Neurological Disorders & Epilepsy Journal

SCIENTIFIC LITERATURE

Short Reviews

Unconventional Therapies in Super-Refractory Status Epilepticus

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ARTICLE INFO

Received Date: August 01, 2022
Accepted Date: August 24, 2022
Published Date: August 26, 2022

KEYWORDS

Status epilepticus
Neurostimulation
Ketogenic diet
Immune modulation

Citation for this article: Keren Altman and Nicola Maggio. Unconventional Therapies in Super-Refractory Status Epilepticus. Neurological Disorders & Epilepsy Journal. 2022; 6(2):149.

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ABSTRACT

Status Epilepticus (SE) is a neurological emergency with high mortality and morbidity, despite having a well-defined initial therapeutic approach. In up to 40% of cases, SE is resistant to conventional therapy, namely antiseizure medications. This resistance to treatment can be to antiseizure medications alone, leading to Refractory Status Epilepticus (RSE), or to their combination with anesthesia in the case of Super Refractory Status Epilepticus (SRSE). Although both conditions are of high risk and require acute therapy, there is lack of evidence based therapeutic approaches to guide physicians in their next step. In this scenario of limited guidelines for management and urgency of aggressive therapy, the possibility rises for novel treatment alternatives to emerge in an attempt to improve patient prognosis. Here, we discuss both classical and unconventional therapeutic strategies currently considered for SRSE, and the advantages and disadvantages of each approach. As data are still scarce regarding those treatments, it is highly important to explore and compare the alternative therapies for SRSE and decide which can prove most beneficial for patients suffering from this devastating condition.

INTRODUCTION

Status Epilepticus (SE) is a life threatening neurological emergency, caused by an abnormally prolonged seizure. SE has a significantly high mortality rate of up to 40%, depending on patient age, type of SE, etiology and duration [1]. The deadliest subtype of SE is the Super Refractory Status Epilepticus (SRSE), or SE that is unresponsive to anesthesia and occurs in nearly 15% of all admitted SE cases [2]. Another definition, laying between SE and SRSE, is Refractory Status Epilepticus (RSE), which can harm 29-43% of SE patients [3]. RSE is defined as SE that is unresponsive to both first line (benzodiazepines) and second line drugs (antiseizure medications, such as valproic acid, phenytoin, phenobarbital, levetiracetam and lacosamide [2]), but is responsive to anesthesia [2]. Here, we will discuss the various etiologies leading to SRSE, the classical treatment approach and emerging new therapies that were recently proposed to resolve this hazardous and resistant condition.

In the past, many definitions were proposed to unify specific subtypes of SE based on pathophysiology, etiology, prognosis or epidemiology of this condition. Still, most definitions failed to address these factors altogether, thus preventing a joined consensus. Recently, The International League Against Epilepsy (ILAE) decided

to introduce a new SE classification based on the type of SE (tonic-clonic, focal and absence) and two different time points, which vary according to the type of SE: t1 - when treatment must be administered, and t2 - when long-term injury develops [4]. This classification contemplates the temporal aspect of SE, providing a strict time frame for acute clinical intervention prior to the occurrence of irreversible neuronal damage [4]. However, despite trying to set measurable management goals, it does not address the critical issue, which is the significant number of cases that are unresponsive to initial treatment. In those cases where conventional therapies fail, both the clinician and patient enter uncharted territory, without proper guidelines for management. Therefore, when SE progresses to RSE and SRSE, there is a dire need for a novel approach to overcome this condition and ultimately prevent immense morbidity and mortality.

To understand which suitable treatments are needed to manage resistant SE, it is important to acknowledge the basic mechanisms underlying SRSE pathophysiology. Current knowledge regarding the pathophysiology of SRSE points to the existence of an intensification of "receptor trafficking", leading to a decrease in intrasynaptic GABA receptors and increase of NMDA receptors at the surface of cells affected by SE [5,6]. Consequently, there is extensive glutamatergic activity, which leads to a substantial calcium influx and to excitotoxicity, contributing to cell death [7]. The cellular changes related to the loss of GABA receptors could explain the poor response to benzodiazepines in the treatment of SRSE [2], as the drugs lose their target receptors. Another proposed mechanism for the development of SRSE involves downstream mitochondrial dysfunction and loss of the antioxidative system, glutathione, resulting in neuronal apoptosis [6,8,9]. Evidence of the immense neuronal death is supported by the rise in serum neuron-specific enolase, a marker of neuronal injury in humans, after SE [9]. An additional explanation involves blood brain barrier breakdown due to acute inflammatory reaction [6], which helps to clarify the reasons for improvement in some SRSE patients after use of corticosteroids [5] and other immune modulators [7]. While these theories influence the rational of management, successful treatment also depends on the specific etiology leading to each case of SRSE.

SRSE ETIOLOGIES

There are various causes of SRSE that seem to differ from the known etiologies of SE. The latter involves mainly known epilepsy patients with improper antiseizure medication treatment, acute stroke, traumatic brain injury, central nervous system infections, systemic metabolic disorders and tumors [2]. Differently, SRSE was found to be related mainly to encephalitis (either infectious or autoimmune) [10]. In addition to the cases of SRSE where a cause is evident, there is the entity of New Onset Refractory Status Epilepticus (NORSE), when no clear etiology is present. NORSE is defined by the presence of RSE or SRSE without previous history of epilepsy or any obvious structural, toxic or metabolic insult that can be identified during initial clinical investigation [2,11]. However, the etiology of NORSE can be recognized at later stages in some cases, usually connected to autoimmune encephalitis [11]. In addition to encephalitis based SRSE and NORSE, there is an sub-entity of NORSE known as Febrile Infection-Related Epilepsy Syndrome (FIRES), which typically occurs when fever is present from 24 hours and up to two weeks before the onset of SRSE [11]. It is crucial to elucidate the exact etiology of SRSE when possible, as directed treatments might prevent deterioration to more radical options.

CONVENTIONAL SRSE TREATMENT

As discussed above, finding the optimal treatment for SRSE stems from identification of the underlying etiology, when possible. However, a prolonged clinical investigation without immediate treatment initiation is impractical in such a fatal condition, justifying the administration of maximal conventional treatment available meanwhile. Conventional treatment for SRSE includes antiseizure medication and general anesthesia. Regarding anesthesia, it is usually maintained for at least 48 hours from the onset of therapy, and frequently comprises continuous infusions of midazolam, propofol, barbiturates (pentobarbital or thiopental) or ketamine [12,13]. Regarding seizure control, there is no current evidence pointing to a specific antiseizure medication as being more potent than others in the management of SRSE [6,7], and each of the first or second lines of treatment mentioned above are applicable. In general, patients usually receive a combination of several intravenous antiseizure medications in maximal doses,

depending on patient history and co-morbidities. New attempts to improve the management of SRSE include the repurposing of antiseizure medications, commonly used in the context of chronic epilepsy only. For example, data from animal studies support the use of brivaracetam in SE, due to its fast onset of action and rapid penetration of the blood brain barrier [14]. It also showed to be effective in a model of self-sustaining SE, markedly reducing the duration of SE in treated rats, both in high dose monotherapy and in lower doses associated with diazepam [15]. However, the clinical results were not conclusive, as a study of 11 patients which tested the efficacy of brivaracetam use in RSE and SRSE found complete resolution of SE after 24 hours only in 3 of them [16]. Another drug that has been evaluated in the management of RSE and SRSE is perampanel, which was successful in the resolution of SE in a lithium-pilocarpine model after development of resistance to diazepam [17]. Still, the clinical evidence of perampanel is very limited and the results are modest, as data from a study with 30 patients with RSE or SRSE that received perampanel as add-on showed cessation of SE only in 5 of them. One possible factor might be the problematic drug absorption in intensive care patients, since perampanel is available only in oral formulation [18]. To conclude, despite the efforts in improving the management of SRSE by adding novel antiseizure medications, current evidence regarding these treatments is limited, justifying the urgency of alternative therapies for such critical conditions.

IMMUNOMODULATORY TREATMENT OF SRSE

As discussed above, RSE occurs when there is no response to benzodiazepines and to antiseizure medications, while SRSE is defined by persistence of SE for 24 hours or more after institution of anesthesia [2]. Once SRSE is established, alternative approaches need to be attempted. As mentioned above, a new approach that can be efficient for specific cases of SRSE is immune modulation, especially when an immune etiology is probable [2]. This is the case of autoimmune encephalitis, characterized by the presence of antibodies against central nervous system proteins [19]. The autoimmune encephalopathies more commonly associated with development of SE are the ones related to the presence of the antibodies anti-NMDAR, anti-LG1 and anti-GAD [19]. Clinical suspicion of these entities arises with the appearance of cognitive and behavioral disturbances with seizures, combined with pleocytosis of the cerebrospinal fluid and suggestive imaging with negative investigation for infectious and metabolic causes. Identification of specific antibodies provides confirmation of the diagnosis but is not mandatory for treatment initiation [19,20]. Immune based treatment options include intravenous corticosteroids, plasma exchange, Intravenous Immunoglobulin (IVIG) [21] as first line options, and cyclophosphamide, rituximab, mycophenolate mofetil and azathioprine as second line alternatives [7].

It is also important to highlight the neurosteroids, a novel pharmacological option for SRSE treatment. These agents act mainly through allosteric modulation of extra synaptic GABA [22], thus are not affected by the internalization of intra synaptic GABA receptors mentioned above [23]. One example is allopregnanolone, an endogenous neurosteroid whose cerebrospinal fluid levels drop during SE [24]. In animal models, this drug had an important antiseizure effect, both in epilepsy and in SE models [25]. Furthermore, studies with allopregnanolone analogs in rats reveal that, differently from benzodiazepines, there is no development of tolerance [25]. The experience with neurosteroids in the context of SRSE in humans is scarce, and currently includes a case report of two patients with SRSE of unknown etiology that were successfully treated with allopregnanolone [26]. Clinical trials using two drugs with similar mechanism are currently ongoing and might clarify the relevance of these agents in the clinical setting [27,28].

METABOLIC BASED THERAPIES OF SRSE

In addition to immune modulation, another simple yet effective treatment is the use of metabolic supplements. In specific cases such as eclampsia and porphyria, magnesium infusion is a viable treatment option [5]. The anticonvulsant effect of magnesium is poorly understood, but was speculated to act through inhibition of NMDA receptors [29]. Magnesium was also reported to be efficient in a few cases of FIRES [30]. Other than magnesium, Pyridoxine (Vitamin B6) was found to be an option for patients with SRSE associated with altered pyridoxine metabolism, especially in the pediatric population [5]. Another possibility that do not involve drug treatment are

the Ketogenic Diets (KD), which proved to be effective in a study of 15 patients, leading to resolution of SRSE in 78.5% of the cases [31]. In a small study, in which 2 patients were enrolled, the introduction of KD also showed resolution of SRSE [32]. This treatment has several advantages. First, it showed to be effective in withdrawal of mechanical ventilation [33]. Additionally, it is relatively easy to be administered and controlled in SRSE patients who are in the intensive care unit where they are totally dependent on external feeding. Despite its efficacy and relative safety in the management of SRSE, it is important to acknowledge some adverse effects associated with this approach. KD may cause electrolyte disturbances, acidosis and hypertriglyceridemia [10,34] and require intense monitoring. Therefore, currently there is no definitive guideline to determine when to institute KD in the treatment of SRSE, although it remains a reasonable option due to its relative feasibility and reversibility.

INTERVENTIONAL SRSE TREATMENTS

In spite of their possible beneficial effect, the treatments mentioned above still provide limited contribution for most SRSE patients. Therefore, the need for more radical therapies is emerging in intractable cases. Interventional therapies today can be divided into neurostimulation, as in Deep brain stimulation (DBS), vagal nerve stimulation (VNS) and responsive neurostimulation (RNS) or brain resection surgery.

Brain resection surgery includes various procedures such as focal resections, multilobar resections, corpus callosotomy and hemispherectomies [10,35]. This approach is designed especially for patients with SE that is unresponsive to conventional measures and whose epileptogenic foci is clear [35]. Epileptogenic foci can be identified by an extensive workup that includes both regular and functional imaging and EEG, comprising scalp and invasive monitoring [36]. Reported cases include several etiologies, such as mesial temporal sclerosis, autoimmune encephalitis and cortical dysplasia [37], although it is unclear if there is a specific etiology that benefits more from brain resection [37]. Further studies are needed to define this along with other factors such as the proper timing to institute this invasive approach. Meanwhile, acute resective procedures for SRSE should be reserved only for patients with a clear focus or lateralization that failed to respond to other types of management.

Another option that might take a larger part in treating SRSE cases in the future, is the use of Deep Brain Stimulation (DBS), Vagus Nerve Stimulation (VNS) and Responsive Neurostimulation (RNS). DBS is based on the placement of electrodes and a pacemaker-like system to generate direct influence on specific parts of the brain [38]. It is done in two main locations, the anterior and centromedian nuclei of the thalamus [39], but can be also performed in the left caudal zona incerta [39]. DBS is a promising option for resistant cases. According to cumulative data from a collection of sporadic case reports, implantation of DBS electrodes led to significant seizure frequency reduction and even total seizure suppression in 5 out of 8 patients with RSE and SRSE. Adverse effects reported were related to infection of the DBS and development of upper limb tremor [39] .Another available approach in the neurostimulation spectrum is VNS, currently approved as adjunctive therapy of refractory epilepsy [40]. Interestingly, it was suggested that VNS might be effective especially in patients with recurrent SE, influencing both the number of episodes and SE severity [41]. Based on results from animal models, several mechanisms were proposed to explain the effectiveness of VNS for SE treatment. Current theories include increased blood flow in the thalamus combined with a rise of inhibitory neurotransmitters [40], and acute desynchronization of ictal rhythms [42]. The use of VNS in the management of RSE and SRSE was reported in a case series that includes 38 patients in total, and was associated with positive results in up to 74% of patients [42]. These results especially include generalized RSE cases, as focal RSE cases seem to benefit less from this therapy [42]. Regarding adverse effects, one of the patients developed bradycardia and asystole, although those could be attributed to thiopental coma which was used simultaneously [42]. The third option available in the neuromodulation field is RNS, currently approved for the treatment of refractory focal seizures [43]. RNS, representing an additional approach for focal RSE and SRSE, consists of a cranially implanted device that monitors neural activity and responds when abnormal electrographic activity is detected [43]. The use of RNS in SRSE is currently limited. So far, there is one case reported of a young patient with history of drug

resistant epilepsy and SRSE that did not respond to multiple pharmacological treatments or to KD. In this patient, RNS implantation led to a complete return to neurological baseline after 15 days [44]. Thus, neurostimulation seems to be a potential option for SRSE, a condition with high mortality and morbidity that demands aggressive treatment. However, major limitations challenge the drawing of definitive conclusions and require extreme caution in the interpretation of current data. Such limitations include the small number of patients, the heterogeneity of the parameters of neurostimulation used in each study, the paucity of information regarding the profile and specific outcomes of each patient, the high risk for publication bias and the evidence available from anecdotal cases only. Therefore, larger prospective studies are critical to identify the ideal timing of implantation and which combinations with other therapies are more advantageous.

An additional therapy that was proposed for SRSE is Electroconvulsive Therapy (ECT). Commonly applied in the psychiatric setting, it involves a cortical stimulation to the brain, inducing a seizure [45]. The mechanism of action of ECT is not clear, however some theories were proposed. One of them proposes the elevation of seizure threshold after the end of the treatment, while an additional one suggests a rise in the action of GABA [46]. Reports of the use of ECT in RSE point to reduced seizure frequency in nearly 58% of the cases, however with a transient effect of up to three months [46]. Adverse effects were relatively mild, related mainly to short term amnesia, and in some cases repeated sessions were required [46]. Despite the fact that more data is needed, at this point, as the results of ECT in the control of SE appear to be temporary at best, its role as a durable treatment in this context seems questionable.

CONCLUSION

SE is a life-threatening condition with high morbidity and mortality, especially in its refractory forms of RSE and SRSE. Despite the urgency to start treatment, specific guidelines for appropriate management of these patients are limited and therapies other than traditional pharmacological treatment with antiseizure medications and anesthesia are not well defined. In this scenario, unconventional approaches are proposed to improve the poor prognosis of this condition. The novel therapies are diversified and include immunotherapy, metabolic based therapies, neurostimulation, brain resection surgery and ECT. In light of these novel alternatives, larger multi-center comparative and controlled studies are required to establish which options are superior for specific etiologies and the proper timing to institute them.

CONFLICT OF INTEREST

The authors declare no conflict of interest

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