concealment. The groups were assigned on an alternate day basis. The analysis was per protocol.
[2] Single study.
[3] Major etiology was cerebral malaria.
[4] Study done in children.

[Updated 2015]

Table 9. Buccal midazolam vs. rectal diazepam for treatment of acute seizures

Author: P Jain
Question: Should buccal midazolam vs. rectal diazepam be used for treatment of acute seizures in adults?
Bibliography:

- McIntyre J, Robertson S, Norris E, Appleton R, Whitehouse WP, Phillips B, Martland T, Berry K, Collier J, Smith S, Choonara I (2005). Safety and efficacy of buccal midazolam versus rectal diazepam for emergency treatment of seizures in children: a randomized controlled trial. Lancet.366(9481):205–210.
- Mpimbaza A, Ndeezi G, Staedke S, Rosenthal PJ, Byarugaba J (2008). Comparison of buccal midazolam with rectal diazepam in the treatment of prolonged seizures in Ugandan children: a randomized clinical trial. Pediatrics.121(1):e58–64. doi:10.1542/peds.2007-0930.
- Nakken KO and Lossius MI (2011). Buccal midazolam or rectal diazepam for treatment of residential adult patients with serial seizures or status epilepticus. Acta Neurologica Scandinavica.124(2):99–103. doi:10.1111/j.1600-0404.2010.01474.x.
- Scott RC, Besag FM, Neville BG (1999). Buccal midazolam and rectal diazepam for treatment of prolonged seizures in childhood and adolescence: a randomized trial. Lancet.353(9153):623–626.
- Ashrafi MR, Khosroshahi N, Karimi P, Malamiri RA, Bavarian B, Zarch AV, Mirzaei M, Kompani F (2010). Efficacy and usability of buccal midazolam in controlling acute prolonged convulsive seizures in children. European Journal of Paediatric Neurology.14(5):434–438. doi:10.1016/j.ejpn.2010.05.009.

Quality assessment							No. of patients		Effect		Quality	Importance
No. of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Buccal midazolam	Rectal diazepam	Relative (95% CI)	Absolute		
Seizure cessation within 10 minutes (assessed with clinical observation)												
5	Randomized trials	Serious[1]	Serious[2]	Serious[3,4]	Serious[5]	None	307/400 (76.8%)	268/406 (66%)	RR 1.16 (0.89 to 1.51)	106 more per 1000 (from 73 fewer to 337 more)	⊕OOO VERY LOW	CRITICAL
								0%		-		
Respiratory depression requiring intubation (assessed with clinical observation)												
5	Randomized trials	Serious[1]	No serious inconsistency	Serious[4]	Very serious[6]	None	2/400 (0.5%)	3/406 (0.74%)	RR 0.67 (0.11 to 3.95)	2 fewer per 1000 (from 7 fewer to 22 more)	⊕OOO VERY LOW	CRITICAL
								0%		-		

[1] Nakken et al. (2011) was a quasi-randomized (groups were assigned alternatively) study; all studies were open label; allocation concealment only mentioned in Mpimbaza et al. (2008).
[2] High heterogeneity, I^2=94%.
[3] Nakken et al. (2011) was done in adults.
[4] Majority of the study participants were children.
[5] Wide confidence interval crossing line of no effect.
[6] Small number of events; Wide CI crossing line of no effect.

Figure 4. Results of a new meta-analysis: Outcome 1 – Seizure cessation within 10 minutes with buccal midazolam vs. rectal diazepam

Study or Subgroup	Buccal Midazolam Events	Total	Rectal Diazepam Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
Soctt 1999	30	40	23	39	17.1%	1.27 [0.93, 1.75]
McIntyre 2005	71	109	45	110	18.5%	1.59 [1.22, 2.07]
Mpimbaza 2008	125	165	114	165	21.4%	1.10 [0.96, 1.25]
Ashrafi 2010	49	49	49	49	22.5%	1.00 [0.96, 1.04]
Nakken 2011	32	37	37	43	20.6%	1.01 [0.84, 1.20]
Total (95% CI)		**400**		**406**	**100.0%**	**1.16 [0.89, 1.51]**
Total events	307		268			

Heterogeneity: Tau² = 0.08; Chi² = 67.39, df = 4 (P < 0.00001); I² = 94%
Test for overall effect: Z = 1.09 (P = 0.28)

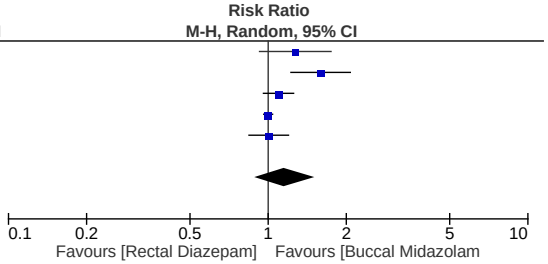

Figure 5. Results of a new meta-analysis: Outcome 2 – Respiratory depression requiring intubation with buccal midazolam vs. rectal diazepam

Study or Subgroup	Buccal Midazolam Events	Total	Rectal Diazepam Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Ashrafi 2010	0	49	0	49		Not estimable
McIntyre 2005	2	109	3	110	100.0%	0.67 [0.11, 3.95]
Mpimbaza 2008	0	165	0	165		Not estimable
Nakken 2011	0	37	0	43		Not estimable
Scott 1999	0	40	0	39		Not estimable
Total (95% CI)		**400**		**406**	**100.0%**	**0.67 [0.11, 3.95]**
Total events	2		3			

Heterogeneity: Not applicable
Test for overall effect: Z = 0.44 (P = 0.66)

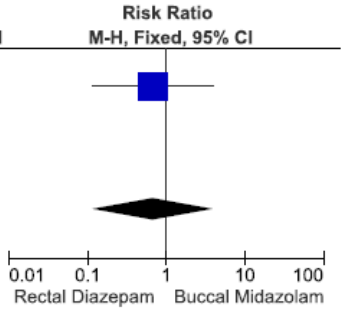

Table 10. Rectal diazepam vs. IN midazolam for treatment of acute seizures

Author: P Jain
Question: Should rectal diazepam vs. IN midazolam be used for treatment of acute seizures in adults?
Bibliography: Holsti M, Dudley N, Schunk J, Adelgais K, Greenberg R, Olsen C, Healy A, Firth S, Filloux F (2010). Intranasal midazolam vs. rectal diazepam for the home treatment of acute seizures in pediatric patients with epilepsy. Archives of Pediatrics & Adolescent Medicine.164(8):747–753. doi:10.1001/archpediatrics.2010.130.

Quality assessment							No. of patients		Effect		Quality	Importance
No. of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Rectal diazepam	IN midazolam	Relative (95% CI)	Absolute		
Seizures when emergency medical services arrived (assessed with clinical observation)												
1	Randomized trials	No serious risk of bias	No serious inconsistency	Serious[1]	Serious[2]	None	8/42 (19%)	8/50 (16%)	RR 1.19 (0.49 to 2.9)	30 more per 1000 (from 82 fewer to 304 more)	⊕⊕OO LOW	CRITICAL
								0%		-		
Respiratory depression requiring Intubation (assessed with clinical Observation)												
1	Randomized trials	No serious risk of bias	No serious inconsistency	Serious[1]	Very serious[3]	None	0/42 (0%)	1/50 (2%)	-	20 fewer per 1000 (from 20 fewer to 20 fewer)	⊕OOO VERY LOW	CRITICAL
								0%		-		

[1] Study done in children.
[2] Single study, less number of events.
[3] Single study, small number of events.

**Outcome 1 (Seizure cessation within 10 minutes) not reported in the study.*

[Updated 2015]

Table 11 . IM paraldehyde vs. IN lorazepam for treatment of acute seizures

Author: P Jain
Question: Should IM paraldehyde vs. intranasal lorazepam be used for treatment of acute Seizure in adults?
Bibliography:

- Appleton R, Macleod S, Martland T (2008). Drug management for acute tonic-clonic convulsions including convulsive status epilepticus in children. Cochrane Database of Systematic Reviews.3:CD001905.
- Ahmad S, Ellis JC, Kamwendo H, Molyneux E (2006). Efficacy and safety of intranasal lorazepam versus intramuscular paraldehyde for protracted convulsions in children: an open randomized trial. Lancet.367(9522):1591–1597. doi:10.1016/S0140-6736(06)68696-0.

Quality assessment							No. of patients		Effect		Quality	Importance
No. of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**IM paraldehyde**	**IN lorazepam**	**Relative (95% CI)**	**Absolute**		
Seizure Cessation within 10 minutes (assessed with clinical observation)												
1	Randomized trials	No serious risk of bias	No serious inconsistency[1]	Serious[2]	Serious[3]	None	49/80 (61.3%)	60/80 (75%)	RR 0.82 (0.66 to 1.01)	135 fewer per 1000 (from 255 fewer to 7 more)	⊕⊕OO LOW	CRITICAL
								0%		-		
Respiratory depression requiring ventilation (assessed with clinical observation)												
1	Randomized trials					None	-	-	-	-		CRITICAL
								0%		-		

[1] Single study.
[2] Study done in children.
[3] Only one study included; less than 100 patients per treatment arm; very wide CI crossing line of no effect.

PART 2: FROM EVIDENCE TO RECOMMENDATIONS

Summary of evidence table

Non-IV route compared to IV Route					
Outcomes	*Buccal midazolam vs. IV diazepam (Number of studies, RR [95% CI], quality)*	*IM midazolam vs. IV diazepam (Number of studies, RR [95% CI], quality)*	*IM midazolam vs. IV lorazepam (Number of studies, RR [95% CI], quality)*	*IN midazolam vs. IV diazepam (Number of studies, RR [95% CI], quality)*	*IN lorazepam vs. IV lorazepam (Number of studies, RR [95% CI], quality)*
Seizure cessation within 10 minutes	1 study, RR-0.91 (0.8-1.03) No difference, LOW quality	3 studies, RR-0.96 (0.87-1.07) No difference, VERY LOW quality	1 study, RR- 1.16 (1.06-1.27) Favours IM midazolam, MODERATE quality	3 studies, RR-1.0 (0.91-1.08) No difference, VERY LOW quality	1 study, RR-1.04 (0.89-1.22) No difference, LOW quality
Respiratory depression requiring intubation	N/A	N/A	1 study, RR-0.98 (0.71-1.35) No difference, LOW quality	N/A	N/A
Non-IV route compared to other non-IV route					
	Rectal diazepam vs. rectal lorazepam (Number of studies, RR [95% CI], quality)	*Rectal diazepam vs. sublingual lorazepam (Number of studies, RR [95% CI], quality)*	*Buccal midazolam vs. rectal diazepam (Number of studies, RR [95% CI], quality)*	*Rectal diazepam vs. IN midazolam (Number of studies, RR [95% CI], quality)*	*IM paraldehyde vs. IN lorazepam (Number of studies, RR [95% CI], quality)*
Seizure cessation within 10 minutes	1 study, RR-0.32 (0.16-0.61) Favours rectal diazepam, VERY LOW quality	1 study, RR – 1.41 (1.24-1.62) Favours sublingual lorazapam, VERY LOW quality	5 studies, RR-1.16 (0.89-1.51) No difference, VERY LOW quality	1 study, RR 1.19 (0.49 to 2.9) No difference, LOW quality	1 study, RR 0.82 (0.66 to 1.01) No difference, LOW quality
Respiratory depression requiring intubation	N/A	N/A	5 studies, RR 0.67 (0.11-3.95) No difference, VERY LOW quality	N/A	N/A

NOTE: Various non-IV routes of midazolam as a whole were also compared to IV diazepam; RR was 0.97 (95% CI 0.91-1.03) with very low quality of evidence.

Evidence to recommendation table

Benefits	Where no IV access is available, there is generally no clinically important difference between non-IV routes of administration of benzodiazepines compared to IV routes. Analysis of IM midazolam vs. IV lorazepam found a difference in effectiveness in favour of IM midazolam. There was no suitable evidence found for the effectiveness of IM Paraldehyde. Given that the evidence regarding head-to-head comparison of different non-IV interventions is of low to very low quality, it is not possible to determine if there is a clinically important difference between non-IV antiepileptic medications for control of acute convulsive seizures. The evidence compiled pertains to a conclusion that where no IV access is available, rectal diazepam is no more effective than buccal midazolam and is possibly more effective than sublingual lorazepam (however, this is derived from low quality of evidence). Rectal lorazepam may be more effective than rectal diazepam, but the evidence is very low quality and number of patients small.
Harms	Not many studies reported on respiratory depression. However, when reported, all treatments appear to be similar in relation to respiratory depression requiring intubation. Given that the evidence is limited, it is not possible to determine if there is a clinically important difference between IM midazolam and IV lorazepam, or for intranasal lorazepam and IV lorazepam.
Summary of the quality of evidence	Most of the data is available for children; therefore, this evidence can be considered indirect. Quality of evidence varies between MODERATE and VERY LOW.

Value and preferences	
In favour	In a convulsing child or adult, establishing an IV access may be difficult. Additionally, lack of trained health care workers and lack of IV equipment compounds the problem of IV medication use in resource-limited settings. For patients and their families, non-IV treatment options may increase patient and family satisfaction.
Against	In some settings, rectal administration may not be acceptable. Intranasal administration of anti-epileptic medicines can cause discomfort in patients with focal seizures or in partially conscious patients. Sedative effects of benzodiazepines may interfere with neurological examinations.
Uncertainty or variability?	There is no uncertainty with regards to value and preferences.

Feasibility (including resource use considerations)	Buccal or intranasal or intramuscular preparations of midazolam or lorazepam are not readily available. However, the majority of the available studies have used IV preparations for buccal or intranasal administration; therefore, these alternative routes may be acceptable. Both IV lorazepam and IV diazepam are included in the WHO Essential Medicine List. IV midazolam is also included, but under the section on preoperative medication and sedation for short-term procedures and not under anti-epileptics. The use of intramuscular paraldehyde carries particular issues of feasibility in resource-limited settings. These include the need to use a glass syringe and light sensitivity (and therefore requiring particular storage solutions). Furthermore, paraldehyde does not appear on the WHO Essential Medicine List and is seldom available in low- and middle-income countries, which further contributes to issues of availability.
Uncertainty or variability?	There is some variability with regards to the feasibility of different medications in resource-limited settings.

[Updated 2015]

Recommendation and remarks

Recommendation

When intravenous access is not available for the control of acute seizures in adults, non- parenteral routes of benzodiazepine administrations should be used. Options include rectal diazepam, buccal or intranasal midazolam, rectal or intranasal lorazepam. The preference may be guided by availability, expertise and social preference. Some benzodiazepines (lorazepam or midazolam) may be given by intramuscular route, which requires additional expertise. Intramuscular administration of diazepam is not recommended because of erratic absorption.

Rationale: A strong recommendation was made even with low quality evidence because the risk associated with not attempting to control seizures (e.g., sequelae of prolonged seizure or death) far outweighs any harms associated with using the interventions recommended. Although the quality of the evidence is low, there is no clinically important difference between non-intravenous routes of administration of benzodiazepines compared to intravenous routes for management of acute convulsive seizures. In a convulsing child or adult, establishing an intravenous access may be difficult; there may be lack of trained health care workers and lack of equipment in resource-limited settings. For patients and their families, non-intravenous treatment options may increase patient and family satisfaction. The availability of non-parenteral formulations of benzodiazepines may be a feasibility issue.

Remarks

Relevant scenarios for using non-intravenous formulations may include community settings (pre-hospitalisation) or in a health care facility that is not equipped to administer intravenous medications or which does not have trained health care workers.
Intravenous formulations can be used for non-intravenous administration routes. If this should occur, particular caution should be taken with dosages to avoid administration errors.

Judgements about the strength of a recommendation

Factor	Decision
Quality of the evidence	□ High □ Moderate **X Low** □ Very low
Balance of benefits versus harms	**X Benefits clearly outweigh harms** □ Benefits and harms are balanced □ Potential harms clearly outweigh potential benefits
Values and preferences	**X No major variability** □ Major variability
Resource use	**X Less resource-intensive** □ More resource-intensive
Strength	**STRONG**

OTHER REFERENCES

Anderson GD and Saneto RP (2012). Current oral and non-oral routes of antiepileptic drug delivery. Advanced Drug Delivery Reviews.64: 911–918. doi:10.1016/j.addr.2012.01.017.

Chen JJ, Caller TA, Mecchella JN, Thakur DS, Homa K, Finn CT, Konbylarz EJ, Bujarski KA, Thadani VM, Jobst BC (2014). Reducing severity of comorbid psychiatric symptoms in epilepsy clinic using a colocation model: Results of a pilot intervention. Epilepsy & Behavior.39:92-96. doi:10.1016/j.yebeh.2014.07.015

Shorvon S (2012). Clinical trials in acute repetitive seizures and status epilepticus. Epileptic Disorders.14(2):138-147.

APPENDIX 1

MEDLINE search strategy

1. randomized controlled trial.pt.
2. controlled clinical trial.pt.
3. exp Randomized Controlled Trial/
4. exp Random Allocation/
5. exp Double-Blind Method/
6. exp Single-Blind Method/
7. exp Clinical Trial/
8. clinical trial.pt.
9. (clin$ adj trial$).tw.
10. ((singl$ or doubl$ or trebl$ or tripl$) adj (blind$ or mask$)).tw
11. randomi$.tw.
12. (random$ adj (allocate$ or assign$)).tw.
13. crossover.tw.
14. 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13
15. epilep$.tw.
16. seizure$.tw.
17. convulsion$.tw.
18. exp Epilepsy/
19. exp Seizures/
20. 15 or 16 or 17 or 18 or 19
21. exp Epilepsy, Tonic-Clonic/
22. tonic clonic.tw.
23. status epilepticus.tw.
24. exp Status Epilepticus/
25. 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24
26. 14 and 25
27. (animals not human).sh.
28. 26 not 27
29. pediatr$.tw. or paediatr$.tw
30. child$.tw.

31. exp child/ or exp child, preschool/ or exp infant/
32. 29 or 30 or 31
33. 28 and 32
34. emergency.tw

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[i] McMaster University, Canada search strategy details: http://hiru.mcmaster.ca/hiru/HIRU_Hedges_MEDLINE_Strategies.aspx.