


Seizure clusters

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ABSTRACT

Acute repetitive seizures, also called seizure clusters, are common phenomena in patients with epilepsy. They are a burden on patients and their caregivers and may be very disruptive to the patients' lives. They may progress to prolonged seizures or status epilepticus if they are not aborted as soon as possible. However, their definition, recognition, and classification still suffer from a lack of consensus among healthcare professionals in the field. This review aims to shed light on various aspects of seizure clusters with particular attention to their treatments.

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Introduction

Epilepsy is one of the most common neurological diseases with 70 million people in the world suffering from it and around 4.6 million developing the condition each year^{1–3}. In the US, around 150,000 people are diagnosed with epilepsy each year⁴. Many people with epilepsy (PWE) report seizures which occur in close successions; these are termed seizure clusters (SC), acute repetitive seizures (ARS), or crescendo seizures. These repetitive seizures are not uncommon and place a burden on patients and their caregivers^{5,6}. These tightly grouped seizures represent an alarming clinical condition, and if not treated vigorously and efficiently, may lead to status epilepticus (SE), a very serious life-threatening condition⁷.

The definition of SC has been very actively debated for more than two decades. While no definition has been universally accepted, it is generally agreed that a seizure cluster represents closely grouped seizures over minutes to two days, representing an increase in seizure frequency compared with baseline. A very similar phenomenon to SC called the “rebound effect” is manifested by an increased occurrence of epileptic seizures following an abrupt withdrawal of Antiseizure Medications (ASMs); as in SE, the possible underlying mechanism of this phenomenon is a defect in neurosteroidogenesis, especially allopregnanolone (AP), a neuroactive steroid increasingly considered as a relevant modulator of neuronal activity. Significantly lower AP levels were found in the CSF of patients suffering from SE^{8–10}.

Many recent studies have addressed treatment and outcome of SC^{11–13}. In the current narrative review, we will

discuss the proposed definitions of SC, their prevalence, and their management and outcome.

Epidemiology

Patients with epilepsy (PWE) may experience acute repetitive seizures or seizure clusters. Seizure cluster is defined as a closely grouped series of seizures. There is no universally accepted definition for a cluster of seizures in PWE and previous studies have used various definitions, including two to four seizures per < 48 h, 3 seizures per 24 hrs, three times the baseline seizure frequency, etc.^{14–19}. Therefore, it is difficult to accurately estimate the prevalence of seizure clusters; prevalence of seizure clusters depends on the definition used.

However, previous studies have indicated that seizure clustering in PWE is a relatively common phenomenon with a reported prevalence ranging from 10% to 50% in some previous studies^{19–23}. In animal models of epilepsy (Temporal lobe Epilepsy), this phenomenon is well known, more defined and consistent^{24,25}. Prevalence of seizure clusters is also dependent on the study population and study design. In one previous study, 43% of PWE, who were keeping a seizure diary, met the clinical definition of 3 or more seizures in 24 hrs²⁰. In a study of PWE in an outpatient setting, the prevalence of seizure clusters (3 or more seizures in 24 hrs or 3 times the baseline frequency) was 15%²³. Another population based study in Finland identified seizure clusters (3 or more seizures in 24 hrs) in 22% of PWE¹⁶. However, many previous studies on seizure clusters have been performed in tertiary epilepsy centers^{21–23,26}, where patients with drug-

resistant epilepsy and uncontrolled seizures are particularly more prevalent; the reported prevalence from these studies might be an overestimation¹⁹.

Some other studies have definitely overestimated the prevalence of seizure clusters. In the inpatient setting of epilepsy monitoring units antiseizure medications (ASMs) are often temporarily reduced or even withdrawn, that can trigger seizure clusters ("rebound effect")^{10,15}. The prevalence of 3 or more seizures in 24 hrs in patients undergoing pre-surgical evaluation and video-EEG monitoring was 61.5% in a previous study²⁶. On the other hand, one retrospective chart review study with no structured interviews to identify seizure clusters, significantly underestimated the prevalence of seizure clusters (with only 3% of PWE having seizure clusters)²⁷.

On the other hand, some PWE are intrinsically at higher risk to developing seizure clusters than others. Multifocal epilepsy, symptomatic generalized epilepsy, frontal lobe epilepsy, and mesial temporal sclerosis, are some of the known risk factors for experiencing episodes of seizure clusters¹⁹. In one previous study, patients with symptomatic generalized epilepsy ($n = 240$) were more likely to develop seizure clusters (27.1%) than patients with focal epilepsy ($n = 2911$; 16.3%; $p < .001$; OR = 1.91) or patients with idiopathic generalized epilepsy ($n = 632$; 7.4%; $p < .001$; OR = 4.62; logistic regression, univariate analysis, $p < .05$)²³. Furthermore, sleep deprivation, stress, fever or illness, missing or changing ASMs, alcohol, and menstruation may trigger seizure clusters in some patients¹⁹.

Future well designed prospective population based studies are needed to clarify the prevalence of seizure clusters. In designing such studies all confounding variables such as epilepsy syndrome (e.g. idiopathic generalized epilepsy vs. focal epilepsy vs. symptomatic generalized epilepsy), drug regimen, age, sex, life style, etc., should be considered meticulously.

Management of seizure clusters

Seizure clusters can be very disruptive to the patient and the family, particularly when they are severe and have had a history of progression to prolonged seizures or status epilepticus. They may be a constant source of anxiety to the patient and the family. They may prevent travel for fear of a cluster occurring where medical care is not immediately available. They may force a family member to remain at home with the patient for monitoring. They may cause missed school days, missed work, and loss of income. When they cannot be controlled at home, they result in emergency room visits, which are costly and time-consuming. An effective outpatient treatment is needed, one that caregivers can administer quickly and easily to stop seizure clusters early outside the hospital setting.

The treatment of seizure clusters must be individualized. It must depend on the type, frequency, severity, and duration of seizures in a cluster, and whether episodes have been known to progress to prolonged seizures or status epilepticus. Treatment should be commensurate with the severity of the cluster; it should depend on how severe the

seizures are and how close they are to each other. The timing of treatment depends on how early the onset of a cluster can be recognized reliably by the patient or caregiver. Some individuals have an aura or prodrome that is specific for a cluster, while others recognize a cluster is in progress only after having two or three seizures with shorter than usual inter-seizure intervals. The prescriber and caregiver should have a written seizure action plan, which includes when to treat and what to observe and what to do after treatment²⁸.

Common seizure cluster treatments for mild seizure clusters include extra doses of the usual antiseizure medications and oral or sublingual benzodiazepines, in particular diazepam, and lorazepam. Orally disintegrated clonazepam and oral clobazam have also been used in SC; however the efficacy of such approaches has not been studied in controlled trials¹⁹. Interestingly, a significant reduction in seizure clustering has been reported in patients with refractory epilepsy who had the Vagus Nerve Stimulation (VNS) device implanted²⁹.

Patients must be awake and cooperative for safe administration of oral medications. The onset of action following oral intake may not be sufficiently fast to terminate more severe seizure clusters. An ideal therapy for severe seizure clusters should have a broad spectrum of efficacy against a variety of seizure types, should have a rapid delivery system and a rapid onset of action, should have minimal serious adverse effects, and should be easily and safely administered by caregivers in various settings, without requiring the cooperation of an unresponsive patient.³⁰

Benzodiazepines have been the focus of most clinical trials for treatment of seizure clusters. They were favored because of their broad spectrum of efficacy and rapid penetration of the blood-brain barrier due to their lipid solubility. Their shared mechanism of action is enhancing the inhibitory effect of Gamma-aminobutyric acid (GABA) at the GABA_A receptors, increasing the opening frequency of the associated chloride channel. Diazepam was first used off-label by rectal route of administration. Evidence of clinical utility resulted in the development of a commercial rectal diazepam gel (Diastat). Its bioavailability was around 90%, and an effective plasma concentration was reached within 15 min, even though the time to maximal concentration (Tmax) was about 1.5 h. Two positive multicenter double-blind, placebo-controlled clinical trials secured the regulatory approval of rectal diazepam gel for out-of-hospital treatment of seizure clusters by the United States Food and Drug Administration (FDA) in 1997^{14,31}. The first study enrolled 91 patients (47 children 44 adults) who received a first dose of rectal diazepam gel ($n = 45$) or placebo ($n = 46$) at the onset of an identifiable seizure cluster, then a second dose 4 h later, and a third dose in adults only 12 h after the first dose. Time to the next seizure was significantly longer after diazepam ($p < .001$, chi-square = 13.75 with 1df, modified Wilcoxon test). During the observation period, 78% of diazepam patients were seizure-free, compared to 19% of placebo patients¹⁴. The second study enrolled 114 patients (53 children and 61 adults) who received a single dose of diazepam ($n = 56$) or placebo ($n = 58$) at the onset of an identifiable seizure cluster. Time

to the next seizure was significantly longer for the diazepam group (Kaplan-Meier survival analysis for time to next seizure). During the observation period, 55% of diazepam patients were seizure-free as compared to 34% of placebo patients ($p = .031$; Wilcoxon's rank sum test stratified by number of seizures)³¹. The most common adverse experience was somnolence, noted in 23% of diazepam patients and 8% of placebo patients. The recommended rectal diazepam dosing is age and weight dependent, 0.5 mg/kg for children aged 2–5 years, 0.3 mg/kg for children aged 6–11 years, and 0.2 mg/kg for those aged 12 years or older. The maximum recommended dose is 20 mg. A second dose may be given 4–12 h later, if needed. It was recommended that rectal diazepam gel should be used for no more than one seizure cluster every 5 days and no more than 5 seizure clusters per month.

For many years, rectal diazepam was the only formally approved seizure cluster treatment. However, rectal diazepam had a number of issues. Rectal administration is embarrassing for older children and adults, particularly in public. Caregivers who are not first-degree relatives may have concerns about sexual abuse allegations associated with rectal administration. In addition, rectal administration could be difficult in overweight individuals and those who are in wheelchairs. Thus, alternatives were needed.

Buccal midazolam was approved in the European Union in 2011 for the treatment of seizure clusters and prolonged convulsive seizures, based on several studies. Its pharmacokinetics were evaluated in 10 healthy adult volunteers who were asked to hold 10 mg of midazolam in a 2 mL solution for 5 min before spitting it out. Venous midazolam concentrations showed a rapid increase for the first 20–30 min, and EEG changes were observed even earlier³². Buccal midazolam was compared to rectal diazepam for prolonged seizures lasting more than 5 min in a randomized study of 42 patients. The difference in efficacy was not clinically significant: buccal midazolam stopped 75% of 40 seizures in 14 subjects as compared to 59% of 39 seizures in 14 subjects randomized to rectal diazepam ($p = .16$, χ^2 test as independent variables)³³. In another multicenter trial 177 children ≥ 6 months of age were randomized to receive either buccal midazolam or rectal diazepam. Therapeutic success, defined as cessation of seizures within 10 min and for at least 1 h without respiratory depression requiring intervention was 56% (61 of 109 seizure episodes) for buccal midazolam and 27% (30 of 110 seizure episodes) for rectal diazepam. The difference was significantly in favor of buccal midazolam after controlling for several factors ($p < .001$; odds ratio 4.1, 95% CI 2.2–7.6, logistic regression analysis)³⁴. Another study randomized 120 patients presenting with convulsive seizure activity to either buccal midazolam 0.2 mg/kg or intravenous diazepam 0.3 mg/kg. Control of convulsive activity within 5 min was not significantly different (85% for buccal midazolam and 93.3% for intravenous diazepam, $p = .142$). While mean time for controlling seizure activity after administration was shorter with intravenous diazepam ($p \leq .001$), the mean time for initiation of treatment was significantly shorter with buccal midazolam ($p \leq .001$). As a result, the mean time for

controlling seizure activity after diagnosis was significantly less with buccal midazolam ($p = .004$) (χ^2 test, Fisher's and Student's t -test)³⁵. Buccal midazolam is approved from age 3 months to < 18 years. The approved dosing is age dependent: 2.5 mg for those younger than 1 year, 5 mg for 1 year to < 5 years, 7.5 mg for 5 years to < 10 years, and 10 mg for 10 years to < 18 years.

Buccal midazolam was not approved or marketed in the USA, and rectal diazepam was the only approved treatment for seizure clusters until intranasal spray formulations of midazolam and diazepam were approved by the FDA in 2019 and early 2020. The marketed intranasal midazolam formulation was optimized for delivery, with appropriate concentration and volume for nasal route of administration. Pharmacokinetic and pharmacodynamic effects of intranasal midazolam were evaluated in 25 healthy adults³⁶. The optimized intranasal formulation had a 134% greater bioavailability than the intravenous solution given intranasally. T_{max} was 10–12 min and the half-life was 3.6–3.8 h. The optimized intranasal midazolam preparation underwent a randomized double-blind placebo controlled trial in patients aged ≥ 12 years. Following a 5 mg test dose given in clinic, patients were randomized to receive 5 mg of midazolam spray intranasally when the onset of a seizure cluster was identified. The primary efficacy endpoint was treatment success, defined as seizure termination within 10 min and no recurrence 10 min to 6 h after administration. Treatment success was significantly better with intranasal midazolam, achieved in 53.7% of 134 patients receiving midazolam and 34.3% of 67 patients receiving placebo ($p = .0109$)³⁷. The most common adverse effect was nasal discomfort. Somnolence occurred in less than 10% of patients. Intranasal midazolam is FDA approved for patients 12 years and older. The recommended dosing is 5 mg in one nostril, which may be repeated after 10 min if needed. The prescribing information suggests that no more than one episode should be treated every 3 days, with a maximum of five episodes per month.

The diazepam intranasal spray preparation was formulated with vitamin E to improve the nonaqueous solubility of diazepam and with Intravail A3, a nonionic surfactant that enhances absorption across mucosa. It was approved based on pharmacokinetic studies demonstrating a bioavailability of 97%, T_{max} of 1.5 h, and 2–4 fold less intra-subject pharmacokinetic variability than rectal diazepam³⁸. It also had equivalent pharmacokinetics when administered interictally or peri-ictally³⁹. The most common adverse effects were dysgeusia and nasopharyngitis/nasal discomfort. It was approved in patients 6 years or older. Its age and weight-based dosing is similar to that of rectal diazepam: 0.3 mg/kg for ages 6–11 years and 0.2 mg/kg for those 12 years and older. The prescribing information suggests that the dose can be repeated in 4 h if needed. It was recommended that no more than one seizure cluster episode be treated every 5 days, with a maximum of five treated episodes per month.

Another seizure cluster treatment that was successfully investigated but not developed for marketing is diazepam intramuscular autoinjector. Its pharmacokinetics were investigated in comparison with rectal diazepam in a crossover

Table 1. Advantages and disadvantages of various modes of administration for the treatment of seizure clusters (adapted from reference 23).

Route of administration	Advantages	Disadvantages
Oral	Convenient; inexpensive	Requires patient cooperation; slow absorption; risk of aspiration
Rectal	Rapid absorption	Social inhibition; slow access
Buccal or sublingual	Rapid administration; rapid absorption	Risk of aspiration
Intramuscular	Rapid administration	Local pain
Intranasal	Rapid administration; rapid absorption	Nasal irritation
Intrapulmonary (inhalation)	Fastest absorption	Requires patient cooperation
Intravenous	Fastest delivery after access	Requires medical expertise; delayed access

study in 24 healthy volunteers. Intramuscular autoinjector administration resulted in more rapid and less variable drug absorption than rectal delivery, with significantly higher area under the curve⁴⁰. The autoinjector was evaluated in a randomized double-blind placebo-controlled multicenter study. The primary endpoint of time to next seizure or rescue intervention from 15 min to 12 h after study drug administration was superior for the diazepam autoinjector. A seizure event recurred within 12 h of dosing in 55.6% of placebo patients ($n=81$) as compared to 35.4% of the diazepam group ($n=82$) ($p=.010$)¹¹. In the open-label follow-up study 128 subjects were treated at least once, with a total of 1380 treatments during 6 years. Overall 78% of treatments were effective with no subsequent seizure or rescue in the following 12 h⁴¹. The company that sponsored the diazepam autoinjector studies decided not to pursue development and marketing due to production issues and commercial considerations.

Other seizure cluster treatments in development include the diazepam buccal film, and intrapulmonary staccato alprazolam. The diazepam buccal film is a thin soluble film less than the size of a postage stamp, affixed to the buccal mucosa inside the cheek by the patient or caregiver. Diazepam is mainly absorbed trans-buccally, but is also swallowed, so that a portion of the dose is absorbed in the gastrointestinal system. It has dose-proportional kinetics, consistent maximal concentrations, and a median T_{max} of 1 h⁴².

The Staccato system aerosolizes a drug and delivers it deep into the lung *via* inhalation. Absorption through the pulmonary route is facilitated by a large surface area for drug absorption, high perfusion rate and exceptionally thin alveolar capillary membrane⁴³. Staccato alprazolam inhalation was evaluated in five photosensitive women who received staccato alprazolam 0.5, 1, and 2 mg and staccato placebo in random order. Photostimulation was performed before and at seven time points after the alprazolam dose. All doses of Staccato alprazolam reduced the photosensitivity range at 2 min, corresponding to a T_{max} of 2 min (descriptive statistics, no formal size estimate). It remains to be determined if the rapid absorption predicts a clinically relevant faster onset of action.

In conclusion, benzodiazepines are the mainstay of treatment to abort seizure clusters. New routes of administration have been approved and others are under investigation. Each route of administration has advantages and disadvantages, making it acceptable or desirable for some patients, but not others (Table 1)⁴⁴. It is important for each patient to have a seizure action plan that includes rescue therapy for seizure clusters, detailing when to administer treatment and what medication and dose to administer. The patient and

caregivers have to be counseled and trained on the administration of rescue treatment. Early treatment outside the hospital reduces morbidity and mortality of seizure clusters, reduces cost of treatment, and improves quality of life for patients and their families and caregivers.

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