Review Article

Benzodiazepines in Status Epilepticus: Use It Correctly for Effective Results

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Abstract

Status epilepticus (SE) is a neurological emergency with a mortality rate influenced by its aetiology and duration. Prompt and effective treatment, from prehospital care (PHC) to emergency department (ED) management, is critical for improving outcomes. Benzodiazepines (BZDs) are the first-line treatment for SE because of their rapid onset, efficacy, and tolerability. The BZDs of choice are intravenous (IV) lorazepam, IV diazepam, and non-IV midazolam. A treatment gap exists owing to the underutilisation of non-IV midazolam in PHC settings. Despite their effectiveness, BZDs are also frequently underdosed or delayed, contributing to refractory SE and poor outcomes driven by unfounded fears of respiratory depression. Adequate BZD dosing has demonstrated benefits in generalised convulsive SE but not in other forms. This review explores the role of BZDs in SE management, associated challenges, and strategies to optimise treatment in the critical early hours.

Keywords: *status epilepticus, benzodiazepines, pre-hospital care, emergency department*

INTRODUCTION

Status epilepticus (SE) is a life-threatening neurological emergency with a mortality rate that can reach 37% and is influenced primarily by its underlying cause and duration. Mortality risk increases significantly, tripling in cases of refractory and super-refractory SE. The incidence of SE in adults ranges from 10-40 per 100,000 per year, and approximately 30-40% of these patients experience reduced functional capacity upon discharge.[1] Thus, prompt and effective treatment is critical, starting from prehospital care and continuing seamlessly in the emergency department (ED).

Benzodiazepines (BZDs) are recommended as the first-line treatment for SE because of their efficacy, tolerability, and rapid onset of action. However, BZDs are effective in achieving seizure control in only approximately two-thirds of SE cases.[2] This review discusses the use of BZDs in SE management, the associated challenges, and recommendations for optimizing SE treatment within the first critical hours.

PATHOPHYSIOLOGY OF STATUS EPILEPTICUS

The management of SE requires an understanding of its underlying pathophysiological basis. One of the well-known hypotheses is receptor trafficking. There are two essential neurotransmitter receptors, i.e., gamma-amino-butyric acid (GABA) and N-methyl-D-aspartate (NMDA), that maintain the check and balance at the neuromuscular junction. At baseline, GABA receptors, which are inhibitory receptors, predominate over NMDA receptors. During seizures and when seizures progress, GABA receptors are internalized, and more NMDA receptors are assembled and mobilized to the postsynaptic membrane, causing excitatory NMDA receptors to accumulate, leading to self-sustaining seizures and resistance to drugs acting at GABA receptors.[3,4]

PHARMACOLOGY AND ROUTES OF DELIVERY OF BENZODIAZEPINES

BZDs terminate seizures by enhancing inhibitory neurotransmission via increased opening of GABA-A receptor-dependent channels, leading to a subsequent increase in chloride conduction and neuronal hyperpolarization, resulting in central nervous system (CNS) depression.[5]

BZDs can be administered through various routes during a seizure and SE. Intravenous (IV) administration remains the gold standard when

vascular access is available, as it enables the fastest cessation of seizure activity. For example, peak plasma levels are achieved approximately 30–60 minutes following intramuscular (IM) injection, 10–45 minutes with rectal administration, 45 minutes with intranasal administration, and only within 5 minutes after IV administration.[6] However, establishing IV access may be challenging, particularly in actively seizing patients or in prehospital settings.[7] Consequently, alternative routes, including intranasal, buccal, rectal, and intramuscular (IM) administrations, have been extensively studied. Many of these routes are also accessible for use by non-medical personnel in emergency situations.[6]

MANAGING STATUS EPILEPTICUS IN PREHOSPITAL CARE

Malaysia's prehospital care (PHC) system is unique and tailored to meet diverse medical needs swiftly and effectively. At one end of the spectrum is basic transport, or "scoop and run", where the primary goal is rapid transportation to a healthcare facility. Government agencies such as firefighters and the Civil Defence Force or non-governmental organizations such as the Malaysian Red Crescent Society and St. John Ambulance Malaysia usually provide this service. On the other hand, advanced life support is provided by highly trained paramedics capable of offering advanced care, including administering medications in prehospital settings.[8]

For the PHC management of SE, Malaysian guidelines recommend the administration of 0.2 mg/kg buccal or IM midazolam or rectal diazepam with age-specific dosing.[9] These routes are preferred over parenteral methods because of their ease of administration and reduced preparation time. The American Epilepsy Society also recommends the use of BZDs (IV lorazepam, IV diazepam, and non-IV midazolam) as first-line BZD in PHC settings.[10] Although paramedics are trained to administer both diazepam and midazolam, they frequently choose rectal diazepam because it comes in a pre-filled 5 mg tube, eliminating the need for IV access. Both medications are regulated under the Poisons (Psychotropic Substances) Regulations 1989, which require locked storage and meticulous documentation of usage.[11]

Consequently, these essential medications are not routinely stocked in ambulances and are only carried out for suspected or active seizure cases. According to a recent national survey, IV diazepam was available in 93.3% of district hospitals and 80.5% of tertiary hospitals for PHC management of seizures. Additionally, buccal and intranasal midazolam was only available in a limited number of tertiary and university hospitals (14.6% and 4.9%, respectively) in Malaysia.[12]

Studies have shown that early initiation of SE treatment by paramedics reduces the number of patients with persistent seizures on ED arrival and intensive care admissions for refractory SE. Traditionally, diazepam has been the agent most frequently used by emergency medical services (EMSs) to treat patients with seizures. In the last decade, midazolam has been adopted in EMS because of its rapid absorption via the IM and transmucosal routes compared with diazepam or lorazepam and has excellent stability and safety profiles.[13,14]

Two landmark trials have evaluated the administration of BZDs for the treatment of SE in prehospital settings. The Prehospital Treatment of Status Epilepticus (PHTSE) Trial 2001, which was a prospective, randomized, double-blind, placebo-controlled study, revealed that SE was terminated upon ED arrival more often in patients treated with BZDs (lorazepam, 59.1% or diazepam, 42.6%) than in those receiving placebo (21.1%) (p=0.001). Rates of respiratory or circulatory complications were lower in the BZD groups (Lorazepam 10.6% vs. Diazepam 10.3% vs. Placebo 22.5%).[15]

A decade later, the Rapid Anticonvulsant Medications Prior to Arrival Trial (RAMPART) 2011, a double-blind randomized non-inferiority clinical trial evaluating the efficacy of IM midazolam versus IV lorazepam in the treatment of SE by paramedics in PHC, was published. The team reported that seizures were aborted without rescue therapy more often in the IM midazolam group than in the IV lorazepam group (73.4% vs 63.4%, p<0.001 for both noninferiority and superiority).

Table 1: The use of benzodiazepine in prehospital settings

Benzodiazepines	Routes	Dosages
Midazolam	Buccal	0.2 mg/kg (max 10 mg)
	IM	0.2 mg/kg (max 10 mg for those > 40 kg, 5 mg for 13-40 kg, single dose)
Diazepam	Rectal	0.5 mg/kg (2-5 years old), 0.3 mg/kg (6-11 years), 0.2 mg/kg (12 years and above)
Lorazepam	IV	0.1 mg/kg/dose (max 4 mg); or 2 mg for paediatric patients (13-40 kg)

Table 2: The use of benzodiazepines in the emergency department

Benzodiazepines	Routes	Dosages	Pitfalls
Diazepam	IV	0.2 mg/kg (max 10 mg per dose) over 2 to 5 minutes. Give IV undiluted	Too low and too slow in administering BZD
Diazepam	Rectal	0.2 -0.5 mg/kg (up to 20 mg per dose); onset 2-10 minutes	
Lorazepam	IV	0.1 mg/kg (up to 4 mg per dose)	

In terms of the need for intubation and recurrence of seizures, both treatment groups were similar (14.1% vs 14.4%; 11.4 vs 10.6%).The median time to administer active treatment was significantly shorter with the IM route than with the IV route (1.2 vs. 4.8 minutes), but the median time from active treatment to cessation of seizures was shorter with the IV route than with the IM route (1.6 vs. 3.3 minutes). The time saved by using the IM midazolam appears to offset the delay in the drug's onset of action.[16] Nevertheless, a significant treatment gap exists owing to the underutilisation of non-IV midazolam.[12]

MANAGEMENT OF STATUS EPILEPTICUS IN THE EMERGENCY DEPARTMENT

BZDs also remain the first-line treatment for SE in the ED. However, careful assessment of the patient's physical appearance, respiratory status, and circulatory stability is essential, especially if BZDs were previously administered during PHC. This evaluation guides decisions on whether to administer a second dose of BZDs; initiate other anti-seizure medications (ASMs), such as phenytoin, sodium valproate, or levetiracetam; or consider intubation. Optimizing the dose of BZDs is crucial to ensure therapeutic efficacy prior to introducing ASMs.

Lorazepam is the most commonly used and preferred BZD in the ED because of its prolonged duration of action.[17] However, the BZD of choice in most ED settings in Malaysia is diazepam. The initial dose of IV diazepam is undiluted at 0.2 mg/kg (up to 10 mg per dose) over 2 to 5 minutes.[17] The second dose or repeat dose can be given once after 10 to 20 minutes if seizures continue.[9] The maximum dose of diazepam used is 20 mg/day. Medication timing and dosing are pillars of emergent therapy; delaying administration may lead to refractory SE, poor clinical outcomes, and neuronal death.[17] Too low and too slow are not known in the practice of administering BZDs in SE.[1,2] The Established Status Epilepticus Treatment Trial (ESETT) revealed that less than one-third of patients received a first dose of BZDs that met the minimum guideline recommendations.[1] Fear of respiratory depression is baseless, as the guideline-recommended doses of BZDs have been shown not to be a safety concern.[2] Sufficient BZD dosing was beneficial in generalised convulsive SE but not in other forms of SE.[18]

BENZODIAZEPINE RESISTANCE IN STATUS EPILEPTICUS

A few critical factors have been identified for causing BZD resistance in SE management, namely, underdosing of BZDs, delayed administration of BZD or duration of seizures, and the underlying aetiology causing SE.[2,19] Studies have shown that the BZD dose given is almost always too low.[20] The anticonvulsant potency of BZD can decrease by 20 times within 30 minutes of self-sustaining SE. The response to BZDs is generally poor in SE secondary to acute brain injury, even when these drugs are given promptly.[21]

Concerns regarding BZD overdosing are often based on myths, such as the belief that BZDs induce respiratory depression or that lower doses are equally effective. SE itself can lead to respiratory depression, and studies have shown that recommended BZD doses are not associated with an increased need for respiratory support.[22] In fact, treatment with subtherapeutic BZD doses has been linked to a greater risk of recurrent seizures. Patients receiving higher doses of midazolam were significantly less likely to require rescue therapy. In cases of generalized convulsive SE, BZD underdosing has been associated with prolonged ventilation duration, extended ICU stays, and increased overall hospital length of stay.[22,23]

CONCLUSION

The timing and dosing of benzodiazepines (BZDs) are fundamental to effective seizure cessation in SE patients. The time-dependent development of pharmacoresistance, which can lead to treatment failure, is a significant contributor to the high morbidity and mortality associated with SE. Emergency doctors and paramedics must understand the importance of early administration of BZDs at optimal doses. IM midazolam should be strongly advocated for SE management in prehospital care settings, as it allows timely intervention and can improve patient outcomes.

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