



health

Department:
Health
REPUBLIC OF SOUTH AFRICA



**South African National Essential Medicine List
Primary Healthcare Medication Review Process
Component: Emergencies and injuries**

1. Executive Summary

Date: 31 August 2017
Medicine (INN): Midazolam, IM
Medicine (ATC): N05CD08
Indication (ICD10 code): Status epilepticus (G41.0)
Patient population: Children < 12 years of age
Prevalence of condition: 17-23/100 000 in developed countries 2.3/1000 cases of convulsive status epilepticus in African multisite survey – 61% of these juveniles(1)
Level of Care: Primary Health Care
Prescriber Level: Emergency medicine – Nurse
Current standard of Care: Single dose of buccal midazolam or up to 2 doses of rectal diazepam. If no response, phenobarbital administered through nasogastric tube.
Efficacy estimates: (preferably NNT): Midazolam, IM vs diazepam, rectal (seizure control): 96% vs 94%, p = 0.061; NNT =50 (15).
Motivator/reviewer name(s): Dr Sandy Picken
PTC affiliation: n/a

2. Name of author(s)/motivator(s)

Dr Sandy Picken

3. Author affiliation and conflict of interest details

Affiliation: PHC Technical Sub-committee of NEMLC; Knowledge Translation Unit, University of Cape Town.
Conflict of interest: None

4. Introduction/ Background

Generalized convulsive status epilepticus (SE) is a serious and potentially life threatening medical emergency that requires prompt intervention.

Although the definition of SE has varied over time, for pragmatic clinical purposes of this review, the accepted definition of SE (early) will be a single unremitting seizure lasting longer than **five minutes** or frequent clinical seizures without return to the baseline clinical state. This corresponds with the time at which urgent treatment should be initiated.

Current standard of care includes buccal midazolam and rectal diazepam. The PHC Technical Sub-committee queried why intramuscular midazolam is not given as an alternative option as pre-hospital treatment by a non-intravenous route.

5. Search 1: PICO #1

Purpose/Objective i.e. PICO question 1

-P (*patient/population*): children < 12 years old in status epilepticus

-I (*intervention*): intramuscular midazolam

-C (*comparator*): any other benzodiazepine (diazepam; lorazepam; clonazepam; midazolam by another RoA)

-O (*outcome*): Efficacy (time to cessation of seizures), side effects (respiratory depression, respiratory arrest, death, neurological sequelae)

(P) Amongst children < 12 years old with status epilepticus, is (I) intramuscular midazolam compared to (C) another benzodiazepine by any other route of administration (O) safe and effective in terms of time to cessation of seizures, side effects (respiratory depression, respiratory arrest), neurological sequelae, death?

6. Search 2: PICO #2

Purpose/Objective i.e. PICO question 2

-P(patient/population): children < 12 years old in status epilepticus

-I(intervention): intramuscular midazolam

-C(comparator): rectal diazepam; or buccal midazolam

-O(outcome): Efficacy (time to cessation of seizures), side effects (respiratory depression, respiratory arrest, death, neurological sequelae)

(P) Amongst children < 12 years old in status epilepticus, is (I) intramuscular midazolam compared specifically to (C) buccal midazolam or rectal diazepam (O) safe and effective in terms of time to cessation of seizures, side effects (respiratory depression, respiratory arrest), neurological sequelae, death?

7. Methods:

a. Data sources: Pubmed, cochrane library

b. Search strategy 1

((("child"[MeSH Terms] OR "child"[All Fields]) AND ("status epilepticus"[MeSH Terms] OR ("status"[All Fields] AND "epilepticus"[All Fields]) OR "status epilepticus"[All Fields])) AND (("injections, intramuscular"[MeSH Terms] OR ("injections"[All Fields] AND "intramuscular"[All Fields]) OR "intramuscular injections"[All Fields] OR "intramuscular"[All Fields]) AND ("midazolam"[MeSH Terms] OR "midazolam"[All Fields])) AND (("benzodiazepines"[MeSH Terms] OR "benzodiazepines"[All Fields] OR "benzodiazepine"[All Fields]) OR ("diazepam"[MeSH Terms] OR "diazepam"[All Fields]) OR ("clonazepam"[MeSH Terms] OR "clonazepam"[All Fields]) OR ("lorazepam"[MeSH Terms] OR "lorazepam"[All Fields]) OR ("buccal"[All Fields] AND ("midazolam"[MeSH Terms] OR "midazolam"[All Fields])) OR ("intranasal"[All Fields] AND ("midazolam"[MeSH Terms] OR "midazolam"[All Fields])) OR ("IV"[All Fields] AND ("midazolam"[MeSH Terms] OR "midazolam"[All Fields])))) AND (("safety"[MeSH Terms] OR "safety"[All Fields]) OR efficacy[All Fields] OR effective[All Fields] OR ("adverse effects"[Subheading] OR ("adverse"[All Fields] AND "effects"[All Fields]) OR "adverse effects"[All Fields]) OR ("adverse effects"[Subheading] OR ("adverse"[All Fields] AND "effects"[All Fields]) OR "adverse effects"[All Fields]) OR ("side"[All Fields] AND "effects"[All Fields]) OR "side effects"[All Fields]) OR ("respiratory insufficiency"[MeSH Terms] OR ("respiratory"[All Fields] AND "insufficiency"[All Fields]) OR "respiratory insufficiency"[All Fields]) OR ("respiratory"[All Fields] AND "depression"[All Fields]) OR "respiratory depression"[All Fields]) OR (neurological[All Fields] AND ("complications"[Subheading] OR "complications"[All Fields] OR "sequelae"[All Fields])) OR ("death"[MeSH Terms] OR "death"[All Fields]))

Search strategy 2:

((("child"[MeSH Terms] OR "child"[All Fields] OR "children"[All Fields]) AND ("status epilepticus"[MeSH Terms] OR ("status"[All Fields] AND "epilepticus"[All Fields]) OR "status epilepticus"[All Fields])) AND (("injections, intramuscular"[MeSH Terms] OR ("injections"[All Fields] AND "intramuscular"[All Fields]) OR "intramuscular injections"[All Fields] OR "intramuscular"[All Fields]) AND ("midazolam"[MeSH Terms] OR "midazolam"[All Fields])) OR ("administration, rectal"[MeSH Terms] OR ("administration"[All Fields] AND "rectal"[All Fields]) OR "rectal administration"[All Fields] OR "rectal"[All Fields]) AND ("diazepam"[MeSH Terms] OR "diazepam"[All Fields]) OR (non-intravenous[All Fields] AND ("midazolam"[MeSH Terms] OR "midazolam"[All Fields])) OR ("injections, intramuscular"[MeSH Terms] OR ("injections"[All Fields] AND "intramuscular"[All Fields]) OR "intramuscular injections"[All Fields] OR "intramuscular"[All Fields]) AND ("benzodiazepines"[MeSH Terms] OR "benzodiazepines"[All Fields])) AND (("safety"[MeSH Terms] OR "safety"[All Fields]) OR efficacy[All Fields] OR effectiveness[All Fields] OR ("time"[MeSH Terms] OR "time"[All Fields]) AND cessation[All Fields] AND ("seizures"[MeSH Terms] OR "seizures"[All Fields] OR "seizure"[All Fields]) OR ("adverse effects"[Subheading] OR ("adverse"[All Fields] AND "effects"[All Fields]) OR "adverse effects"[All Fields]) OR ("side"[All Fields] AND "effects"[All Fields]) OR "side effects"[All Fields]) OR ("adverse effects"[Subheading] OR "adverse"[All Fields] AND "effects"[All Fields]) OR "adverse effects"[All Fields]) OR (neurological[All Fields] AND ("complications"[Subheading] OR "complications"[All Fields] OR "sequelae"[All Fields])) OR ("apnea"[MeSH Terms] OR "apnea"[All Fields] OR ("respiratory"[All Fields] AND "arrest"[All Fields]) OR "respiratory arrest"[All Fields])) NOT ((intravenous[All Fields] AND ("midazolam"[MeSH Terms] OR "midazolam"[All Fields])) OR (intravenous[All Fields] AND ("diazepam"[MeSH Terms] OR "diazepam"[All Fields])) OR (intravenous[All Fields] AND ("benzodiazepines"[MeSH Terms] OR "benzodiazepines"[All Fields] OR "benzodiazepine"[All Fields]))

c. Search strategy 1:

Search strategy 1 retrieved 17 articles, of which 2 were relevant to the PICO clinical question. Of the remaining 15, 5 were excluded for reasons outlined in the table below. Of the remaining 10, there was: 1 systematic review; 1 meta-analysis; 1 narrative review; 1 synthesized evidence based guideline; 5 randomized trials of which 3 were duplicate publications/publications and 1 secondary analysis.

	Author, date	Type of study	Reason for exclusion
1	Zelcer, 2016 (2)	Review article	Primary focus of study on intranasal MDZ – no additional information on IM MDZ
2	Appleton, 2008 (3)	Systematic Cochrane review	Focus did not examine for IM MDZ
3	Sofou, 2009 (4)	Review	Only included study examining IM MDZ was Chamberlain (5), which has been included in later review by Jain (6)
4	De Negri, 2001 (7)	Review article	No new information on IM MDZ.
5	Trinka, 2016	Expert opinion	Expert opinion

Search strategy 2:

Search strategy 2 retrieved 22 articles, of which 13 were not relevant to the clinical question. Of the remaining 9, 6 studies were excluded and the remaining 3 comprised a meta-analysis, a randomized trial and cost-effectiveness analysis.

Excluded studies for search 2:

	Author, date	Type of study	Reason for exclusion
1	Sánchez-Carpintero, 2014 (8)	Review	Focus is on buccal midazolam versus PR diazepam
2	Vlaskamp, 2014 (9)	Retrospective cohort study (observational)	Focus was on buccal midazolam versus PR diazepam
3	Komur, 2012 (10)	Retrospective cohort study (observational)	Focus was ICU setting in Turkey, with small sample size.
4	Wolf, 2011 (11)	Review	Review of acute administration of drugs in epilepsy for indications other than status epilepticus.
5	Raj, 2011 (12)	Guideline	Guide for Indian setting.
6	Krocicka, 2005 (13)	Retrospective cohort study (observational)	Hospital/ specialist setting

d. Evidence synthesis –

The reviews, in particular Jain (6) summarise the few randomized trials that are available and support the view that IM MDZ midazolam is as effective as diazepam by any route as well as IV lorazepam.

The McMullen meta-analysis (14) below concludes that midazolam (MDZ), by any route of administration, is superior to diazepam, by any route (route (relative risk [RR] = 1.52; 95% confidence interval [CI] = 1.27 to 1.82), the only study included in this review looking specifically at IM MDZ, was Chamberlain (5), the rest focusing on intranasal and buccal MDZ.

A later randomized trial of 100 children, Momen [2014,(15)], showed IM midazolam is not superior to alternative acute anticonvulsants, in particular buccal midazolam or rectal diazepam, but may be at least as effective these in controlling status epilepticus in children and may be an useful alternative where IV access is difficult/unavailable (e.g. in community settings).

A recent cost-effectiveness analysis (16) showed that the most cost-effective rescue medication was buccal midazolam followed by nasal midazolam with PR diazepam being the least cost-effectiveness.

IM MDZ fared well against IV lorazepam in the RAMPART trial and the follow up analysis (17, 18).

Author, date	Type of study	n	Population	Comparators			Primary outcome	Effect sizes	Comments
Systematic reviews/ meta-analyses									
Jain et al, 2016 (6)	Systematic Review	26 studies - RCTs and quasi-randomized controlled trials, irrespective of blinding included.	> 1 month old (children and adults)	Inter-vention	Com-parator	Seizure cessation within 10 min	Time to seizure cessation after drug administration	Time to seizure cessation after presentation	Significant respiratory depression requiring ventilation/apneas/bradypneas
				IM MDZ	IV DZP	3 studies (5, 19, 20) (137 episodes) No significant difference (RR 0.98; 95% CI, 0.88–1.09)	2 studies (5, 19) (56 episodes) Significantly higher in the IM MDZ group (MD 1.10; 95% CI, 0.65–1.55)	2 studies (5, 19) (56 episodes) Significantly lower in the IM MDZ group (MD:3.33; 95% CI, –5.03 to –1.63)	No significant adverse effects reported
				IM MDZ	IV L	1 study (893 subjects) (17, 21); this outcome not reported Children with seizure cessation at the time of arrival in the hospital was significantly higher in the IM MDZ group (RR1.16; 95% CI, 1.06–1.27; p = 0.0013); In the secondary analysis (120 subjects), 24 it was lower in the IM MDZ group (68.3%) (71.6%) [RR 0.95; 95% CI, 0.75–1.21; p = 0.69] MODERATE quality	1 study (893 subjects) (17) Faster in the IV LZP group as compared to the IM MDZ group (3.3 min)	1 study (893 subjects) (17) Higher in the IM MDZ group as compared to the IV LZP group (OR 1.59; 95% CI, 1.20–2.12); In the secondary analysis, (18) the same was lower in the IM MDZ group (RR 0.85; 95% CI, 0.39–1.86)	No difference for children requiring intubation within 30 min of arrival in the hospital (RR 0.98; 95% CI, 0.70–1.34); Hypotension was also similar between the two groups (RR 0.92; 95% CI, 0.42–1.98); In the secondary analysis, (18) 5 children in the IM MDZ group and 9 children in the IV LZP group required intubation within 30 min of arrival (RD –7; 99% CI, –22 to 8).
IM MDZ	PR DZP	1 study (15) (100 participants) Similar (RR 1.02; 95% CI 0.93–1.12; p = 0.46) LOW quality	1 study (15) (100 participants) Median time significantly lower in the IM MDZ group (66 s) vs. PRDZP group (130 s) (p < 0.001)	1 study (15) (100 participants) Median time significantly lower in the IM MDZ group (127 s) as compared to the PR DZP group (243 s) (p < 0.001)	No significant adverse effects reported				

Mcmullan et al, 2010 (14)	Meta-analyses	6 studies with 774 subjects			<p>If non-intravenous (non-IV) midazolam is as effective as diazepam, by any route, in terminating SE seizures in children and adults.</p> <p>Time to seizure cessation and respiratory complications examined.</p>	<p>For seizure cessation, midazolam, by any route, was superior to diazepam, by any route (relative risk [RR] = 1.52; 95% confidence interval [CI] = 1.27 to 1.82).</p> <p>Non-IV midazolam is as effective as IV diazepam (RR = 0.79; 95% CI = 0.19 to 3.36), and buccal midazolam is superior to rectal diazepam in achieving seizure control (RR = 1.54; 95% CI = 1.29 to 1.85). Midazolam was administered faster than diazepam (mean difference = 2.46 minutes; 95% CI = 1.52 to 3.39 minutes) and had similar times between drug administration and seizure cessation. Respiratory complications requiring intervention were similar, regardless of administration route (RR = 1.49; 95% CI = 0.25 to 8.72)</p>	<p>Only 1 of the studies included, Chamberlain et al. 1997 (5), examined IM midazolam versus IV diazepam – the other studies looked at buccal or intranasal MDZ.</p>
Sánchez Fernández et al, 2017 (16)	Cost-effective analysis	Decision analysis model populated with effectiveness data from the literature and cost data from publicly available market prices			<p>Cost per seizure stopped (\$/SS)</p> <p>IN MDZ</p> <p>Buccal MDZ</p> <p>IM midazolam</p> <p>IN lorazepam</p> <p>PR diazepam</p>	<p>The most cost-effective rescue medication was buccal midazolam (incremental cost-effectiveness ratio ([ICER]: \$13.16/SS) followed by nasal midazolam (ICER: \$38.19/SS). Nasal lorazepam (ICER: -\$3.8/SS), intramuscular midazolam (ICER: -\$64/SS), and rectal diazepam (ICER: -\$2,246.21/SS) are never more cost-effective than the other options at any willingness to pay.</p> <p>Second-order Monte Carlo simulations showed the following:</p> <p>(1) IN midazolam and IM midazolam were the more effective options</p> <p>(2) the more cost-effective option was buccal midazolam for a willingness to pay from \$14/SS to \$41/SS and IN midazolam for a willingness to pay above \$41/SS;</p> <p>(3) cost-effectiveness overlapped for buccal midazolam, IN lorazepam, IM midazolam, and IN midazolam; and</p>	

						(4) PR diazepam was not cost-effective at any willingness to pay, and this conclusion remained extremely robust to wide variations of the input parameters.
Studies –						
Welch et al, 2015 (18) Secondary analysis of RAMPART trial for < 18 years	Included in Jain systematic review above (6)					
Momen et al, 2014 (15)	Included in Jain systematic review above (6)					
Portela et al, 2014 (19)	Included in Jain systematic review above (6)					
Silbergliet et al, 2013 (23)	RAMPART - Duplicate publication/commentary					
Silbergleit et al, 2012 (17) RAMPART trial (<i>Rapid Anticonvulsant Medication Prior to Arrival Trial</i>)	Included in Jain systematic review above (6)					
Silbergleit et al, 2011 (21)	RAMPART - Duplicate publication/commentary					
Shah et al, 2005 (20)	Included in Jain systematic review above (6)					
Chamberlain et al, 1997 (5)	Included in Jain systematic review above (6)					
Guidelines (evidence based)						
Glauser et al, 2016 (24)	Guideline based on literature review	38 RCTs split into adult and paediatric	RCTs of anticonvulsant treatment for seizures longer than 5 minutes	N/A	-	
Shah et al, 2014 (25)	Using a National Prehospital EBG Model and GRADE methodology, a paediatric seizure guideline has been developed that emphasizes the routine assessment of capillary blood glucometry and the use of buccal, IM, or intranasal benzodiazepines over IV or rectal routes for seizure cessation				<p>Recommendation #7: We recommend that prehospital protocols for seizure management in children utilize alternative (non-IV) routes of drug administration as first-line therapy for treating children with status epilepticus. Evidence quality: Moderate; Recommendation strength: Strong</p> <p>Recommendation #9: We suggest IM midazolam over PR diazepam for prehospital seizure cessation and control. Evidence quality: Very low; Recommendation strength: Weak.</p>	

a. **Evidence quality:** Moderate to low quality RCTs.

8. **Alternative agents:** Buccal midazolam or rectal diazepam.

EVIDENCE TO DECISION FRAMEWORK

	JUDGEMENT	SUPPORTING EVIDENCE & ADDITIONAL CONSIDERATIONS						
QUALITY OF EVIDENCE	<p>What is the overall confidence in the evidence of effectiveness?</p> <p>Confident Not confident Uncertain</p> <p><input checked="" type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/></p>							
BENEFITS & HARMS	<p>Do the desirable effects outweigh the undesirable effects?</p> <p>Benefits outweigh harms Harms outweigh benefits Benefits = harms or Uncertain</p> <p><input checked="" type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/></p>							
THERAPEUTIC INTERCHANGE	<p>Therapeutic alternatives available:</p> <p>Yes No</p> <p><input type="checkbox"/> <input checked="" type="checkbox"/></p> <p>List the members of the group.</p> <p>List specific exclusion from the group:</p>	<p>Rationale for therapeutic alternatives included:</p> <p>References:</p> <p>Rationale for exclusion from the group:</p> <p>References:</p>						
VALUES & PREFERENCES / ACCEPTABILITY	<p>Is there important uncertainty or variability about how much people value the options?</p> <p>Minor Major Uncertain</p> <p><input checked="" type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/></p> <p>Is the option acceptable to key stakeholders?</p> <p>Yes No Uncertain</p> <p><input checked="" type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/></p>							
RESOURCE USE	<p>How large are the resource requirements?</p> <p>More intensive Less intensive Uncertain</p> <p><input type="checkbox"/> <input checked="" type="checkbox"/> <input type="checkbox"/></p>	<p>Cost of medicines/ month:</p> <table border="1"> <thead> <tr> <th>Medicine</th> <th>Cost (ZAR)*</th> </tr> </thead> <tbody> <tr> <td>Midazolam 1mg/mL 5mL ampoule</td> <td>R4.53</td> </tr> <tr> <td>Midazolam 5mg/mL 10mL vial</td> <td>R26.22</td> </tr> </tbody> </table> <p>*Contract circular HP06-2017SVP</p> <p>Additional resources: Sanchez Fernandez I, Gainza-Lein M, Loddenkemper T. Nonintravenous rescue medications for pediatric status epilepticus: A cost-effectiveness analysis. <i>Epilepsia</i>. 2017;58(8):1349-59.</p>	Medicine	Cost (ZAR)*	Midazolam 1mg/mL 5mL ampoule	R4.53	Midazolam 5mg/mL 10mL vial	R26.22
Medicine	Cost (ZAR)*							
Midazolam 1mg/mL 5mL ampoule	R4.53							
Midazolam 5mg/mL 10mL vial	R26.22							

EQUITY	Would there be an impact on health inequity? Yes No Uncertain <input type="checkbox"/> <input checked="" type="checkbox"/> <input type="checkbox"/>	
FEASIBILITY	Is the implementation of this recommendation feasible? Yes No Uncertain <input checked="" type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>	

Type of recommendation	We recommend against the option and for the alternative <input type="checkbox"/>	We suggest not to use the option or to use the alternative <input type="checkbox"/>	We suggest using either the option or the alternative <input type="checkbox"/>	We suggest using the option <input type="checkbox"/>	We recommend the option <input checked="" type="checkbox"/>
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Recommendation: The Primary Health Care Committee recommends the addition of a IM midazolam as a first line alternative to rectal diazepam or buccal midazolam in the treatment of children < 12 years with status epilepticus in a primary health care setting.

Rationale: Limited evidence from available RCTs suggests that midazolam, IM is as effective as diazepam, IV and lorazepam, IV for the initial management of status epilepticus in children with regards to time to seizure cessation after presentation. (Although, the median time for seizure cessation after presentation was significantly lower in the midazolam, IM vs diazepam, rectal group; 127 s vs 243 s, p<0.001). Buccal midazolam has been shown to be comparable to rectal diazepam (refer to the medicine review: Midazolam, buccal vs diazepam, rectal for the control of seizures in children, 28 May 2014).

Level of Evidence: II Systematic review of low to moderate quality RCTs

Review indicator:

Evidence of efficacy	Evidence of harm	Price reduction
<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>

VEN status:

Vital	Essential	Necessary
<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

Monitoring and evaluation considerations

Research priorities

Jain et al (6): "Studies with uniform definition of status epilepticus/acutes seizures would be desirable. Studies comparing different non-intravenous routes to each other for efficacy, safety and pharmacokinetics should be carried out. More efficient ways of delivering drugs by these local routes should also be researched".

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