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Cluster reduction in patients in a pilot treatment trial for psychogenic nonepileptic seizures

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ABSTRACT

Introduction: The present study examined seizure clusters as a primary outcome in patients receiving treatment for PNES. Cluster reduction is examined longitudinally using frequency threshold and statistical definitions of seizure cluster for patients. Possible risk factors for clustering will be examined along with clustering as a risk factor for poorer secondary outcomes.
Methods: Participants were from a pilot randomized treatment trial for PNES where they received cognitive behavioral therapy-informed psychotherapy (CBT-ip), sertraline, combination therapy, or treatment as usual. Seizure data are from patients' seizure dairies.
Results: Cluster reduction was observed for those receiving CBT-ip or combination treatment using all definitions of daily clusters and weekly clusters. No risk factors of clustering were observed. Those who were identified as having clusters during the trial had poorer secondary outcomes on several measures at baseline relative to those who were not identified as having clusters.
Discussion: This is the first study known to the authors to not only examined seizure clusters as a primary outcome for those with PNES, but also the first study to suggest that CBT-ip and combination therapy may be effective in reducing the frequency of clusters.

1. Introduction

It is estimated that up to 33 per 100,000 people in the general population [1] and up to 20% of those with epilepsy suffer from psychogenic nonepileptic seizures (PNES) [2]. Despite being as prevalent as Multiple Sclerosis and Parkinson's disease [3], to date, relatively few randomized controlled trials (RCTs) have been conducted examining treatment for PNES. An early single-arm cognitive behavioral therapy (CBT) trial demonstrated significant seizure frequency reduction over 12 weeks [4] while a subsequent two-arm pilot RCT found those in the CBT arm reported greater reduction in seizure frequency relative to those receiving standard medical care (SMC) [5]. Another two-arm pilot RCT found those receiving sertraline reported a significant decrease in seizure frequency, while those in the placebo arm did not [6]. These same researchers also conducted a single arm trial which found that patients receiving cognitive behavioral informed psychotherapy (CBT-ip) experienced a reduction in seizures, improvement with comorbidities, and increased functioning [7]. Recently, a four-arm pilot RCT examining CBT-ip, CBT-ip + sertraline, sertraline medication (MED), and treatment as usual (TAU) found that those receiving CBT-ip or CBT-ip + sertraline experienced a significant reduction in seizure frequency, while the reduction in those receiving sertraline alone only approached significance; no significant reduction in seizures or comorbidities was found in those receiving TAU [8].

What is common in all five treatment trials is the primary outcome of interest was seizure frequency, though many important secondary outcomes, such as quality of life and depression, were also examined. Just as seizure frequencies are the primary outcome in epilepsy trials, so too, were they in the PNES clinical trials. Focus on seizure frequency as the primary outcome of interest is understandable, given that seizures are the defining feature of a PNES diagnosis [9] along with seizure events being a major source of disability, dysfunction, and subjective distress for patients.

Given that individual seizure events can be both debilitating and distressing, it follows that when seizure events are more frequent than usual, their impact may be more disruptive than usual. Where it may be more difficult to consistently, objectively, and empirically measure distress and debilitation caused by an individual or group of seizures, a seizure count is a distinct event that can be observed and measured. Within the epilepsy literature, Haut has examined the phenomenon of seizure clustering, whereby multiple seizure events happening within a specified time interval are considered a cluster [10]. Research on seizure

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clusters indicates that clustering is associated with poorer outcomes in the population with epilepsy [11].

Though the occurrence of seizure clustering in patients with PNES is both acknowledged in the review literature [12] and known to clinicians, presently, only one study known to the authors has examined clustering in patients with PNES [13]. That study is the paired paper to this study and examined seizure clusters as events using three different definitions of cluster, along with estimating prevalence of clustering and frequency of clusters in the population with PNES. Currently, there is no published research known to the authors examining cluster events as a primary outcome of interest for a RCT treatment trial for PNES, or examining both risk factors associated with clustering and clusters as risk factors for poorer outcomes for patients with PNES.

The present study examines seizure cluster events, as examined in and defined by Baird et al. [13], a primary outcome of interest in patients enrolled in a four-arm RCT for PNES. In addition, this study also examines possible risk factors for clustering along with examining clustering as a risk factor for poorer secondary outcomes. We hypothesize that the arms receiving the psychotherapy (without and with medication treatment) will experience a reduction in cluster frequency, while the TAU arm will experience no significant reduction in cluster frequency. In addition, we hypothesized that those who are identified as having clusters also will have poorer outcomes relative to those who do not have clusters.

2. Methods

2.1. Sample and design

The sample and design for this study is from a pilot RCT with four treatment arms: CBT-ip, sertraline medication and CBT-ip combination (COMB), sertraline medication alone (MED), and TAU. In total, 34 patients were followed over 11 to 34 weeks, where patients prospectively recorded their daily seizures on calendars for the duration of the trial. These logs were reviewed and discussed by clinicians with patients in the two CBT-ip containing arms at weekly appointments and at bi-weekly appointments for patients in the sertraline and TAU arms. Further details concerning this trial and its sample can be found in the study article [8].

The trial [8] was approved by the institutional review boards of Rhode Island Hospital, Stanford University, and University of Cincinnati, and all enrollees provided written informed consent.

2.2. Cluster identification

Cluster events were identified using the three definitions examined previously (see Baird et al. [13]). Briefly, Baird et al. operationalize a cluster event as a specific time interval in which the number of seizure events experienced by a patient exceeds what would be expected for that patient given the time interval. This operational definition of cluster was advanced for a number of reasons. Because individual seizure events vary in duration, intensity, and impact on functioning and distress, both between patients and within patients, clusters were defined using the unit of the seizure, as it is defined for the patient, along with its frequency. Because a patient's typical seizure frequency itself also varies between patients, a cluster event could not be based on frequency alone, but rather relative frequency. Thus, a cluster is defined as such when a patient's seizure frequency for a given day exceeds what would be expected, using either the patient's subjective seizure rate or their actual seizure rate of the previous seven days, as the reference.

It should be noted, from the outset, we acknowledge the complexity of PNES and that this single measure or event does not capture the multi-dimensionality of the comorbidities and psychosocial stressors present in patients with PNES, just as a blood glucose reading does not capture the complexity of diabetes. We offer a means for clinicians and researchers to address one of the symptoms of PNES (that is, the ictus) in a systematic manner, using a count, which is done similarly in other paroxysmal disorders, (e.g. epilepsy, migraines, panic attacks, and the like). We do not intend to oversimplify the condition, but rather to provide one metric that could be examined in clinic and in research to further understand the disorder.

Therefore, two definitions are considered from Baird et al. that use Poisson modeling. Specifically, for both statistical definitions, a cluster event was identified when three or more seizures for a given day statistically exceeded the number of expected seizures. Each statistical definition differed in how the expected seizure frequency was calculated. These expected seizure rates were:

a. subjective average seizure occurrence at trial entry (i.e., "subjective");
b. observed seizure rate for the previous 7 days of the day in question (i.e., "seven").

A full discussion of why each expected seizure rate was considered can be found in Baird et al. [13]. Last, the threshold frequency only approach was also considered, which defines a cluster as three or more seizures in a given day. This definition was included as a comparison, given that it is sometimes clinically used to identify clusters for PNES.

As with Baird et al. [13], statistical definitions use the three or more seizure requirement as a necessary but not sufficient condition of cluster identification — thus making these statistical definitions conceptual extensions of the threshold approach. Evidence that the observe seizure count exceeded the expected count was established when $p < 0.05$. Though the level of significance could be increased or decreased, in concept, the Poisson test provides researchers and clinicians a framework by which a higher frequency of seizures occurring than expected, a cluster, may be discriminated from several seizures occurring.

As in Baird et al. [13] for clarity, the three or more seizure definition is referred to as "threshold"; statistical definitions of cluster is distinguished by their respective expected seizure rate references: thus statistical definitions are referred to as "subjective" and "seven".

2.3. Risk factors

Several patient characteristics, such as demographics, medical history, comorbidities, neurological results, and current medications, were examined as possible risk factors for clustering.

2.4. Secondary outcomes

The following secondary measures were used to assess other aspects of patient functioning: the Beck Depression Inventory–II (BDI), Beck Anxiety Inventory (BAI), Barratt Impulsiveness Scale (BIS), Davidson Trauma Scale (DTS), Dissociative Experiences Scale (DES), Symptom Checklist 90 (SCL), Quality of Life in Epilepsy Inventory 31 (QoLIE-31), Burden to Family Scale, Expectations Scale, Global Assessment of Functioning (GAF), Hamilton Depression Rating Scale (HAM-D), Oxford Handicap Scale (OHS), Clinical Global Impressions–Improvement scale (CGI-Imp), and Clinical Global Impressions — Severity Scale (CGI-Sev). Other outcomes that were examined include utilization and functioning variables: emergency room (ER) visits, urgent physician (MD) visits, hospital admission, disability status, driving status, and unemployment status. Because this trial was not powered to detect differences between those who clustered and those who did not within treatment arm, potential impact of clustering on secondary measures could only be assessed at baseline.

2.5. Statistical methods

All analyses were conducted using SAS 9.2 (SAS Software Inc., Cary, NC). Cluster events were examined over time for each treatment arm using each of the three cluster definitions as previously described. Daily cluster events were modeled using generalized estimating