Preparing an interdisciplinary guidance for the management of generalised paediatric status epilepticus

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ABSTRACT

Background

A guidance was created to assist family doctors in managing generalized paediatric status epilepticus (GPSE) at Primary HealthCare (PHC) clinics.

Aim

The article aims to discuss the process by which the GPSE guidance was prepared.

Objectives

The authors intend to provide information on how the literature review was carried out, what clinical threshold was decided as appropriate for the administration of rescue medication, and what treatments may be used in PHC.

Method

An initial search and guidance draft was forwarded to a Joint Working Group (JWG) composed of professionals working at PHC and Mater Dei Hospital (MDH). The names of benzodiazepines and their formulations available at PHC clinics were forwarded to the JWG by the clinical Chairperson of Primary HealthCare. A Pubmed search was carried out for the terms "status epilepticus," "children", and "prehospital", filtering for free full text publications, humans, English language, and dating from 1999 to 2019, yielding seventeen results in the English language. Eight were relevant. A second Pubmed search for "diazepam use in paediatric seizures" and "midazolam use in paediatric seizures" yielded fifty-five results, filtering for English and dating from 2010-2019. Two were relevant. Several guidelines and literature were directly referenced. The literature review process and results were summarised and modified into a flowchart.

Results

An interdisciplinary approach was used to decide how GPSE should be treated. Consensus was agreed that if a seizure lasts more than five minutes, benzodiazepines midazolam and diazepam available at PHC clinics, may be used. Intramuscular, intranasal, buccal, or rectal routes are preferred per the child's weight; and time the duration of seizure activity.

Conclusion

GPSE may terminate during the first five minutes of ictal activity. Midazolam and diazepam may be administered by different methods if seizures persist, depending on the clinical scenario.

Keywords

Family practice; status epilepticus; pediatrics; emergency medicine.

INTRODUCTION

Seizures occur as part of "an abnormal, unregulated electrical discharge within the brain's cortical grey matter and transiently interrupts normal brain function" (Adamolekun, 2022). Paediatric Convulsive Status Epilepticus (PCSE) peaks neonatally, tailing off at five years of age, and commonly presents as the first seizure in childhood. A third of children are later diagnosed with epilepsy (Trinka et al., 2015).

Seizures tend to last less than five minutes, with prolonged episodes ranging from five to thirty minutes. Status epilepticus (SE) is conventionally defined as a seizure with persistent ictal activity lasting more than thirty minutes or a lack of recovery between two or more bouts. The International League against Epilepsy (ILAE) recommended treatment at the five-minute mark in cases of convulsive SE and ten minutes for non-convulsive SE since prolongation is more likely to incur significant morbidity and mortality (Trinka et al., 2015).

Aim

The authors aim to communicate how a guideline for the management of GPSE in Primary Healthcare Centres was prepared.

Objectives

The authors intend to provide the method by which the literature review concerning the management of PCSE was conducted, the clinical threshold at which rescue medication should be administered and the medications that may be administered in PHC clinics for GPSE.

METHOD

Two doctors training in family medicine and a specialist in family medicine conducted the initial search and guidance draft. A list of benzodiazepines, and respective formulations, were forwarded by Primary HealthCare administration (Table 1). A Pubmed search was carried out for full-text sources of manuscripts with relevant titles and abstracts. The national clinical practice guideline employed by the national health service was directly included (Mater Dei Hospital, 2016).

Table 1: Benzodiazepines available in Primary HealthCare centres

- Diazepam 10mg Injectable
- Diazepam 2mg Tablets
- Diazepam 5mg Tablets
- Diazepam 5mg Rectal
- Diazepam 10mg Rectal
- Diazepam 10mg Injectable
- Midazolam 10mg Injectable

The following sources were directly referenced:

- the definition of status epilepticus as delineated by the International League Against Epilepsy (ILAE) (Trinka et al., 2015),
- the National Institute for Health and Excellence (NICE) Pathway: treating prolonged or repeated seizures and status epilepticus (2022),
- the British National Formulary (BNF) (Joint Formulary Committee, 2020),
- the American Epilepsy Society: Convulsive Status Epilepticus Guideline (Glauser et al., 2016),
- Joint Royal Colleges Ambulance Liaison Committee (JRCALC) Clinical Guidelines (2019),
- European Medicines Agency (2022).

The draft was forwarded to a Joint Working Group (JWG) composed of PHC and Mater Dei Hospital (MDH) professionals. The JWG included a specialist in family medicine qualified in emergency medicine, a paediatric specialist, a specialist in paediatric neurology, and a pharmacist qualified in clinical care.

RESULTS

An initial Pubmed search was carried out for the terms "status epilepticus," "children", and "prehospital", yielding seventeen results in the English language. Eight were relevant.

A second Pubmed search for "diazepam use in paediatric seizures" and "midazolam use in paediatric seizures" yielded fifty-five results in English. Two were relevant. Several guidelines and literature were directly referenced (Table 2).

Table 2: Guidelines and literature directly referenced

• Drug Preparation and Administration in Neonatal and Paediatric Status Epilepticus (Agius et al., 2020)
• British National Formulary (Joint Formulary Committee, 2020)
• BMJ Best Practice (Hartman et al., 2020)
• American Epilepsy Society Guideline (Glauser et al., 2016)
• Holsti et al. (2010)
• Humphries and Eiland (2013)
• Joint Royal Colleges Ambulance Liaison Committee (JRCALC) Clinical Guidelines (2019)
• Status epilepticus management (Mater Dei Hospital, 2016)
• Epilepsies in children, young people and adults (NICE, 2022)
• Intranasal Administration of Midazolam Treatment Guideline Sheet compiled by Primary HealthCare (Abela et al., 2011)
• European Resuscitation Council Guidelines 2021: Paediatric Life Support Guidelines (Van de Voorde et al., 2021)
• Zelcer and Goldman (2016)

The availability of several benzodiazepines in the primary healthcare clinics allowed the JWG to consider different approaches to treating GPSE (Table 1). The JWG reviewed the summary of the search and discussed the appropriate administration methods of benzodiazepines and the management of comorbid factors (see Table 3 and Appendix). The guidance was styled into a flowchart and forwarded to two hundred thirty-two doctors and three hundred and twenty nurses working in PHC clinics via email for generic feedback (Figure 1). The background information collected in the initial review was also included in the feedback request. The replies were discussed amongst the JWG and included in the guidance.

Table 3: Benzodiazepines recommended, treatment thresholds and study conclusions (NB: IV – intravenous; IM – intramuscular; IN – intranasal; IO - intraosseus)

Geography	Source	Medicine, Dose, Route, Findings	Threshold of administration
National	Agius et al. (2020).	IV diazepam. IV lorazepam. If vascular access is not available: Rectal siazepam Buccal midazolam. Intramuscular IM midazolam. Intranasal IN midazolam.	Five minutes of seizure onset.
European	Van de Voorde et al. (2021).	Benzodiazepine administration.	Five minures of seizure onset.
	Hartman et al. (2022)	Rectal diazepam and buccal (dosing according to specialist guidance) or IN midazolam	Five minutes of clusters of seizure within gain of consciousness
	Joint Royal Colleges Ambulance Liaison Committee (2019).	If IV or IO routes are unavailable, buccal midazolam or rectal diazepam.	After five minutes of seizure onset; After a second seizure occurring within ten minutes of the initial seizure of if lasts over five minutes from onset. A third dose may be given after twenty-five minutes.
	NICE (2022).	Midazolam 0.5 mg/kg buccally in a non-hospital setting or rectal diazepam if unavailable. IV Lorazepam is an option if resuscitation facilities are available.	Not available.
American	Glauser et al. (2016)	IV lorazepam and IV diazepam. Rectal diazepam, IM, buccal or IN midazolam are probably adequate.	Five minutes.

Geography	Source	Medicine, Dose, Route, Findings	Threshold of administration
Studies	Furyk et al. (2017).	IV benzodiazepines. IM or IN if IV route not available.	Not available.
	Au et al. (2017).	Non-IV parenteral midasolam and rectal diazepam as first-line treatement.	
	Chin (2014).	Non-IV parenteral routes of midazolam, clonazepam, and diazepam.	
	Portela et al. (2015).	Midazolam via the IM route would provide a superior therapeutic effect than IV diazepam.	
	Silbergleit et al. (2011).	IM midazolam was as safe and effective as IV lorazepam for seizure cessation in the prehospital setting. Irrespective of the route of administration, midazolam was a safe and effective rescue therapy.	
	Holsti et al. (2010).	IN midazolam group terminated attacks earlier than the rectal diazepam group. Both groups showed similar efficancy with fewer side effects when terminating seizure compared to cumbersome rectal diazepam.	
	Zelcer and Goldman (2016).	IN midazolam took longer to abort seizures when compared to IV diazepam following administration but took less time to abort an episode on arrival at the hospital, given the ease of administration.	
	Humphries and Eiland (2013).	Approval of IN midazolam.	
	Shah et al. (2014).	Non-IV parenteral routes if IV access was difficult.	

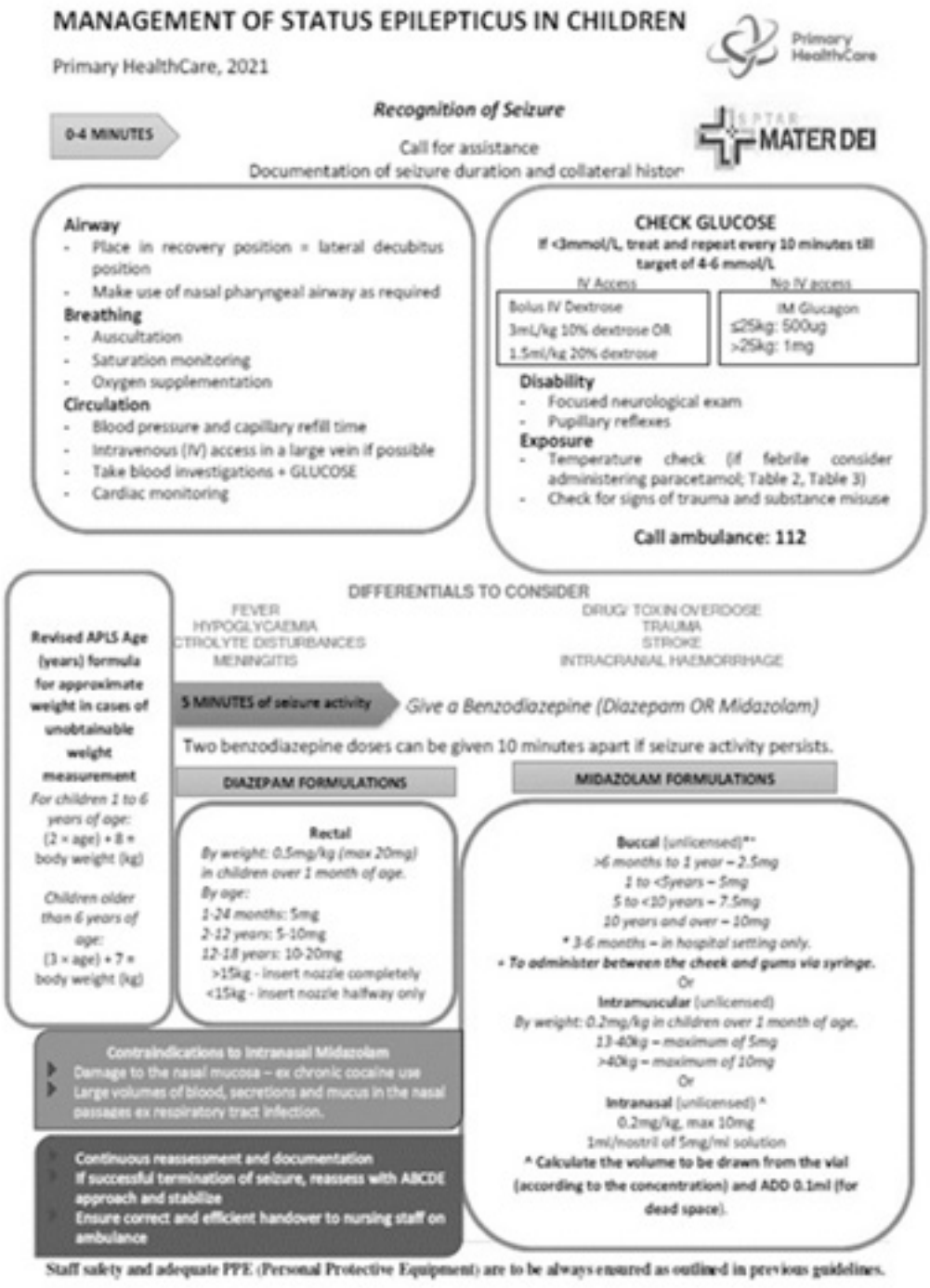

Figure 1: Flowchart delineating management of status epilepticus in children in Primary HealthCare clinics (Santucci, Baldacchino et al., 2021)

The JWG recommended that hypoglycaemia be highlighted earlier in the flowchart. The IV route of benzodiazepine administration was inadequate since resuscitation facilities might not be as readily available should severe respiratory depression develop. The flowchart guidance integrated the Updated Paediatric Life Support (APLS) formulae for approximate weight measurements based on age (Cattermole and Manirafasha, 2021). Reversal of fever was not prioritised as it did not affect seizure outcomes and was omitted.

DISCUSSION

This review included professionals from secondary and primary care backgrounds. The concept framework in Figure 2 outlines the process of providing a clinical guideline managing GPSE.

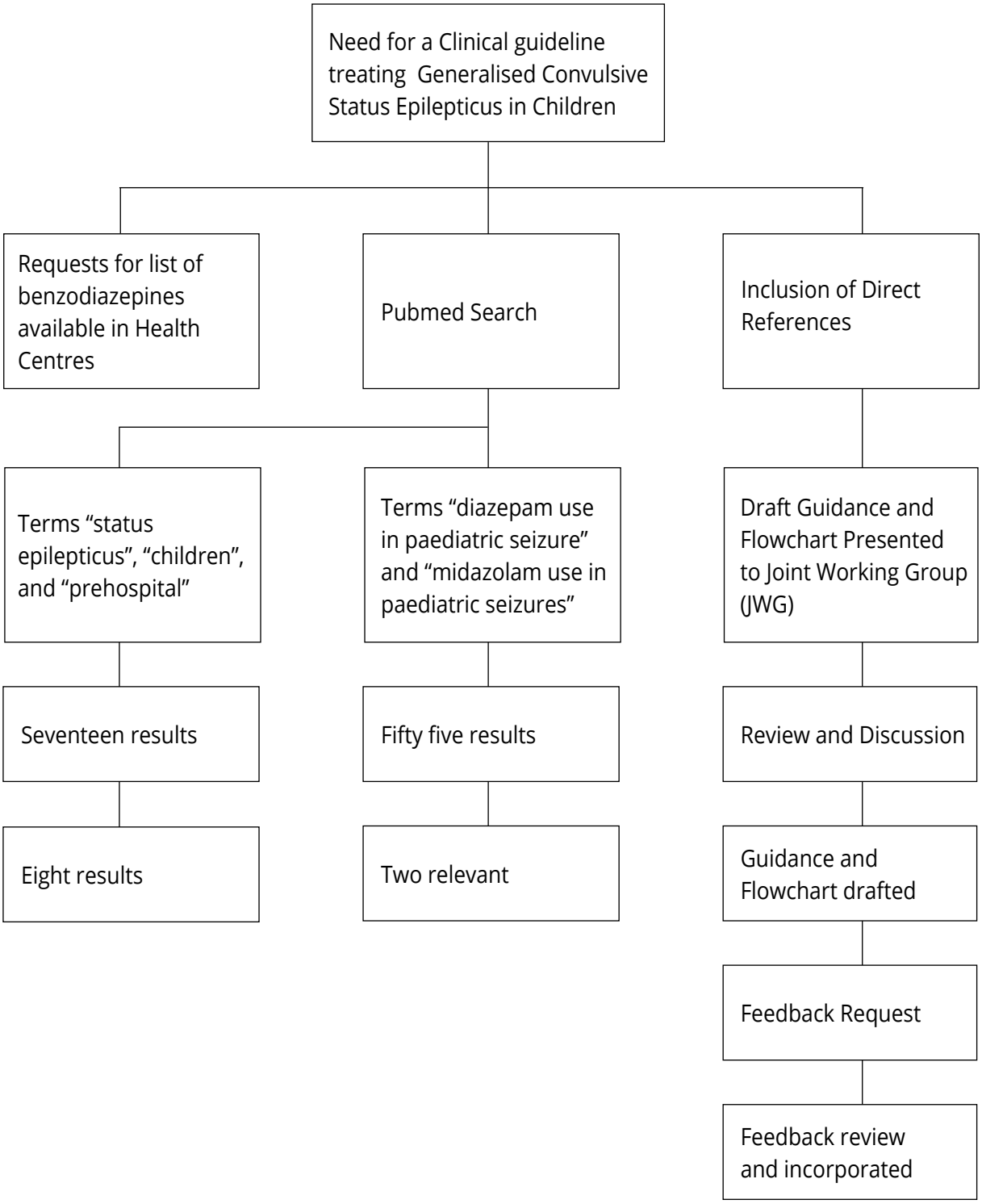

Figure 2: Conceptual framework of methodology

Several national, European and American guidelines addressed GCSE treatment. Oromucosal or IN midazolam, recommended in the national hospital guidance, are currently off-licence. This may change after the introduction of intranasal midazolam to the list of approved European medicines in 2022 (European Medicines Agency, 2022).

Pre-hospital seizure management in all the guidelines focuses on initial cardiopulmonary stabilisation and reversal of secondary causes, followed by benzodiazepine treatment at the five-minute threshold from seizure onset, or when recurrent episodes occur in a short span of time (Hartman et al., 2022, 2019; NICE, 2022; Van de Voorde et al., 2021) – see Figure 1.

CONCLUSION

The creation of a guidance for primary care physicians to treat GPSE involves an interdisciplinary approach involving paediatric neurologists, paediatric trainees, specialist and trainee family doctors, and feedback from professionals who will eventually implement its recommendations.

Healthcare providers may use the benzodiazepines midazolam and diazepam available at health centres to stop prolonged seizures.

When treating children, it is recommended to administer a single total dose using routes such as IM, IN, buccal, or rectal after five minutes of seizure duration. Dosage should be based on the child's weight, and the duration of seizure activity should be timed.

APPENDIX

National Guidance

Once seizure activity has been ongoing for 5-20 minutes and vascular access is obtained, the following drugs may be used as first-line:

- Intravenous (IV) diazepam.
- IV lorazepam.

If vascular access is not available, the following may be used instead:

- Rectal diazepam.
- Buccal midazolam.
- Intramuscular (IM) midazolam.
- Intranasal (IN) midazolam (Agius et al., 2020).

European Guidance

European Resuscitation Council Guidelines 2021: Paediatric Life Support Guidelines

SE presents with an overall mortality of 3%. Increasing evidence shows that early aggressive treatment is safe and associated with less morbidity and mortality. Spontaneous termination is unlikely at five minutes of seizure activity and is recommended as a treatment threshold. Benzodiazepines are the first-line treatment of choice; however, resources and clinical settings determine routes of administration. The guidance also outlines the management of seizures secondary to hypoglycaemic events and metabolic causes (Van de Voorde et al., 2021).

British National Formulary (BNF), 2020

Oromucosal midazolam solution is licensed for children older than three months, whilst IV and IM midazolam is not approved for use in status epilepticus in the paediatric cohort.

The formulary recommends administering diazepam intravenous solution as a slow IV injection over 3-5 minutes. Diazepam rectal tubes may also be used and are the preferred route of administration in neonates (Joint Formulary Committee, 2020).

British Medical Journal (BMJ) Best Practice, 2020

The BMJ recommends that minors be in recovery with a clear airway and administered treatment after 5 minutes of continuous seizure activity or when a cluster of seizures occurs without regaining consciousness. First-line options include rectal diazepam and buccal (dosing according to specialist guidance) or IN midazolam. Evidence suggests that midazolam is more effective in terminating seizures than diazepam (Hartman et al., 2022).

Joint Royal Colleges Ambulance Liaison Committee (JRCALC) Clinical Guidelines, 2019

Drug treatment should start after airway, breathing and circulation (ABC) resuscitation therapies occur while observing physiological endpoints. The JRCALC recommends rescue medication within five minutes of seizure onset as delays hamper effectivity.

Buccal midazolam or rectal diazepam are first-line agents for:

i) seizures lasting more than five minutes,
ii) another seizure lasting more than five minutes, or if it occurs within ten minutes of the end of the first seizure,
iii) three or more seizures lasting less than five minutes but occurring within 1 hour or has not regained consciousness between each convulsion.

Previous domestic administration of anticonvulsants should not preclude treatment administration via other routes. If IV or intraosseous (IO) options are unavailable, buccal or rectal routes may be used.

After twenty-five minutes, a third dose may be given via IV/IO methods.

Children with epilepsy do not need hospital transfer if a convulsion follows the same rite of manifestation. Provision of secondary care is recommended for children:

i) ≤ 2 years old,
ii) with a first febrile convulsion,
iii) receiving > 1 dose of anticonvulsant,
iv) without full recovery.

The repeated rhythmic jerking of the limbs lessens after a tonic-clonic seizure and eventually stops. Post-ictal features mistaken for attacks include brief, irregular jerks of one or more limbs, eye deviation, nystagmus, or noisy breathing. (Joint Royal Colleges Ambulance Liaison Committee, 2019)

National Institute for Health and Care Excellence (NICE), 2022 (Reviewed 2022)

NICE guidelines recommend that parents, guardians, or ambulance crew of paediatric patients administer midazolam 0.5 mg/kg buccally in a non-hospital setting or rectal diazepam if unavailable. IV lorazepam is an option if resuscitation facilities are available (NICE, 2022).

American Guidance

American Epilepsy Society Guideline, 2016

The American Epilepsy Society Guidelines support IV lorazepam and IV diazepam when aborting seizures lasting at least 5 minutes. The guidance noted rectal diazepam, IM, buccal or IN midazolam as probably adequate. It did not support IV lorazepam over IV diazepam. Sublingual lorazepam was less effective than rectal diazepam. IN, IM, or buccal midazolam-controlled seizures were terminated earlier than IV diazepam when the time to establish IV access was included. Initial therapy as a single rescue dose was preferred.

Respiratory depression was the most significant side effect of anticonvulsant treatment. There was no substantial difference in the rate of respiratory depression when comparing midazolam, lorazepam or diazepam delivered via different routes. Child cohorts reported fewer benzodiazepine-related adverse effects than adult groups (Glauser et al., 2016).

Studies

A narrative review conducted by Furyk et al. (2017) reflected the evidence for Australasian pre-hospital SE protocols in children. The study used the contemporary definition of SE as a seizure with a duration of more than 5 minutes, and basic resuscitation requirements were prioritised in a stepwise approach. Two doses of benzodiazepines were first line, preferably given by IV access; otherwise, the IM/IN routes would be indicated. The rectal route was considered socially unacceptable.

Au et al. (2017) systematically reviewed thirteen articles addressing the variance in pre-hospital national or regional guidelines on managing status epilepticus in the paediatric population. Pubmed and Google Scholar databases were searched against keywords in the English language. Manuscripts that fulfilled the author's criteria were considered via the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) 2009 Group statement (Moher et al., 2009). Guidelines (n=6) recommended non-IV parenteral midazolam and rectal diazepam (n=5) as first-line treatment.

Chin (2014) addresses the best method of delivering benzodiazepine therapy to children with GPCSE. By referencing pharmacological experiments on stability, absorption and *in vivo* studies, Chin concludes that non-IV parenteral routes of midazolam, clonazepam and lorazepam appreciate practicality and efficiency. Chin referenced research by Lahat et al. (2000) of 47 patients treated for febrile seizures and compared it with another study that included 70 patients suffering from febrile and afebrile seizures conducted by Mahmoudian and Zadeh (2004). From both these randomised controlled trials (RCTs), Chin determined that although nasal midazolam would not be considered in a young febrile child with small nares and rhinitis, it appeared to work. Chin also remarked that although the buccal route may theoretically lead to aspiration in semi-conscious patients, this was never reported in 600 children administered buccal midazolam in four studies comparing outcomes with rectal diazepam (Ashrafi et al., 2010; McIntyre et al., 2005; Mpimbaza et al., 2008; Scott et al., 1999). In all four studies, rectal diazepam was inferior in terminating seizures within five minutes of administration (Chin, 2014).

Portela et al. (2015) conducted a randomised controlled trial that accepted 36 patients at a paediatric emergency department in Brazil. They aimed to compare the therapeutic efficacy of IM midazolam against IV diazepam. It was concluded that giving midazolam via the IM route would provide a superior therapeutic effect since it was easier to administer and was well absorbed (time from admission to active treatment (min) 2.8 ± 1.5 IM midazolam vs 7.4 ± 4.1 IV diazepam, p=0.001).

The Rapid Anticonvulsant Medication Prior to Arrival Trial (RAMPART) is an American double-blind, randomised, non-inferiority clinical trial comparing IM midazolam to IV lorazepam. RAMPART aimed to witness the outcomes of seizure abortive treatments before arrival at the emergency department after a first dose. IM midazolam was "blinded" with IV or IM placebo, respectively, in 445 patients per treatment group. IM midazolam was as safe and effective as IV lorazepam for seizure cessation in the prehospital setting. Irrespective of the route of administration, midazolam was a safe and effective rescue therapy (Silbergleit et al., 2011).

Holsti et al. (2010) aimed to compare IN midazolam and rectal diazepam when used by carers. They followed up with families after prescribing IN midazolam with a mucosal atomisation device. The IN midazolam group terminated attacks earlier. Both groups showed similar efficacy with fewer side effects when terminating seizures compared to cumbersome rectal diazepam.

Zelcer and Goldman (2016) studied whether there were alternative non-IV methods for seizure cessation in children. In a short review comparing several studies, they concluded that IN midazolam took longer to abort seizures when compared to IV diazepam following administration but took less time to abort an episode on arrival at the hospital, given the ease of administration.

Humphries and Eiland (2013) compare the delivery modes for rectal diazepam and IN midazolam. They addressed cost, pharmacokinetics, time to seizure cessation, ease of use, and safety. Retrospective studies were reviewed, and the authors went further than the initial research question. The manuscript concluded with an overall approval of IN midazolam regarding safety, practicality, efficacy, and cost.

Osborne's narrative review in 2014 oversaw the pre-hospital care following a seizure in the United Kingdom. The MEDLINE database search, supplemented by hand searches, addressed 50 clinical guidelines and studies. The manuscripts that studied benzodiazepine administration included cross-over studies (n=1), randomised control trials (n=7), retrospective reviews (n=7), and prospective observational studies (n=2) (Osborne et al., 2015).

Shah et al.'s study was based on an initial literature review carried out in 2009 and updated in 2012. Several experts from multidisciplinary areas participated in the data gathering. The panel had the input of an evidence-based medicine specialist trade in the constituents in the GRADE method of interpretation. This was followed by a PICO (patient, information,

comparison, outcome) format of evidence retrieval and recommendations. Most of the GRADE evidence quality in this study was low, given few high-quality studies. The panel strongly recommended early seizure treatment and preferred alternative non-IV parenteral routes if IV access was difficult. The lack of neurologist and parent perspectives limited the study. The delay in feedback from Federal sources also resulted in the need to update the literature. The impact on patients and the health systems was not assessed (Shah et al., 2014).

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