



Published: March 31, 2024

Citation: Seinfeld S, 2024. Pre-Hospital Treatment of Seizures: A Review of Out-of-Hospital Treatment Options for Seizure Emergencies, Medical Research Archives, [online] 12(3).

<https://doi.org/10.18103/mra.v12i3.5161>

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DOI

<https://doi.org/10.18103/mra.v12i3.5161>

ISSN: 2375-1924

Pre-Hospital Treatment of Seizures: A Review of Out-of-Hospital Treatment Options for Seizure Emergencies

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ABSTRACT

This article reviews the out of hospital treatment options for seizure emergencies. This review article includes recently approved out of hospital options, therapies currently being studied and evidence to support use of current routes administration. The pre-hospital treatment of seizure emergencies helps to prevent consequences of these seizures. This includes seizure clusters and prolonged seizures. The potential routes of administration, medication options and side effects of each treatment are reviewed. This article also addresses the current gaps in treatment and the areas where further research is needed. The need for a seizure action plan to allow rescue medication to be properly used is comprehensively discussed. Early and adequate treatment of seizure emergencies is necessary to prevent consequences. Since most seizure emergencies occur outside of the hospital, creating a seizure action plan is important to successfully utilize out of hospital treatments. Educating patients and families regarding treatment options is necessary for all patients with epilepsy. It is critical that patients and families are aware of the treatment options, and when and how to correctly use them.

Keywords: seizure emergency; seizure cluster; seizure treatment; status epilepticus; pre-hospital; acute repetitive seizure; epilepsy

Introduction

Epilepsy is one of the most common neurological disorders. There are an estimated 70 million people affected worldwide with epilepsy, with more than 3 million in the United States¹. Seizure emergencies in these patients can be prolonged seizures, status epilepticus or acute seizure clusters. Seizure clusters, also known as acute repetitive seizures, occur in a subgroup of patients with intractable epilepsy². Close to half of patients with active epilepsy will experience seizure clusters³. Acute seizure clusters can occur in the inpatient and outpatient setting and should be treated to prevent consequences. There was a review done in 2015 that reported that the prevalence of seizure clusters ranged from 13% to 76% for outpatient studies and from 18% to 61% for inpatient monitoring studies². Seizure clustering is an indicator of drug resistant epilepsy⁴, and between 30%-40% of individuals with epilepsy are considered drug-resistant^{5,6}. It is important to use a broad definition of seizure cluster to allow patients to receive individualized treatment based on their own baseline of seizures. Although acute seizure clusters are characteristically seen in those that have drug resistant epilepsy, the fear of experiencing a seizure emergency is experienced by everyone with the diagnosis of epilepsy.

Acute seizure clusters are a seizure emergency that can evolve into status epilepticus and require early and adequate treatment. Early treatment of seizure emergencies improves outcome and decreases associated morbidity and mortality. Studies have found that pre-hospital treatment of seizure emergencies can lead to a decrease in seizure duration and incidence of respiratory complications^{7,8}. Any type of seizure can occur in a cluster, but the cluster becomes a seizure emergency when the seizure duration or frequency increases from a person's baseline. If a person does not fully recover between individual seizures within a cluster, then it becomes an emergency and is considered status epilepticus. It has been proven that the terminal seizure of a cluster is longer in duration than intra-cluster seizures⁹.

If a seizure emergency is recognized, and a treatment plan is in place, acute seizure clusters can be treated outside of the hospital setting. A rescue plan should be made for all epilepsy patients, and this is facilitated by the increased availability of at home rescue medications. It is crucial to treat acute seizure clusters to prevent consequences such as injury, hospitalizations, and progression to status epilepticus. In the United States pre-hospital emergency services and treatments vary by region, and the available

treatment of a seizure emergency can vary from hospital to hospital in the same community⁸. Studies have shown that rescue medications are frequently underutilized, even though it has been proven that the use of rescue medication is associated with fewer injuries and emergency department visits¹⁰.

Treatment options

The treatment of seizures with adequate doses of an appropriate medication is essential. There is often a delay of treatment. The reason for the delay has been studied, but no solution has been found and there continues to be a delay of treatment seen. It is important to treat seizure emergencies early and adequately to help prevent consequences⁸. When choosing a rescue medication it should be broad spectrum, have an intermediate duration of action, and act rapidly to stop the seizures¹¹. Additionally, the route of administration becomes important. The first line of treatment is the provider prescribing the medication to be used by a non-medical professional. This makes the ease of use, safety, low inter- and intra-patient variability, and shelf life of the medication prescribed important¹¹. At this time, all FDA approved and available out-of-hospital treatment options utilize benzodiazepines, which are the first line treatment for seizure emergencies. The recent increase in FDA approved rescue medication options for out of hospital treatment of seizure clusters will decrease off label use of medications and help to standardize patient treatment.

A study of adult patients with seizure clusters showed that fewer than half of them were prescribed at least one benzodiazepine rescue medication¹². This study was prior to recent FDA approval of multiple intranasal (IN) formulations, which has increased available options for patients. Treatment goals of a seizure emergency include stabilizing the patient to ensure adequate brain oxygenation and terminate seizures to prevent complications. Patient age, seizure semiology and personal preference of patients/caregivers will be important factors when choosing a rescue medicine. Numerous studies have been performed on the FDA approved medications, which demonstrates they are comparable with regards to their efficacy and/or time to effectiveness.

The evaluation of different routes of administration is not recent. A systematic literature review published in 2016 suggested that non-rectal and non-IV benzodiazepine formulations provide equal or improved efficacy and safety outcomes compared with rectal and IV formulations for the treatment of seizure emergencies¹³. The study

demonstrated time to seizure termination, seizure recurrence rates, and adverse events were generally similar among different routes of medication administration, but non-rectal administration led to improved patient and caregiver satisfaction. At the time of this publication, only a rectal formulation was FDA approved for out of hospital treatment of seizure emergencies.

The availability of a medication that can be administered outside of a hospital setting is important for people with epilepsy to prevent the morbidity and mortality of epilepsy. It has been found that the main predictor for having a rescue medicine is having a prolonged seizure in the past¹⁴. Acute seizure clusters can evolve into status epilepticus and can result in respiratory distress. Families need to be educated that rescue medication is not just for prolonged seizures, but also for acute seizure clusters. It is important for providers to educate families on when and how to use the medication, and prescribe the correct dose of medication. It is essential to continue to update the weight based dosage of medications for children since children can have significant weight changes over short periods of time. First line treatment for seizure emergencies is a benzodiazepine, but the choice a provider needs to make is what route of administration is best for the patient. These medications can be administered via rectum, intranasal, buccal or oral/sublingual routes. There is data evaluating the use of the alprazolam, diazepam, lorazepam, clonazepam and midazolam.

INTRANASAL

Intranasal Diazepam

The most recently FDA approved medication is IN diazepam, which was approved January 2020. The brand, VALTOCO[®], is indicated for use for the acute treatment of seizure clusters and acute repetitive seizures for children 6 years and older¹⁵. The dosing is similar to rectal formulations 0.3 mg/kg for children 6 to 11 years and 0.2 mg/kg for children 12 and older. Based on weight and age, the dose may require 1 or 2 nasal spray devices to administer the rescue dose. It is available in 5 mg, 7.5 mg, and 10 mg strengths. This branded medication has a proprietary formulation including Intravail[®], which increases bioavailability and is non-irritating¹⁵. Intravail, an absorption enhancer, provides therapeutic nasal dosing of intranasal diazepam with comparable bioavailability to rectal diazepam with no damage to the nasal mucosa¹⁶.

This formulation of diazepam has the potential to be self-administered. Patients and caregivers from

the phase 3 safety study were surveyed and were overall satisfied with this product and were comfortable using the product¹⁷. It has been shown that for all routes of administration the onset of diazepam absorption is rapid, but there is variability in the bioavailability of diazepam when comparing the intranasal route to the rectal route¹⁶.

Intranasal Lorazepam

Although not commercially available, and not typically prescribed, there have been multiple studies that have examined the use of lorazepam as an IN formulation. A study published in 2006 found IN lorazepam to be an alternative option for the treatment of prolonged seizures¹⁸. The study compared IN lorazepam with intramuscular paraldehyde. Use of paraldehyde has been replaced by more effective medications. This study did confirm the cardio-respiratory safety of IN lorazepam. In 2011 a study was published comparing IV lorazepam to IN lorazepam and found them to be equally effective in children¹⁹.

Intranasal Midazolam

In 2019 IN midazolam was the first out of hospital rescue medication to be FDA approved in more than 2 decades ago. The phase III, randomized, double-blind placebo-controlled trial results were published in 2019. The study found that IN midazolam was safe and was superior to placebo in providing seizure control for patients experiencing seizure clusters in the outpatient setting²⁰. NAYZILAM[®] nasal spray is used for treatment of acute seizure clusters in children 12 years and older²¹. This medication has been well studied and is safe for intermittent use for acute treatment of patients experiencing seizure clusters. This medication is well tolerated over an extended period and maintains its efficacy without the development of tolerance²². This route of administration is associated with a T_{max} of 10.3 minutes and a half-life of 3.25 hours²³. This formulation also has the potential to be self-administered.

Previously IN administration of the injectable solution of midazolam was found to be effective for patients with acute seizures, but its use was not standardized, and availability varied. This was one of the most frequently used off label rescue treatment for seizure emergencies prior to the approval of Nayzilam[®]. The IV solution has a low pH and can cause significant irritation, which was problematic for patients who were receiving the medication when not actively having a seizure, especially pediatric patients. Relatively large volumes of midazolam were required, and

positioning was extremely important to prevent drug loss to the environment²².

A study published in 2020 evaluated the use of IN midazolam nasal spray in patients with epilepsy who were admitted to the epilepsy monitoring unit (EMU) for seizure characterization and pre-surgical evaluation²⁴. This randomized study showed the IN midazolam was well tolerated and had clinical meaningful effect. The importance of this study was that it evaluated this medication in a high risk population. Although, this study didn't show statistical significance compared to a placebo, other studies have demonstrated effectiveness of IN midazolam in the EMU compared to IV lorazepam for seizure clusters²⁵.

RECTAL

Rectal Diazepam

Rectal Diazepam gel was the first FDA approved medication for the treatment of repetitive seizures outside of the hospital. This was approved in 1997, and changed the paradigm of out of hospital management of seizure emergencies. Until 2019, this was the only FDA approved medication that providers could prescribe to patients to treat seizure emergencies. There are multiple limitations to this route of administration. This medication can't be self-administered, and is not socially appropriate for older children and adults. Furthermore, use of rectal medication for acute seizure clusters can be uncomfortable, since the treatment may occur while the patient is not actively having a seizure.

The route of administration is associated with a T_{max} of 10-45 minutes and a half-life of 21-70 hours²⁶. This shows that rectal diazepam is not as fast acting as other routes of administration, and its longer half-life can lead to prolonged sedation after use. It is a stable formulation, which makes storage easier. Rectal diazepam gel is stable under the temperature and light exposure conditions found in ambulances, including a freeze-thaw cycle, hard freeze (-30°C for 72 hours), and extreme light exposure²⁷.

BUCCAL

Buccal Diazepam

Diazepam buccal film (DBF) is currently in development for treatment of patients experiencing increased seizure activity. In both adults and children, the safety, tolerability, and usability of this medication in the outpatient setting has been studied and published²⁸. The new drug application for the buccal diazepam film, Libervant™, to treat patients between 2 and 5 years of age was accepted by the FDA in 2023. The indication is for

the acute treatment of intermittent, stereotypic episodes of frequent seizure activity. This medication is easily administered by both patients and caregivers, and the packaging of the small, thin DBF film can be easily carried which facilitates patient compliance²⁹. The film is placed in the buccal mucosa inside the cheek, and the diazepam is absorbed trans-buccally and also swallowed. The study showed that there was ease of administration with this medication and the levels of diazepam that were similar to the rectal gel formulation of diazepam²⁹.

Buccal Midazolam

This product is not commercially available in the United States, but it has been available in Europe since 2011³⁰. The pharmacokinetics of buccal midazolam have been well studied. One of the early studies published in 1998³¹, using healthy volunteers found a rapid increase in venous blood concentrations for the first 20-30 minutes following treatment. Scott et al.³² published a study in 1999 that compared buccal midazolam in children and adolescents presenting with prolonged seizures to rectal diazepam. The results of this showed equal efficacy between groups. Other studies have also compared buccal midazolam to rectal diazepam, and it has been found more effective in children and easier to use³³. This 2005 study was a multicenter, randomized controlled trial in the emergency department and included children aged 6 months and older presenting to hospital with active seizures and without intravenous access³³. In another study, performed in an outpatient residential epilepsy center, rectal diazepam and buccal midazolam were compared. In this study 100% of the nursing staff and 86% of patients preferred the oral administration of the medication³⁴.

ORAL/SUBLINGUAL

Oral/Sublingual clonazepam and lorazepam

Prior to the recent FDA approval of IN formulations for treatment of seizure emergencies, oral medication had been frequently prescribed for off-label use. Typically clonazepam and lorazepam were used because they have dissolving tablets available. There is evidence for both children and adults, that there is inter- and intra-subject variability with regards to the effective dose and speed of onset of sublingual lorazepam³⁵⁻³⁷. The variability in absorption when using fast dissolve tablets can lead to decreased effectiveness³⁶. A group of 52 adult patients prescribed sublingual lorazepam at an epilepsy center were highly satisfied with this treatment option, and it was found to be effective with no sedation complications with doses up to 2 mg³⁸.

INTRAMUSCULAR

Intramuscular Midazolam

IM midazolam has been well studied and can be used outside of the hospital setting, although this route is not used by non-medical professionals since the use of an auto-injector has not been approved for in-home use. In 2012, the first results of the RAMPART study (Rapid Anticonvulsant Medication Prior to Arrival Trial) were published³⁹. This large double-blind randomized study, including both children and adults, compared IM midazolam with IV lorazepam. For this intention to treat study, an auto-injector device was designed for rapid IM injection of midazolam. The RAMPART study found that patients treated with IM midazolam were more likely to have stopped seizing at the emergency department and were less likely to require hospitalization or admission to an intensive care unit⁴⁰. The superiority of IM midazolam over IV lorazepam in RAMPART supports that IM midazolam is a good option for the prehospital treatment of status epilepticus by paramedics. Although the study was evaluating the treatment of status epilepticus, if left untreated acute seizure clusters can progress into status.

PULMONARY

Pulmonary Delivered Alprazolam

Alprazolam delivered via the Staccato^R breath-actuated device is currently being studied and is not commercially available. It has a unique pulmonary delivery system that deposits the drug deep into the lung via inhalation. This medication and delivery system has been used for other indications. The results of the randomized phase 2b efficacy study was published in 2023⁴¹. This product is being developed as a potential therapy for rapid epileptic seizure termination. The proof-of-concept for use of staccato alprazolam was published in 2019⁴². The study evaluated multiple doses of pulmonary delivered alprazolam in photosensitive epilepsy patients and was found to rapidly suppress epileptiform activity⁴². The adverse event profile of pulmonary delivered alprazolam is similar to the adverse events seen when alprazolam is used for other indications⁴¹.

Medication side effects

First line treatment options for acute seizure clusters are benzodiazepines, and they all have similar side effect profiles. Seizures rapidly become self-sustaining and pharmaco-resistant secondary to multiple mechanisms. These include alterations of GABA-A receptor physiology and pharmacology, losses of synaptic GABA-A receptors that mediate benzodiazepine action and increases in the surface expression of excitatory receptors⁴³. Early

treatment with a benzodiazepine, before this intractable and deleterious sequence of events occurs, is our best treatment strategy⁴³. Chin *et al.*⁴⁴ showed that respiratory depression can be observed after two or more dosages of a benzodiazepine, which has been confirmed in other studies⁴⁵.

If a medication is going to be used for the management of seizure emergencies, then it requires a rapid onset of action, able to be used in small volumes, have a wide therapeutic index and duration of action that is adequate⁴⁶. Various at home formulations, such as buccal midazolam and rectal diazepam, have been compared and had a similar incidence of respiratory depression³³. The route of administration should be considered for each patient, since it can be associated with additional side effects. For example, the IN formulations can all be associated with nasal discomfort, throat irritation, and runny nose.

Discussion

Identifying patients that are at high risk for seizure clusters, and providing them with formal action plans, can help improve the outcomes in this group of epilepsy patients^{47,48}. Although there can be barriers to implementing a seizure action plan, it can improve education about epilepsy and seizure emergencies⁴⁹. There are numerous medications that are FDA approved for use by non-medical professionals, and seizure action plans should describe the details of what medication should be used to treat a seizure emergency, how to use the medication and when to use them. Although seizure action plans are beneficial for all patients with epilepsy, approximately 70% of patients with epilepsy do not have a seizure action plan⁵⁰. It is important to prescribe these available medications to help prevent consequences of seizure emergencies. Known risk factors associated with seizure clustering are extratemporal epilepsy, remote symptomatic epilepsy, and a history of convulsive status epilepticus⁴. Seizure clusters can lead to status epilepticus, which leads to increased health care utilization. This has a negative impact on the quality of life of both patients and caregivers. By preparing families to treat these patients early and adequately, we can avoid progression to status epilepticus and reduce emergency room visits. Rescue medications are underutilized.

The accessibility of a rescue medication is important, and its access has expanded with recent FDA approvals, but families must be trained on how to use the medications. If a family or patient is uncomfortable administering the medication, then it will not be as effective. A study in 2017 found that

most patients with epilepsy are prescribed rescue medication, but only 61% reported receiving training¹⁴. With the increased number of available products, the number of patients with rescue medication should continue to increase. Results from an observational study showed that only 28% of patients with a recent history of seizure clusters had a rescue medication prescription, and the most frequently prescribed medication for rescue was oral lorazepam¹⁰. Members of the Pediatric Epilepsy Research Consortium published a study in 2019⁵¹, and clonazepam orally disintegrating tablets were the most frequently used medication to treat seizure clusters, except in younger patients. Future studies are needed since the availability of rescue treatments has changed, which should lead to a change in the prescribing preference for providers.

Reasons for delayed treatment are unclear, and we know that most seizures occur outside of the hospital setting, so a rescue medicine available at home leads to improved outcome and a sense of control for individuals that are aware of their seizures. To be effective providers need to make sure that adequate doses of rescue medication are prescribed^{7,8,12,52}. There has been a growth of available rescue medications, and there are multiple options that are safe, efficacious, and highly satisfactory to the patient and their caregivers. This results in more opportunities for physicians and patients to identify treatment options tailored to patient specific needs. This results in increasing treatment adherence and is beneficial to patients¹³. There are continued studies of not only novel formulations, but expansion of the routes of administration. Providers need to utilize these available resources, which will lead to a change in the standard of care.

In addition to the inaccuracy associated with seizure self-reporting, there are other factors that contribute to suboptimal addressing of seizure clusters during the patient-physician encounter. One of the most important factors is the gap in communication between patients, caregivers and

physicians. Since there is no standard definition for seizure clusters, the patients and physicians might be referring to different entities by using the word “clusters” which might result in confusion. A survey of patient opinions based on internet forums revealed that sometimes patients felt lack of understanding and acknowledgement by their physician regarding their concern about seizure clusters⁴⁷. Seizure action plans need to be well designed and able to be followed by both experienced and inexperienced individuals. It is known that protocols improve outcome, and the increased commercial availability of out of hospital treatments can change the rescue treatment paradigm for many patients with epilepsy. Using all the information available in a patient’s seizure diary will help providers to gain information regarding seizure clusters⁵³. The acceptance of a standard definition of seizure clusters is necessary to allow adequate treatment, recognition and future studies³.

Conclusion

There are various options to treat seizure emergencies outside of the hospital. The different medications and the diverse routes of administration enable providers to create an individualized rescue plan for patients. There is continuing research that is evaluating the efficacy and safety of other options to treat seizure emergencies in the pre-hospital setting. The acute treatment of seizure emergencies will substantially improve with the increased availability of approved out-of-hospital therapies. There are still unmet needs, and additional studies are required to determine the most efficacious, maximally safe, and best tolerated treatments. Information can be analyzed from the expanded group of patients using rescue medications. Standardizing definitions and standardizing seizure action plans is an important next step. The standardization will allow providers to optimize treatment for patients of various ages with differing requirements.

Conflict of Interest

None

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