Seizure 68 (2019) 9–15

Contents lists available at ScienceDirect

Seizure

journal homepage: www.elsevier.com/locate/yseiz

Seizure cluster: Definition, prevalence, consequences, and management

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ARTICLE INFO

Article history:
Received 14 February 2018
Received in revised form 18 May 2018
Accepted 19 May 2018

Keywords:
Epilepsy
Acute repetitive seizures
Status epilepticus
Rescue medication
Benzodiazepines
Seizure action plan

ABSTRACT

Purpose: To summarize definitions, prevalence, risk factors, consequences, and acute management of seizure clusters using rescue medications.
Methods: We searched MEDLINE for studies that assessed definitions, clinical characteristics, outcomes, and use of rescue medication for aborting seizure clusters.
Results: Different clinical and statistical definitions for seizure clusters have been proposed, including: ≥3 seizures in 24 h, ≥2 seizures in 24 h, and ≥2 seizures in 6 h. Most studies of seizure clusters have been conducted in tertiary epilepsy centers, with refractory epilepsy patients. Patients with severe and poorly controlled epilepsy are more likely to experience seizure clusters.
Seizure clusters can result in increased health care utilization and have negative impact on the quality of life of patients and caregivers. Use of benzodiazepine rescue medications in acute management of seizure clusters can help avoid progression to status epilepticus and reduce emergency room visits. Rescue medications are underutilized in seizure clusters. Currently, rectal diazepam gel is the only FDA approved rescue medication for seizure clusters. In addition, buccal midazolam is approved in European countries for treatment of prolonged seizures. However, various non-rectal non-IV benzodiazepines are safe and effective in treating acute seizures and clusters. Most patients and caregivers preferred non-rectal routes.
Conclusion: Identifying patients that are at high risk for seizure clusters, providing them with formal action plans and educating them about use of rescue medication for seizure clusters can help ameliorate the outcomes in this group of epilepsy patients.

1. Introduction

Patients with epilepsy often experience acute repetitive seizures or seizure clusters. Surveys of patients and caregivers suggested that seizure clusters have negative impact on quality of life, emotional wellbeing, daily function, and productivity of the patients and their caregivers [1]. They are associated with increased utilization of emergency rooms and underutilization of rescue medications [1].

There is no consensus in terms of definition of seizure clusters. Patients, caregivers and providers use different definitions for seizure clusters. There is a gap in communication among the providers and the patients or caregivers in identifying seizure clusters [2], which contributes to suboptimal use of rescue medications [3]. Lack of rescue plan and underutilization of rescue medication could result in unnecessary emergency room visits. Better definitions of seizure clusters may help better characterize them, and identify the patients that would benefit from intervening with rescue medications [4].

In this paper we provide a review of the literature regarding the definitions, risk factors, consequences, and management of seizure clusters.

2. Definitions

Seizure cluster is not listed in the International League Against Epilepsy (ILAE) Commission on Classification and Terminology [2,5]. Different terminologies have been used to describe this clinical entity: "acute repetitive seizures", "flurries" [6], "cyclical, serial, repetitive, crescendo, and recurrent seizures" [2].

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https://doi.org/10.1016/j.seizure.2018.05.013
1059-1311/

A broad definition of seizure clusters is "acute episodes of deterioration in seizure control" [7]. It could be defined as a series of grouped seizures that have short interictal periods; however, the number of seizures and the interictal period is a subject of controversy [6]. Different studies and authors have proposed various definitions, some using a clinical approach and some based on a statistical approach.

2.1. Clinical definitions

Several studies propose clinical definitions that define a number of seizures during a limited time interval. It is assumed that if seizures occur within 8 h it is more likely that they arise from a concordant focus and thus not actually "independent" [8]. A study showed that seizures with interictal period of less than 8 h were more likely to come from the ipsilateral hemisphere than seizures with longer interictal intervals [9]. Based on these findings, many studies defined seizure clusters as 3 or more seizure in 24 h (interictal period of 8 h or less) [6,10–18].

Other clinical definitions include: two or more seizures in six hours [19], two or more seizures in 24 h [20], two to four seizures in less than 48 h [17,21], and two generalized tonic clonic or three complex partial seizures in 4 h [8]. A randomized controlled trial of rectal diazepam in the treatment of acute of repetitive seizures used the following operational definition: "An episode of multiple complex partial or generalized (tonic, clonic, tonic clonic, atypical absence, or myoclonic) seizures occurring within a 24-h period in adults or a 12-h period in children, with a pattern distinguishable from the patient's usual seizure pattern, and with onset readily recognizable by a caregiver, such as a parent" [22].

2.2. Statistical definitions

Some studies have proposed statistical definitions that describe an increase in seizure occurrence compared with what is expected based on the patient's average seizure frequency [23]. A threefold or fourfold increase in seizure frequency within a 3-day period has been considered as seizure clustering [8]. A more sophisticated statistical approach can be based on a Poisson (random) distribution, where the events occur randomly within independent time intervals. A deviation from this model can reflect seizure clusters, and also indicate periodic patterns or regularity [8]. Deviations could include negative dependence of seizures (having too many seizures in the prior day decreases the chance of having seizure in the following day), and positive dependence (occurrence of seizure in the prior day increases the chance of having seizure) [24]. Departure from a random model can be observed in many patients with refractory epilepsy. In a study of 24 patients with epilepsy who maintained a seizure diary, 10 out of 22 had seizures that were not randomly distributed [25]. In another study of 13 patients with intractable epilepsy who self-reported their seizures using a seizure diary, in almost all the patients studied, seizures did not follow a random pattern [24].

The clinical definitions do not account for the variability in the baseline seizure frequency among different patients, and tend to overestimate the occurrence of seizure clusters in patients who regularly have high frequencies of seizures [20]. However, these definitions could be easier to use clinically and probably more relevant in the acute settings in terms of using rescue medications to prevent status epilepticus. On the other hand, the statistical approach could be useful to identify "false positives". In addition, the statistical definitions can be utilized in seizure detection and prediction algorithms [26] using seizure diaries [3,20] and automated seizure detection systems [27].

3. Prevalence

Prevalence of seizure clusters varies significantly in different studies depending on the definitions used (Table 1) [8]. Prevalence is lower if a statistical model is used [2,10]. Forty-three percent of patients who were keeping a seizure diary met the clinical definition of 3 or more seizures in 24 h, whereas only 22% met the statistical definition [10].

Prevalence is also dependent on the study population. Most studies on seizure clusters have been conducted in tertiary epilepsy centers, where patients with refractory epilepsy are more prevalent [3,8]. Therefore, the reported prevalence might be an overestimation. The prevalence of seizure clusters ranges from 13 to 76% in the outpatient setting and 18 to 83% for the inpatient setting (epilepsy monitoring unit) [6]. In a study of adult patients in the outpatient setting, the prevalence of clusters (3 or more seizures in 24 h or 3 times the baseline frequency) was 14.9% [3]. Another study including both inpatient and outpatient settings reported a prevalence of 29% for 3 or more seizures in 24 h [17]. In the inpatient setting the prevalence has been reported to be 50% or higher. In addition to the selection bias and more severe epilepsy patients in the inpatient setting, in the long-term monitoring units, anti-seizure medications are often temporarily withdrawn, which can trigger seizure clusters [8]. Prevalence of 3 or more seizures in 24 h in patients undergoing pre-surgical epilepsy monitoring was 61.5% [18]. In a retrospective study of long-term inpatient monitoring data, 83% of patients had 2 or more seizures with less than 4 h in between seizures [28].

A population based study in Finland identified seizure clusters (3 or more seizures in 24 h) in 22% of patients with epilepsy [15]. In another population based study in UK, which used the general practice research database, the prevalence of seizure clusters was 2.5/10,000 population (Confidence Interval: 2.3–2.7) using the definition of 3 or more seizures in 24 h. The prevalence was lower than many other studies (only 3% of patients with epilepsy) [16]. However, in the retrospective chart review studies, lack of structured interviews to identify seizure clusters might underestimate the prevalence of seizure clusters.

4. Patients at risk for seizure clusters

Some patients with epilepsy are at higher risk to develop seizure clusters than others. Several studies have looked into factors that are associated with seizure clusters (Table 1). Some studies have suggested that patients with extratemporal epilepsy [17], especially frontal lobe epilepsy [8], are more likely to have seizure clusters. However, mesial temporal sclerosis has also been shown to be associated with seizure clusters.[18, 29] Multifocal epilepsy [29], symptomatic generalized epilepsy, remote history of CNS infection, and focal cortical dysplasia [3] are also identified as risk for seizure clusters. History of seizure clusters [18] and status epilepticus [3,17,30], head trauma [17], earlier age of seizure onset [3,29], and high seizure frequency in the first 12 months after the onset of epilepsy (one weekly seizure or more) [15] are associated with seizure clusters.

The most significant risk factor for seizure clusters is having intractable epilepsy [3,8] with high average seizure frequency [10,15,17,20,29]. In other words, clustering of seizures could be an indicator of poorly controlled epilepsy [17]. However, as mentioned above in the definitions section, having a high baseline seizure frequency might result in an overestimation of prevalence of seizure clusters defined clinically. The higher number of seizures per day, the more likely they fall into the clinical definition of clusters (3 or more seizures in 24 h) [8].

Rather than identifying the risk factors for "being a clusterer", it could also be clinically relevant to identify "periods of vulnerability"

Table 1
Clinical factors associated with seizure clusters.

Author	Year	Study design	Study setting	Study population	Age (year)	Number of patients (%cluster)	Definition of clusters	Risk factors for seizure clusters	Analysis type	OR (CI)
Chen et al. [3]	2017	Retrospective	Outpatient	Epilepsy patients	≥16	4116 (15%)	≥3/24 h (or 3 times the daily average for patients with daily seizures)	Symptomatic Generalized Epilepsy History of CNS infection Cortical dysplasia Complex partial seizure Status epilepticus Age at seizure onset Absence of 1-year seizure freedom Having failed 2 or more AEDs	Multivariate	NA 2.01 (1.41, 2.88) 2.83 (1.79, 4.48) 1.91 (1.44, 2.53) 1.80 (1.32, 2.46) 0.78 (0.73, 0.83) 2.13 (1.69, 2.7) 2.41 (1.58, 3.66)
Asadi-Pooya et al. [21]	2016	Retrospective	Inpatient	Drug resistant epilepsy patients who underwent epilepsy surgery	>10	978 (18%)	≥2/48 h	No association of extratemporal epilepsy with seizure clusters	Univariate	NA
Fisher et al. [20]	2015	Cross-sectional	Electronic seizure diary data	Epilepsy patients	<1 to >70, mostly adults	5098 (23%)	≥2/24 h (midnight-to-midnight calendar day)	Higher daily seizure frequency	Univariate	NA
Sinha et al. [86]	2013	Prospective	Inpatient	Patients with new-onset seizures	68.0 ± 7.5	201 (26%)	3/24 h	Risk factors for new-onset SE or seizure clusters: Lower GCS score Higher number of seizures	Multivariate	1.22 (1.04–1.41) 1.03 (1.00–1.07)
Sillanpaa et al. [15]	2008	Retrospective cohort	Outpatient	Epilepsy patients	≤15	120 (21%)	≥3/24 h	High seizure frequency at onset of epilepsy	Multivariate	4.6 (1.01–16.38)
Haut et al. [17]	2005	Prospective	Outpatient	Epilepsy patients	≥18	141 (29%)	≥3/24 h	History of head trauma with LOC Extratemporal localization	Multivariate	4.2 (1.6–11) 3.0 (1.1–7.8)
Haut et al. [10]	2005	Prospective	Outpatient	Epilepsy patients	Median: 39.6	87 (43% by definition a, or 22% by definition b)	a: ≥3/24 h b: deviation from a Poisson distribution Subjects reporting ≥3 seizures every day were excluded	Higher seizure frequency (by either definition)	Univariate	NA
Haut et al. [18]	2002	Prospective	Inpatient	Intractable epilepsy patients undergoing impatient Long-term EEG monitoring for pre-surgical evaluation	33 ± 12.2	91 (61%)	3/24 h	A history of seizure clustering presence of MTS on MRI	Multivariate	NA
Bauer et al. [23]	2001	Retrospective	Outpatient-seizure diary data	Refractory epilepsy patients	33.7 ± 13.8	63 (57%)	A significant increase of seizure occurrence compared to the rate expected from the individual mean	Lower age at seizure onset	Univariate	NA

CNS: Central Nervous System; GCS: Glasgow Coma Scale; LOC: Loss of Consciousness; SE: Status Epilepticus.

to seizure clusters [10]. Different triggers have been described, such as sleep, waking, or sleep deprivation [20], stress, fever or illness [29], missing or changing medications, alcohol, and menstruation [20]. However, seizure clusters can occur in the absence of any triggers.

5. Consequences

Seizure clusters can result in increased emergency room visits or hospitalization [6,8]. They have negative impact on productivity, disrupting daily life, studies, and work of the patients and caregivers [1,29].

Seizure clusters are dreaded because of their association with status epilepticus, which is potentially life threatening [17,31]. In a study of patients with intractable localization-related epilepsy, convulsive status epilepticus had occurred in 44% of patients who typically had seizure clusters and 12.5% of patients without seizure clustering ($p < 0.002$). Typically clusterers were patients who had more than half of their seizures in clusters of 3 or more seizures in 24 h [32].

The failure of seizure terminating mechanisms seems to be the common pathophysiology in seizure clusters and status epilepticus [32]. Intra-cluster seizures are relatively shorter in duration compared to isolated seizures or the terminal seizure in a cluster. It is hypothesized that the intra-cluster seizures are not long enough to activate the self-regulatory inhibitory mechanism that normally limits seizures [28]. Another hypothesized mechanism is the persistent lowering of seizure threshold by the seizures. Both of these mechanisms could contribute to status epilepticus or seizure cluster. Thus, patients with either condition are predisposed to the other [28].

The association of seizure clusters with mortality is not well stablished. In a prospective population-based study with a long term follow up of 37 years on average, an increased risk of mortality was observed in patients who started to have clusters (defined as 3 or more seizures in 24 h) during treatment, but no increased mortality in patients with clusters prior to treatment compared to patients without clusters [15]. Confounding factors such as severity of epilepsy and the underlying etiology should be taken into account while interpreting these results.

Interestingly, having seizure clusters could be associated with better outcome after epilepsy surgery. In a retrospective study of 681 patients with temporal lobe epilepsy who underwent surgical resection, those who had a history of seizure clusters had a better post-surgical outcome [21].

Seizure-related injury in patients with seizure clusters has not been well studied. In a study of 141 epilepsy patients including 41 (29%) with a history of seizure clusters, there was no association between seizure-related injuries and history of seizure clusters defined as 3 or more seizures in 24 h [17].

6. Management

Use of benzodiazepine rescue medications is the cornerstone in acute management of seizure clusters that can help to abort clusters and reduce emergency room visits [7]. However, studies have shown that benzodiazepines are largely underutilized in patients with seizure clusters. A study of adult patients with seizure clusters showed that fewer than half of them were prescribed at least one benzodiazepine rescue medication [3]. The most common rescue medications used were oral lorazepam (28.9%), followed by rectal diazepam (7.8%), oral diazepam (7.0%), and intranasal midazolam (6.9%) [3].

Rectal diazepam is the only U.S. Food and Drug Administration (FDA) approved rescue medication for bouts of increased seizure activity. It has been shown to be effective and safe in treating acute repetitive seizures [33]. Lethargy is the most common side effect [33]. Oral lorazepam is utilized by many patients for aborting seizure clusters [3]. Other medications and different routes of administration have also been investigated. Buccal, intramuscular and intranasal midazolam, intramuscular and intranasal diazepam are among the alternatives to the rectal diazepam that have been studied for safety and efficacy. In addition to safety and efficacy of non-rectal routes, there is superiority in terms of ease of administration. Non-rectal non-IV routes were more rapidly administered than rectal route [34,35].

Buccal midazolam (Buccolam®) is approved in Europe as a rescue medication for acute seizure emergencies in children >3 months and <18 years of age [29,36]. In studies comparing buccal midazolam with rectal diazepam, buccal midazolam showed comparable [37–39] or superior efficacy [40–42]. Side effect of buccal midazolam include bitter taste [34] and risk of aspiration (although it has not been reported in any of the studies) [34,42].

Oral clonazepam is widely use in the United States, Europe, and Latin America for seizure clusters. However, there is a gap in the literature in terms of its effectiveness in acute treatment of seizure clusters. IV clonazepam is an effective alternative to lorazepam and midazolam in treating status epilepticus [43]. There is a need to formally evaluate the effectiveness of oral clonazepam as a rescue medication for seizure clusters. Intranasal midazolam has shown effectiveness in aborting seizure clusters [44]. Studies comparing midazolam nasal spray to diazepam rectal solution have shown equal [45] or superior efficacy [46] in aborting prolonged seizures (longer than 5 min) [47] or clusters of 3 seizures in 1 h [48]. Furthermore, intranasal midazolam had higher caregiver satisfaction and ease of administration [47]. It has a rapid onset of action, reaching the peak concentration at 10–12 min, and likely reaching therapeutic levels significantly faster. The elimination half-life is between 3.6 and 3.8 h, which is shorter than diazepam (50 h) [49].

Safety and efficacy of intranasal midazolam USL261/Nayzilam in outpatient treatment of seizure clusters has been investigated in a phase 3 double-blind controlled clinical trial (NCT 01390220). Two hundred and one patients with seizure clusters (defined as 2 or more seizures within 6 h) were included. Based on the results presented at the American Epilepsy Society meeting, of patients in the midazolam arm, 53.7% achieved success (seizures terminated within 10 min and maintained seizure freedom from 10 min to 6 h after administration), compared with 34.4% in the placebo group [19]. Mucosal irritation, lethargy, lacrimation, and abnormal taste were the most frequently reported treatment-related side effects for intranasal midazolam in this study [50].

Intranasal diazepam was shown to have good absorption and bioavailability in healthy volunteers [51–53], which was comparable to the bioavailability of rectal diazepam gel [54]. However, the bioavailability of an intranasal diazepam formulation in patients with epilepsy was shown to be suboptimal in a recent clinical trial. The phase 3 clinical trial (NCT 02316847)[55] investigating the long-term safety and tolerability of diazepam intranasal spray in adolescents and adults with seizure clusters was terminated due to unexpectedly low nasal mucosal absorption of the diazepam preparation and its failure to demonstrate its bioequivalence to Diastat® rectal gel [56]. Another phase 3 clinical trial is currently ongoing to assess the safety of repeat doses of intranasal diazepam (NRL-1) administered to epilepsy patients who experience frequent breakthrough seizures or seizure clusters [57].

Midazolam can be successfully administered intramuscularly. Intramuscular midazolam had superior effectiveness in stopping convulsive status epilepticus compared with intravenous lorazepam when administered via an autoinjector by paramedics prior to hospital arrival [58]. In a small prospective randomized clinical trial in children with prolonged seizure, intramuscular midazolam

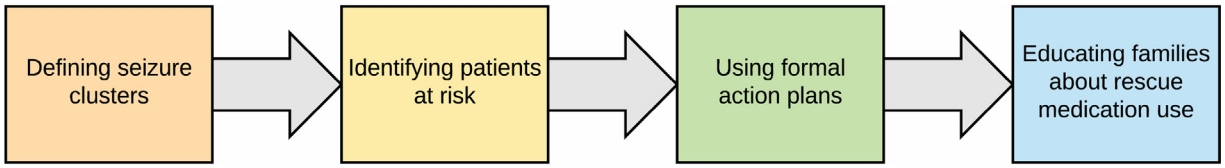

Fig. 1. Steps towards improving seizure cluster outcome.

resulted in more rapid cessation of seizures than intravenous diazepam (7.8 min vs 11.2 min, P = 0.047) [59].

Intramuscular diazepam has also been shown to be safe and effective in aborting seizure clusters [60,61]. The familiarity of the public with auto-injectors (e.g. EpiPen®) is another factor in favor of this route [62]. Adverse effects include local hematoma, pain, and the risk of caregiver needle stick [6,42]. Because of the relatively high volume of solution that needs to be injected (3 ml), and the time of up to 10 s during which the injected site may not move or be moved, intramuscular application of diazepam does not seem to have the potential for acceptance by patients in caregivers. The drug company Pfizer that had sponsored a phase 3 trial for intramuscular diazepam administered by an autoinjector[61] is no longer pursuing this project.

In a recent placebo controlled clinical trial, the Staccato® alprazolam showed promise in reduction of epileptic activity in photosensitive epilepsy [63,64]. The Staccato® system is a novel method for fast drug delivery which comprises the vaporization of drug and rapid generation of drug aerosols that the patient inhales in a single breath. The rapid absorption and onset of action (T max of 2 min) [64] is comparable to the IV administration.

Respiratory adverse events of benzodiazepines are more common in intravenous and rectal forms than other routes [34]. Nevertheless, rectal diazepam did not cause serious events such as respiratory or cardiac problems, even when multiple doses were administered due to inadequate efficacy of the initial standard dose in acute repetitive seizures [65]. In addition, it should be pointed out that in patients with convulsive status epilepticus en route to the hospital, IV benzodiazepines lead to lower rates (about half) of respiratory failure than placebo; stopping the seizures is the way to minimize respiratory issues [66].

The evidence in the literature strongly suggests that many patients, families and care givers prefer other routes of delivery over rectal route [34,42,47,67,68]. Reasons include social considerations, personal dignity, and ease of use [34,6]. Thus, the much anticipated alternatives to the rectal route would likely be widely accepted and adopted by the patients once approved and commercialized [62]. Currently, although not commercially available, intranasal midazolam is already in use off-label as a rescue medication in many institutions (including ours) by using an IV midazolam solution placed in a metered-dose nasal sprayer or a small syringe with an atomizer [29,69].

In addition to benzodiazepines, other treatments are available for seizure clusters. Oral clobazam has been used for aborting seizure clusters when oral therapy is possible [70]. In addition, several studies have shown that intravenous levetiracetam is safe and effective in acute repetitive seizures in pediatric patients [71–75]; briviaracetam is now being studied for this use [76,77]. Vagus nerve stimulation is another method for aborting seizures [78] and is often utilized in patients with seizure clusters via patient or caregiver swiping of a magnet to provide additional stimulation. Its efficacy in aborting seizure clusters has not been well studied [76].

7. Challenges and future directions

Data on seizure frequencies are often obtained through self-report by patients and/or by parents or care givers. However, this method is suboptimal and subject to error and underestimation [79,80]. Patients might be unaware or amnestic about the seizures. Particularly, nocturnal seizures often go unrecognized [81]. Although objective data have shown that epileptic seizures are generally equally distributed among day and night, in a survey of 170 patients with epilepsy, patients reported a three-fold higher frequency of seizures during daytime, which indicates the possibility of under-reporting the nighttime seizures [81]. In a study of 31 patients with epilepsy who were admitted to an epilepsy monitoring unit, only 26% of patients were always aware of their seizures, and 30% were never aware of their seizures [82]. In another study of 91 adult patients with focal epilepsy admitted for video-EEG monitoring, 55% of all recorded seizures went undocumented by the patients [83]. Similarly in pediatric patients, a retrospective review of clinical record of children admitted to the epilepsy monitoring unit showed that the parents/caregivers under-reported 50% of seizures [84]. In addition, in pediatric patients different caregivers might be observing patients in different settings (school/home), resulting in inconsistency in reporting seizures and difficulty in maintaining a comprehensive diary [80].

Even for the recognized seizures, there is often poor compliance in terms of documenting seizures and maintaining seizure diaries [85] (including electronic seizure diaries). Keeping logs of seizures might not be feasible for patients that have a high seizure frequency. Seizure detection devices could provide an objective mean of detecting and keeping track of seizures. However, the currently available devices have some limitations including questionable utility in different seizure types other than tonic-clonic seizures, and have high rates of false detections [85].

In addition to the inaccuracy of patient self-report, 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 clusters [2].

It is important to raise the clinical awareness among the healthcare providers and encourage them to investigate specifically about seizure clusters during their patient encounter. Identifying patients that are at high risk for seizure clusters, providing them with formal action plans and educating them about use of rescue medication for seizure clusters can help ameliorate the outcomes in this group of epilepsy patients (Fig. 1). We will soon have additional approved options for treating clusters. Hopefully this will lead to fewer emergency room visits, fewer injuries, a lower prevalence of status epilepticus, more willingness to participate in activities away from home, and overall better quality of life for our patients with persistent seizures.

8. Conclusion

Seizure clusters are common in patients with refractory epilepsy, and can be associated with adverse outcomes. Rescue

medications can help ameliorate the outcomes, but are generally underutilized in patients with seizure clusters. Non-rectal, non-IV benzodiazepines are safe and effective in the outpatient management of seizure clusters

Disclosure

Dr. Hirsch has received:

- Research support to Yale University for investigator-initiated studies from Eisai, Monteris, and Upsher-Smith.
- Consultation fees for advising from Ceribell, Eisai, Monteris, Sun Pharma, and Engage Therapeutics
- Royalties for authoring chapters for UpToDate-Neurology, chapters for Medlink—Neurology, and from Wiley for co-authoring the book "Atlas of EEG in Critical Care", by Hirsch and Brenner.
- Honoraria for speaking from Neuropace.

Dr. Kellinghaus has received speaker's honoraria from UCB, Cerbomed and Eisai. He has served on advisory boards for UCB and Eisai. He has acted as paid consultant for NrSign Inc, Vancouver, Canada.

Dr. Detyniecki has received Research support to Yale University for investigator-initiated studies from Eisai, Sunovion, Acorda and Upsher-Smith.

Dr. Jafarpour and Dr. Gaínza-Lein have received research support to Boston Children's Hospital for an investigator-initiated study from Upsher-Smith Laboratories.

References

[1] Penovich P.E., Buelow J, Steinberg K, Sirven J, Wheless J. Burden of seizure clusters on patients with epilepsy and caregivers: survey of patient, caregiver, and clinician perspectives. Neurologist 2017;22(6):207–14.
[2] Buelow JM, Shafer P, Shinnar R, Austin J, Dewar S, Long L, et al. Perspectives on seizure clusters: Gaps in lexicon, awareness, and treatment. Epilepsy Behav 2016;57(Pt A):16–22.
[3] Chen B, Choi H, Hirsch LJ, Katz A, Legge A, Wong RA, et al. Prevalence and risk factors of seizure clusters in adult patients with epilepsy. Epilepsy Res 2017;133:98–102.
[4] Koubeissi M. Does seizure duration predict the termination of a seizure cluster? Epilepsy Curr 2016;16(6):391–2.
[5] Berg AT, Berkovic SF, Brodie MJ, Buchhalter J, Cross JH, van Emde Boas W, et al. Revised terminology and concepts for organization of seizures and epilepsies: report of the ILAE Commission on Classification and Terminology, 2005–2009. Epilepsia 2010;51(4):676–85.
[6] Haut SR. Seizure clusters: characteristics and treatment. Curr Opin Neurol 2015;28(2):143–50.
[7] Mitchell WG. Status epilepticus and acute repetitive seizures in children, adolescents, and young adults: etiology, outcome, and treatment. Epilepsia 1996;37(Suppl. 1):S74–80.
[8] Haut SR. Seizure clustering. Epilepsy Behav 2006;8(1):50–5.
[9] Haut SR, Legatt AD, O'Dell C, Moshe SL, Shinnar S. Seizure lateralization during EEG monitoring in patients with bilateral foci: the cluster effect. Epilepsia 1997;38(8):937–40.
[10] Haut SR, Lipton RB, LeValley AJ, Hall CB, Shinnar S. Identifying seizure clusters in patients with epilepsy. Neurology 2005;65(8):1313–5.
[11] Yen DJ, Chen C, Shih YH, Guo YC, Liu LT, Yu HY, et al. Antiepileptic drug withdrawal in patients with temporal lobe epilepsy undergoing presurgical video-EEG monitoring. Epilepsia 2001;42(2):251–5.
[12] Noe KH, Drazkowski JF. Safety of long-term video-electroencephalographic monitoring for evaluation of epilepsy. Mayo Clin Proc 2009;84(6):495–500.
[13] Rose AB, McCabe PH, Gilliam FG, Smith BJ, Boggs JG, Ficker DM, et al. Occurrence of seizure clusters and status epilepticus during inpatient video-EEG monitoring. Neurology 2003;60(6):975–8.
[14] Di Gennaro G, Picardi A, Sparano A, Mascia A, Meldolesi GN, Grammaldo LG, et al. Seizure clusters and adverse events during pre-surgical video-EEG monitoring with a slow anti-epileptic drug (AED) taper. Clin Neurophysiol 2012;123(3):486–8.
[15] Sillanpaa M, Schmidt D. Seizure clustering during drug treatment affects seizure outcome and mortality of childhood-onset epilepsy. Brain 2008;131(Pt 4):938–44.
[16] Martinez C, Sullivan T, Hauser WA. Prevalence of acute repetitive seizures (ARS) in the United Kingdom. Epilepsy Res 2009;87(2–3):137–43.
[17] Haut SR, Shinnar S, Moshe SL. Seizure clustering: risks and outcomes. Epilepsia 2005;46(1):146–9.
[18] Haut SR, Swick C, Freeman K, Spencer S. Seizure clustering during epilepsy monitoring. Epilepsia 2002;43(7):711–5.
[19] Sequeira DJ, Van Ess PJ, Braun TL, Clark AC, Pullman WE. Efficacy of Nayzilam™ (USL261; midazolam nasal spray) in subjects with acute repetitive seizures: results from the randomized, phase 3 ARTEMIS-1 clinical trial. American Epilepsy Society Annual Meeting. Available from: https://www.aesnet.org/meetings_events/annual_meeting_abstracts/view/349298.
[20] Fisher RS, Bartfeld E, Cramer JA. Use of an online epilepsy diary to characterize repetitive seizures. Epilepsy Behav 2015;47:66–71.
[21] Asadi-Pooya AA, Nei M, Sharan A, Sperling MR. Seizure clusters in drug-resistant focal epilepsy. Epilepsia 2016;57(9):e187–90.
[22] Dreifuss FE, Rosman NP, Cloyd JC, Pellock JM, Kuzniecky RI, Lo WD, et al. A comparison of rectal diazepam gel and placebo for acute repetitive seizures. N Engl J Med 1998;338(26):1869–75.
[23] Bauer J, Burr W. Course of chronic focal epilepsy resistant to anticonvulsant treatment. Seizure 2001;10(4):239–46.
[24] Balish M, Albert PS, Theodore WH. Seizure frequency in intractable partial epilepsy: a statistical analysis. Epilepsia 1991;32(5):642–9.
[25] Milton JG, Gotman J, Remillard GM, Andermann F. Timing of seizure recurrence in adult epileptic patients: a statistical analysis. Epilepsia 1987;28(5):471–8.
[26] Haut SR, Hall CB, Borkowski T, Tennen H, Lipton RB. Modeling seizure self-prediction: an e-diary study. Epilepsia 2013;54(11):1960–7.
[27] Ulate-Campos A, Coughlin F, Gainza-Lein M, Fernandez IS, Pearl PL, Loddenkemper T. Automated seizure detection systems and their effectiveness for each type of seizure. Seizure 2016;40:88–101.
[28] Ferastraoaru V, Schulze-Bonhage A, Lipton RB, Dumpelmann M, Legatt AD, Blumberg J, et al. Termination of seizure clusters is related to the duration of focal seizures. Epilepsia 2016;57(6):889–95.
[29] Komaragiri A, Detyniecki K, Hirsch LJ. Seizure clusters: a common, under-studied and undertreated phenomenon in refractory epilepsy. Epilepsy Behav 2016;59:83–6.
[30] Packer RM, Shihab NK, Torres BB, Volk HA. Risk factors for cluster seizures in canine idiopathic epilepsy. Res Vet Sci 2016;105:136–8.
[31] Cereghino JJ. Identification and treatment of acute repetitive seizures in children and adults. Curr Treat Options Neurol 2007;9(4):249–55.
[32] Haut SR, Shinnar S, Moshe SL, O'Dell C, Legatt AD. The association between seizure clustering and convulsive status epilepticus in patients with intractable complex partial seizures. Epilepsia 1999;40(12):1832–4.
[33] Cereghino JJ, Mitchell WG, Murphy J, Kriel RL, Rosenfeld WE, Trevathan E. Treating repetitive seizures with a rectal diazepam formulation: a randomized study. The North American Diastat Study Group. Neurology 1998;51(5):1274–82.
[34] Haut SR, Seinfeld S, Pellock J. Benzodiazepine use in seizure emergencies: a systematic review. Epilepsy Behav 2016;63:109–17.
[35] Hirsch LJ. Intramuscular versus intravenous benzodiazepines for prehospital treatment of status epilepticus. N Engl J Med 2012;366(7):659–60.
[36] Agency EM. Buccolam® 2.5 mg oromucosal solution: summary of product characteristics. 1/31/2018]. 2018 Available from: http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/002267/WC500112310.pdf.
[37] Scott RC, Besag FM, Neville BG. Buccal midazolam and rectal diazepam for treatment of prolonged seizures in childhood and adolescence: a randomised trial. Lancet 1999;353(9153):623–6.
[38] Mpimbaza A, Ndeezi G, Staedke S, Rosenthal PJ, Byarugaba J. Comparison of buccal midazolam with rectal diazepam in the treatment of prolonged seizures in Ugandan children: a randomized clinical trial. Pediatrics 2008;121(1):e58–64.
[39] Sofou K, Kristjansdottir R, Papachatzakis NE, Ahmadzadeh A, Uvebrant P. Management of prolonged seizures and status epilepticus in childhood: a systematic review. J Child Neurol 2009;24(8):918–26.
[40] Ashrafi MR, Khosroshahi N, Karimi P, Malamiri RA, Bavarian B, Zarch AV, et al. Efficacy and usability of buccal midazolam in controlling acute prolonged convulsive seizures in children. Eur J Paediatr Neurol 2010;14(5):434–8.
[41] McIntyre J, Robertson S, Norris E, Appleton R, Whitehouse WP, Phillips B, et al. Safety and efficacy of buccal midazolam versus rectal diazepam for emergency treatment of seizures in children: a randomised controlled trial. Lancet 2005;366(9481):205–10.
[42] Chin RF. What are the best ways to deliver benzodiazepines in children/patients with prolonged convulsive seizures? Epileptic Disord 2014;S50–8 16 Spec No 1.
[43] Alvarez V, Lee JW, Drislane FW, Westover MB, Novy J, Dworetzky BA, et al. Practice variability and efficacy of clonazepam, lorazepam, and midazolam in status epilepticus: A multicenter comparison. Epilepsia 2015;56(8):1275–85.
[44] Scheepers M, Scheepers B, Clarke M, Comish S, Ibitoye M. Is intranasal midazolam an effective rescue medication in adolescents and adults with severe epilepsy? Seizure 2000;9(6):417–22.
[45] Bhattacharyya M, Kalra V, Gulati S. Intranasal midazolam vs rectal diazepam in acute childhood seizures. Pediatr Neurol 2006;34(5):355–9.
[46] Fisgin T, Gurer Y, Tezic T, Senbil N, Zorlu P, Okuyaz C, et al. Effects of intranasal midazolam and rectal diazepam on acute convulsions in children: prospective randomized study. J Child Neurol 2002;17(2):123–6.
[47] Holsti M, Dudley N, Schunk J, Adelgais K, Greenberg R, Olsen C, et al. Intranasal midazolam vs rectal diazepam for the home treatment of acute seizures in

pediatric patients with epilepsy. Arch Pediatr Adolesc Med 2010;164(8):747–53.
[48] de Haan GJ, van der Geest P, Doelman G, Bertram E, Edelbroek P. A comparison of midazolam nasal spray and diazepam rectal solution for the residential treatment of seizure exacerbations. Epilepsia 2010;51(3):478–82.
[49] Kalviainen R. Intranasal therapies for acute seizures. Epilepsy Behav 2015;49:303–6.
[50] Braun TL, Meng T, Sequeira DJ, Van Ess PJ, Pullman WE. Safety and tolerability of Nayzilam™ (USL261; midazolam nasal spray) in subjects with acute repetitive seizures: results from the randomized, phase 3 ARTEMIS-1 clinical trial. American Epilepsy Sociaety Annaul Meeting. Available from: https://www.aesnet.org/meetings_events/annual_meeting_abstracts/view/349486.
[51] Ivaturi VD, Riss JR, Kriel RL, Cloyd JC. Pharmacokinetics and tolerability of intranasal diazepam and midazolam in healthy adult volunteers. Acta Neurol Scand 2009;120(5):353–7.
[52] Ivaturi VD, Riss JR, Kriel RL, Siegel RA, Cloyd JC. Bioavailability and tolerability of intranasal diazepam in healthy adult volunteers. Epilepsy Res 2009;84(2–3):120–6.
[53] Agarwal SK, Kriel RL, Brundage RC, Ivaturi VD, Cloyd JC. A pilot study assessing the bioavailability and pharmacokinetics of diazepam after intranasal and intravenous administration in healthy volunteers. Epilepsy Res 2013;105(3):362–7.
[54] Henney 3rd HR, Sperling MR, Rabinowicz AL, Bream G, Carrazana EJ. Assessment of pharmacokinetics and tolerability of intranasal diazepam relative to rectal gel in healthy adults. Epilepsy Res 2014;108(7):1204–11.
[55] Berg AT, Shinnar S, Levy SR, Testa FM. Status epilepticus in children with newly diagnosed epilepsy. Ann Neurol 1999;45(5):618–23.
[56] Therapeutics A. PLUMIAZ™ (diazepam) Nasal Spray. 1/31/2018]. 2018 Available from: http://www.acorda.com/products/research-development/plumiaz.
[57] Hesdorffer DC, Logroscino G, Cascino G, Annegers JF, Hauser WA. Incidence of status epilepticus in Rochester, Minnesota, 1965–1984. Neurology 1998;50(3):735–41.
[58] Welch RD, Nicholas K, Durkalski-Mauldin VL, Lowenstein DH, Conwit R, Mahajan PV, et al. Intramuscular midazolam versus intravenous lorazepam for the prehospital treatment of status epilepticus in the pediatric population. Epilepsia 2015;56(2):254–62.
[59] Chamberlain JM, Altieri MA, Futterman C, Young GM, Ochsenschlager DW, Waisman Y. A prospective, randomized study comparing intramuscular midazolam with intravenous diazepam for the treatment of seizures in children. Pediatr Emerg Care 1997;13(2):92–4.
[60] Rogin J, Wheless J, Abou-Khalil B, Wolter KD, Pixton GC, Sherman NA, et al. Safety and effectiveness of long-term treatment with diazepam auto-injector administered by caregivers in an outpatient setting for the treatment of acute repetitive seizures. Epilepsia 2014;55(9):1444–51.
[61] Abou-Khalil B, Wheless J, Rogin J, Wolter KD, Pixton GC, Shukla RB, et al. A double-blind, randomized, placebo-controlled trial of a diazepam auto-injector administered by caregivers to patients with epilepsy who require intermittent intervention for acute repetitive seizures. Epilepsia 2013;54(11):1968–76.
[62] Spencer D. Hope for new treatments for acute repetitive seizures. Epilepsy Curr 2014;14(3):147–9.
[63] Staccato Alprazolam and Photoparoxysmal Response. 2018 [cited 1/31/2018; Available from: https://clinicaltrials.gov/ct2/show/NCT02351115?term=alprazolam+using+the+staccato+system&rank=1.
[64] French J, Friedman D, Wechsler R, DiVentura B, Gelfand M, Pollard J, et al. Inhaled alprazolam, a potential rescue medication, works rapidly in patients with photosensitive epilepsy (P6.236). Neurology 2017;88(Suppl. 16).
[65] Brown L, Bergen DC, Kotagal P, Groves L, Carson D. Safety of Diastat when given at larger-than-recommended doses for acute repetitive seizures. Neurology 2001;56(8):1112.
[66] Alldredge BK, Gelb AM, Isaacs SM, Corry MD, Allen F, Ulrich S, et al. A comparison of lorazepam, diazepam, and placebo for the treatment of out-of-hospital status epilepticus. N Engl J Med 2001;345(9):631–7.
[67] Wilson MT, Macleod S, O'Regan ME. Nasal/buccal midazolam use in the community. Arch Dis Child 2004;89(1):50–1.
[68] Gainza-Lein M, Benjamin R, Stredny C, McGurl M, Kapur K, Loddenkemper T, et al. Rescue medications in epilepsy patients: a family perspective. Seizure 2017;52:188–94.
[69] Kay L, Reif PS, Belke M, Bauer S, Frund D, Knake S, et al. Intranasal midazolam during presurgical epilepsy monitoring is well tolerated: delays seizure recurrence, and protects from generalized tonic-clonic seizures. Epilepsia 2015;56(9):1408–14.
[70] Shorvon S. Clinical trials in acute repetitive seizures and status epilepticus. Epileptic Disord 2012;14(2):138–47.
[71] Khongkhatithum C, Thampratankul L, Wiwattanadittakul N, Visudtibhan A. Intravenous levetiracetam in Thai children and adolescents with status epilepticus and acute repetitive seizures. Eur J Paediatr Neurol 2015;19(4):429–34.
[72] Isguder R, Guzel O, Agin H, Yilmaz U, Akarcan SE, Celik T, et al. Efficacy and safety of IV levetiracetam in children with acute repetitive seizures. Pediatr Neurol 2014;51(5):688–95.
[73] McTague A, Kneen R, Kumar R, Spinty S, Appleton R. Intravenous levetiracetam in acute repetitive seizures and status epilepticus in children: experience from a children's hospital. Seizure 2012;21(7):529–34.
[74] Depositario-Cabacar DT, Peters JM, Pong AW, Roth J, Rotenberg A, Riviello Jr. JJ, et al. High-dose intravenous levetiracetam for acute seizure exacerbation in children with intractable epilepsy. Epilepsia 2010;51(7):1319–22.
[75] Abend NS, Monk HM, Licht DJ, Dlugos DJ. Intravenous levetiracetam in critically ill children with status epilepticus or acute repetitive seizures. Pediatr Crit Care Med 2009;10(4):505–10.
[76] Bialer M, Johannessen SI, Levy RH, Perucca E, Tomson T, White HS, et al. Progress report on new antiepileptic drugs: a summary of the Twelfth Eilat Conference (EILAT XII). Epilepsy Res 2015;111:85–141.
[77] Singh RK, Gaillard WD. Status epilepticus in children. Curr Neurol Neurosci Rep 2009;9(2):137–44.
[78] Boon P, Vonck K, Van Walleghem P, D'Have M, Caemaert J, De Reuck J, et al. Vagus nerve stimulation for epilepsy, clinical efficacy of programmed and magnet stimulation. Acta Neurochir Suppl 2002;79:93–8.
[79] Patel AD, Moss R, Rust SW, Patterson J, Strouse R, Gedela S, et al. Patient-centered design criteria for wearable seizure detection devices. Epilepsy Behav 2016;64(Pt A):116–21.
[80] Fisher RS, Blum DE, DiVentura B, Vannest J, Hixson JD, Moss R, et al. Seizure diaries for clinical research and practice: limitations and future prospects. Epilepsy Behav 2012;24(3):304–10.
[81] Blachut B, Hoppe C, Surges R, Stahl J, Elger CE, Helmstaedter C, et al. Counting seizures: the primary outcome measure in epileptology from the patients' perspective. Seizure 2015;29:97–103.
[82] Blum DE, Eskola J, Bortz JJ, Fisher RS. Patient awareness of seizures. Neurology 1996;47(1):260–4.
[83] Hoppe C, Poepel A, Elger CE. Epilepsy: accuracy of patient seizure counts. Arch Neurol 2007;64(11):1595–9.
[84] Akman CI, Montenegro MA, Jacob S, Eck K, Chiriboga C, Gilliam F, et al. Seizure frequency in children with epilepsy: factors influencing accuracy and parental awareness. Seizure 2009;18(7):524–9.
[85] Aghaei-Lasboo A, Fisher RS. Methods for measuring seizure frequency and severity. Neurol Clin 2016;34(2)383–94 viii.
[86] Sinha S, Satishchandra P, Kalband BR, Thennarasu K. New-onset status epilepticus and cluster seizures in the elderly. J Clin Neurosci 2013;20(3):423–8.