Encephalitis

Review Article
pISSN 2765-4559 eISSN 2734-1461
encephalitis |Vol. 3, No. 2| January 6, 2023
https://doi.org/10.47936/encephalitis.2022.00087

Management of convulsive status epilepticus: recent updates

Jung-Ick Byun

Department of Neurology, Kyung Hee University Hospital at Gangdong, Kyung Hee University College of Medicine, Seoul, Korea

Convulsive status epilepticus (SE) is a medical emergency associated with high morbidity and mortality. Recently, clinical trials and meta-analyses investigating medical treatment of SE have been published. Benzodiazepine is well known as the first-line treatment for SE. Recent evidence suggests the equivalence of intravenous fosphenytoin, valproate, and levetiracetam for treatment of established SE. There is lack of evidence regarding treatment for refractory SE. Intravenous midazolam is commonly used, and recent evidence supports the use of ketamine. Additional studies are needed to improve the management of convulsive SE.

Keywords: Status epilepticus, Randomized controlled trial, Drug therapy

Introduction

Status epilepticus (SE) is a neurological emergency associated with time-dependent mortality and morbidity [1]. SE-related mortality in Korean adults was 10.2% within 30 days, and 30.3% within 1 year [2]. The pooled mortality of 30 studies with adult patients with convulsive SE was 15.9% (95% confidence interval [CI], 12.7–19.2). SE is a common symptom of critical neurological disease, and early recognition and prompt treatment are keys to its management [3]. The goal of treatment for SE is seizure control as promptly and safely as possible [4].

The treatment protocol for SE uses a staged approach depending on treatment response [5-7]. Benzodiazepines (BZDs) are commonly used as the initial therapy for SE. Approximately 40% of convulsive SE does not show improvement after BZDs [8,9] and is referred to as established SE. Intravenous (IV) antiseizure medication (ASM), such as fosphenytoin, valproate, or levetiracetam, then is used to manage established SE. However, 31% to 47% of patients with established SE are not controlled with ASMs [10,11], a state referred to as refractory SE.

Several clinical trials have been conducted on SE; however, there is a lack of evidence regarding its management. Recent meta-analyses and clinical trials may help manage convulsive SE patients by supporting evidence-based decisions. This review will focus on recent studies regarding convulsive SE management.

Initial treatment: benzodiazepine

Evidence supports the use of BZDs as the first-line treatment for convulsive SE [4]. Guidelines suggest the use of IV lorazepam (0.1 mg/kg, up to 4 mg), diazepam (0.15 mg/kg, up to 10 mg), or intramuscular (IM) midazolam (0.2 mg/kg, up to 10 mg) for initial management of SE [5,7,12]. Clonazepam, a BZD with rapid onset of action and long half-life, is available in IV form and can be an effective alternative first-line treatment for SE [13]. Add-on IV levetiracetam (2.5 g) to 1 mg IV clonazepam for prehospital treatment of the SE showed no further improvement in seizure cessation [14]. Pharmacokinetically, lorazepam is less lipid soluble and can persist longer than diazepam [15]. However, a meta-analysis comparing the efficacy and safety of IV lorazepam (n = 320) and IV diazepam (n =

Received: October 7, 2022 Revised: October 31, 2022 Accepted: November 15, 2022
Correspondence: Jung-Ick Byun
Department of Neurology, Kyung Hee University Hospital at Gangdong, 892 Dongnam-ro, Gangdong-gu, Seoul 05278, Korea
E-mail: jbyun@khu.ac.kr
ORCID: https://orcid.org/0000-0002-6224-4575

Copyright © 2023 by The Korean Encephalitis and Neuroinflammation Society

This is an open access article distributed under the terms of the Creative Commons Attribution Non-Commercial License (http://creativecommons.org/licenses/by-nc/4.0/) which permits unrestricted non-commercial use, distribution, and reproduction in any medium, provided the original work is properly cited.

336) revealed no significant difference between the two [16]. A recent review of four randomized controlled trials (RCTs) with 1,234 adult patients showed that BZDs are safe and effective for initial treatment of SE, and no significant difference was found between IV lorazepam and IV diazepam. Seizure cessation was approximately 60% with IV lorazepam and 40% with IV diazepam, achieved 2 to 15 minutes after administration. The seizure cessation rate with both BZDs was higher than that of the placebo group, and seizure recurrence was observed in approximately 10% of the patients [17]. Respiratory depression was seen in 6.4% with IM midazolam and 10.6% with IV lorazepam, which was lower than in the placebo group (15.5%). Mortality was 2% to 7.6% with BZD treatment, which was lower than that of the placebo group (6.2%–15.5%) [17].

Approximately 40% of patients with convulsive SE do not respond to BZDs and require further treatment. A recent study suggested that BZD resistance is more common in low- or middle-income countries than in high-income countries and is associated with a longer SE duration [18]. Resistance can be genetic through a mutation in the gamma-2 subunit (R43Q) of the $GABA_A$ receptor [19] or acquired by changes in $GABA_A$ receptor physiology due to network hyperexcitability [18]. A prospective observational study of SE over 4.5 years showed that faster treatment initiation and use of BZDs within 30 minutes of seizure onset were predictive of a shorter seizure duration [20].

For pediatric patients, intranasal midazolam was reported to have similar efficacy to intravenous diazepam for early treatment for SE [21] and was approved by the U.S. Food and Drug Administration for patients ≥12 years old with seizure clusters. However, use in an adult population is understudied [17].

Treatment for established status epilepticus: intravenous antiseizure medication

Several IV ASMs have been used as a second-line treatment for SE, and there is little evidence that any one option is superior to the other [4]. However, RCTs of BZD-resistant convulsive SE have been reported in recent years [22]. Newer ASMs (including levetiracetam or lacosamide) are being used for SE management but might increase the change in SE refractoriness and lower the chance of a return to baseline condition at discharge [22].

Intravenous phenytoin/fosphenytoin, valproate, levetiracetam

The guidelines suggest the use of IV fosphenytoin/phenytoin (20 mg/kg phenytoin equivalent), valproate (20–40 mg/kg), phenobarbital (15–20 mg/kg), and levetiracetam (60 mg/kg or 3,000–4,500 mg) for treatment of established SE that is refractory to BZDs [5,12]. Meta-analysis in 2014 showed that the efficacy of valproate (75.7%; 95% CI, 63.7%–84.8%) and phenobarbital (73.6%; 95% CI, 58.3%–84.8%) may be better than that of levetiracetam (68.5%; 95% CI, 56.2%–78.7%) or phenytoin (50.2%; 95% CI, 34.2%–66.1%) [23]. The ESETT (Established Status Epilepticus Treatment Trial), which is a multicenter randomized double-blind clinical trial of 60 mg/kg levetiracetam (max 4,500 mg), 20 mg/kg phenytoin equivalent fosphenytoin (max 1,500 mg phenytoin equivalent), and 40 mg/kg valproate (max 3,000 mg), showed no significant difference in the rate of seizure cessation or safety. The cessation of clinically evident seizures after one hour of administration was 47% (68 of 145) for levetiracetam, 45% (53 of 118) for fosphenytoin, and 46% (56 of 121) for valproate; and the median seizure duration was 10.5 minutes [11]. The efficacy of the three ASMs was similar in children, adults, and older adults [24].

Most of the recent meta-analyses compared the efficacy and safety of phenytoin to those of other ASMs (valproate, phenobarbital, or levetiracetam). One meta-analysis evaluating 10 RCTs published from 1988 to 2018 comparing phenytoin and other ASMs (valproate, levetiracetam, and phenobarbital) for SE management showed that phenytoin was inferior to ASMs overall in terms of seizure cessation. Subgroup analysis, however, showed no difference between each of the ASMs and phenytoin. Mortality or neurological outcomes were similar between the two [25]. Meta-analysis of five studies comparing phenytoin and valproate showed no significant difference in efficacy or tolerability [26]. Levetiracetam was comparable to (fos)phenytoin in terms of seizure termination rate, time of seizure termination, and drug resistance [27]. Pooled safety outcomes were better for levetiracetam than for fosphenytoin but not for phenytoin [28].

A recent review evaluating levetiracetam for SE found no significant difference in efficacy or safety among levetiracetam, valproate, and phenytoin. The efficacy of levetiracetam for cessation of SE was 46.9% to 81.8%, with more cases of psychiatric adverse events compared to valproate or phenytoin [27]. A multicenter study performed in China comparing valproate and phenobarbital for convulsive SE showed that phenobarbital was better for termination of clinical seizures [29]. A sin-

gle-center study evaluated whether a higher loading dose of valproate can have a greater effect than a normal dose. Among 128 patients with SE, 53 (41%) responded to valproate. This study showed that a higher loading dose (>30 mg/kg) was not associated with a greater response rate and suggested that a loading dose of 25 to 30 mg/kg appears adequate [32].

Lacosamide

Lacosamide is a recently developed sodium channel blocker that acts on the slow activation state in sodium channels [31]. It is not approved for treatment of SE, but several studies have shown that the drug is effective for adjunctive management [32]. A meta-analysis performed in 2017 showed that the success rate of lacosamide was 57% with adverse events, including dizziness, abnormal vision, diplopia, and ataxia [32]. A recent review comparing lacosamide (n = 115) and phenytoin (n = 166) showed similar seizure control rates and adverse event rates, but the serious side effect rate was higher for phenytoin than for lacosamide (5.1% vs. 0.8%, p = 0.049) [33].

Perampanel

Perampanel acts on the α-amino-α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptor to reduce glutamate-mediated postsynaptic excitation. Adjunctive use of perampanel to treat refractory SE was reported to be effective [34]. There is currently no randomized clinical trial evaluating perampanel for SE management. One recent review showed that 36.6% of the patients responded to the perampanel dose of 2 to 36 mg after 30 minutes to 59 days after SE [35].

Brivaracetam

Brivaracetam is a selective synaptic vesicle protein 2A (SV2A) ligand that acts similarly to levetiracetam but with greater affinity to SV2A. A retrospective study reported that more than half of SE patients responded to the median 100 mg loading dose of brivaracetam even when they already received levetiracetam. Higher dose (>1.82 mg/kg) and earlier administration improved treatment response [36,37].

Treatment for refractory status epilepticus

Among those with established SE, 31% to 43% are not controlled with IV ASM. Artificial coma therapy is often used, but there has been no randomized clinical trial, and the treatment has been largely based on expert opinion [38]. A review paper evaluated 1,168 patients who received anesthetic therapy; midazolam-controlled seizure in 78% of the patients, and propofol or thiopental/pentobarbital-controlled seizure in 68% and 64%, respectively [39]. A systematic review suggested a benefit of pentobarbital over midazolam or propofol for short-term treatment outcomes; however, pentobarbital more frequently resulted in hypotension [40].

Another systemic review suggested early use of ketamine, an *N*-methyl-D-aspartate receptor antagonist, for treating refractory SE because it has minimal adverse events. A prospective clinical trial, although terminated early, failed to show differences between propofol and barbiturates [41]. A literature search of six studies using ketamine for super-refractory SE showed seizure control in 64.2% and mortality in 38.6% of the patients. A recent study using 5 mg/kg/hr ketamine for 2 days within a median of 4 days after seizure onset showed control of super-refractory SE in 7 of 11 of the patients (63.6%) but permanent control in only 3 of 11 (27.3%).

An observational cohort study showed that the use of anesthetic drugs for SE was associated with more unfavorable outcomes and mortality [42]. However, a recent study showed that patients directly treated with artificial coma after BZDs were not associated with an increase in complications and had a shorter SE duration and intensive care unit or hospital stay [43].

Ganaxolone

Ganaxolone is a synthetic neuroactive steroid that acts as a positive allosteric modulator of the $GABA_A$ receptor and binds at a site distinct from that of BZD. An RCT of 8-week ganaxolone 1,500 mg/day reduced partial-onset seizure and was well tolerated in adult uncontrolled epilepsy patients [44]. A recent open-label phase 2 trial used a 25 to 30 mg bolus followed by continuous infusion of over 650 mg/day ganaxolone to treat convulsive and nonconvulsive SE patients. Most of the patients were seizure-free for 24 hours following infusion initiation within a median of 5 minutes [45].

Conclusion

"Time is brain" for convulsive SE. BZD is well established as the first-line treatment for SE. Recent studies support the use of IV fosphenytoin/phenytoin, valproate, or levetiracetam for second-line treatment, and selection of the ASM should be

individualized. Recent ASMs, such as lacosamide or perampanel, could be used for adjunctive treatment of SE, although this requires more evidence. For refractory SE, artificial coma therapy is used, and recent studies suggest early use of ketamine. Ganaxolone may be an effective future option for refractory SE treatment.

Conflicts of Interest

No potential conflict of interest relevant to this article was reported.

References

1. Trinka E, Cock H, Hesdorffer D, et al. A definition and classification of status epilepticus: report of the ILAE Task Force on Classification of Status Epilepticus. Epilepsia 2015;56:1515–1523.
2. Choi SA, Lee H, Kim K, et al. Mortality, disability, and prognostic factors of status epilepticus: a nationwide population-based retrospective cohort study. Neurology 2022;99:e1393–e1401.
3. Trinka E, Höfler J, Zerbs A. Causes of status epilepticus. Epilepsia 2012;53 Suppl 4:127–138.
4. VanHaerents S, Gerard EE. Epilepsy emergencies: status epilepticus, acute repetitive seizures, and autoimmune encephalitis. Continuum (Minneap Minn) 2019;25:454–476.
5. Glauser T, Shinnar S, Gloss D, et al. Evidence-based guideline: treatment of convulsive status epilepticus in children and adults: report of the Guideline Committee of the American Epilepsy Society. Epilepsy Curr 2016;16:48–61.
6. Brophy GM, Bell R, Claassen J, et al. Guidelines for the evaluation and management of status epilepticus. Neurocrit Care 2012;17:3–23.
7. Lee SK. Diagnosis and treatment of status epilepticus. J Epilepsy Res 2020;10:45–54.
8. Alldredge BK, Gelb AM, Isaacs SM, et al. A comparison of lorazepam, diazepam, and placebo for the treatment of out-of-hospital status epilepticus. N Engl J Med 2001;345:631–637.
9. Treiman DM, Meyers PD, Walton NY, et al. A comparison of four treatments for generalized convulsive status epilepticus. Veterans Affairs Status Epilepticus Cooperative Study Group. N Engl J Med 1998;339:792–798.
10. Mayer SA, Claassen J, Lokin J, Mendelsohn F, Dennis LJ, Fitzsimmons BF. Refractory status epilepticus: frequency, risk factors, and impact on outcome. Arch Neurol 2002;59:205–210.
11. Kapur J, Elm J, Chamberlain JM, et al. Randomized trial of three anticonvulsant medications for status epilepticus. N Engl J Med 2019;381:2103–2113.
12. Meierkord H, Boon P, Engelsen B, et al. EFNS guideline on the management of status epilepticus in adults. Eur J Neurol 2010;17:348–355.
13. Alvarez V, Lee JW, Drislane FW, et al. Practice variability and efficacy of clonazepam, lorazepam, and midazolam in status epilepticus: a multicenter comparison. Epilepsia 2015;56:1275–1285.
14. Navarro V, Dagron C, Elie C, et al. Prehospital treatment with levetiracetam plus clonazepam or placebo plus clonazepam in status epilepticus (SAMUKeppra): a randomised, double-blind, phase 3 trial. Lancet Neurol 2016;15:47–55.
15. Greenblatt DJ, Divoll M. Diazepam versus lorazepam: relationship of drug distribution to duration of clinical action. Adv Neurol 1983;34:487–491.
16. Brigo F, Bragazzi NL, Bacigaluppi S, Nardone R, Trinka E. Is intravenous lorazepam really more effective and safe than intravenous diazepam as first-line treatment for convulsive status epilepticus?: a systematic review with meta-analysis of randomized controlled trials. Epilepsy Behav 2016;64(Pt A):29–36.
17. Cruickshank M, Imamura M, Counsell C, et al. Management of the first stage of convulsive status epilepticus in adults: a systematic review of current randomised evidence. J Neurol 2022;269:3420–3429.
18. Burman RJ, Rosch RE, Wilmshurst JM, et al. Why won't it stop?: the dynamics of benzodiazepine resistance in status epilepticus. Nat Rev Neurol 2022;18:428–441.
19. Bowser DN, Wagner DA, Czajkowski C, et al. Altered kinetics and benzodiazepine sensitivity of a GABAA receptor subunit mutation [gamma 2(R43Q)] found in human epilepsy. Proc Natl Acad Sci U S A 2002;99:15170–15175.
20. Kellinghaus C, Rossetti AO, Trinka E, et al. Factors predicting cessation of status epilepticus in clinical practice: data from a prospective observational registry (SENSE). Ann Neurol 2019;85:421–432.
21. McTague A, Martland T, Appleton R. Drug management for acute tonic-clonic convulsions including convulsive status epilepticus in children. Cochrane Database Syst Rev 2018;1:CD001905.
22. Neligan A, Rajakulendran S, Walker MC. Advances in the management of generalized convulsive status epilepticus: what have we learned? Brain 2021;144:1336–1341.
23. Yasiry Z, Shorvon SD. The relative effectiveness of five antiepileptic drugs in treatment of benzodiazepine-resistant convulsive status epilepticus: a meta-analysis of published studies. Seizure 2014;23:167–174.
24. Chamberlain JM, Kapur J, Shinnar S, et al. Efficacy of levetiracetam, fosphenytoin, and valproate for established status epilepticus by age group (ESETT): a double-blind, responsive-adaptive, randomised controlled trial. Lancet 2020;395:1217–1224.
25. Hoshiyama E, Kumasawa J, Uchida M, et al. Phenytoin versus other antiepileptic drugs as treatments for status epilepticus in adults: a systematic review and meta-analysis. Acute Med Surg 2022;9:e717.

26. Liampas I, Siokas V, Brotis A, Zintzaras E, Stefanidis I, Dardiotis E. Intravenous sodium valproate in status epilepticus: review and meta-analysis. Int J Neurosci 2021;131:70–84.
27. Webb CA, Wanbon R, Otto ED. Levetiracetam for status epilepticus in adults: a systematic review. Can J Hosp Pharm 2022;75:46–53.
28. Feng Y, Chen Y, Jia Y, et al. Efficacy and safety of levetiracetam versus (fos)phenytoin for second-line treatment of epilepticus: a meta-analysis of latest randomized controlled trials. Seizure 2021;91:339–345.
29. Su Y, Liu G, Tian F, et al. Phenobarbital versus valproate for generalized convulsive status epilepticus in adults: a prospective randomized controlled trial in China. CNS Drugs 2016;30:1201–1207.
30. Vijiala S, André P, Buclin T, et al. Valproate in status epilepticus: correlation between loading dose, serum levels, andclinical response. Eur J Neurol 2022;29:2607–2611.
31. Doty P, Hebert D, Mathy FX, Byrnes W, Zackheim J, Simontacchi K. Development of lacosamide for the treatment of partial-onset seizures. Ann N Y Acad Sci 2013;1291:56–68.
32. Strzelczyk A, Zöllner JP, Willems LM, et al. Lacosamide in status epilepticus: systematic review of current evidence. Epilepsia 2017;58:933–950.
33. Panda PK, Panda P, Dawman L, Sharawat IK. Efficacy of lacosamide and phenytoin in status epilepticus: a systematic review. Acta Neurol Scand 2021;144:366–374.
34. Ho CJ, Lin CH, Lu YT, et al. Perampanel treatment for refractory status epilepticus in a neurological intensive care unit. Neurocrit Care 2019;31:24–29.
35. Perez DQ, Espiritu AI, Jamora RD. Perampanel in achieving status epilepticus cessation: a systematic review. Epilepsy Behav 2022;128:108583.
36. Santamarina E, Parejo Carbonell B, Sala J, et al. Use of intravenous brivaracetam in status epilepticus: a multicenter registry. Epilepsia 2019;60:1593–1601.
37. Moalong KM, Espiritu AI, Fernandez ML. Efficacy and tolerability of intravenous brivaracetam for status epilepticus: a systematic review. J Neurol Sci 2020;413:116799.
38. Byun JI, Kim DW, Kim KT, et al. Treatments for convulsive and nonconvulsive status epilepticus in adults: an expert opinion survey in South Korea. J Clin Neurol 2021;17:20–25.
39. Ferlisi M, Shorvon S. The outcome of therapies in refractory and super-refractory convulsive status epilepticus and recommendations for therapy. Brain 2012;135(Pt 8):2314–2328.
40. Claassen J, Hirsch LJ, Emerson RG, Mayer SA. Treatment of refractory status epilepticus with pentobarbital, propofol, or midazolam: a systematic review. Epilepsia 2002;43:146–153.
41. Rossetti AO, Milligan TA, Vulliémoz S, Michaelides C, Bertschi M, Lee JW. A randomized trial for the treatment of refractory status epilepticus. Neurocrit Care 2011;14:4–10.
42. Hocker SE, Shorvon S. Anesthetic drugs in status epilepticus: risk or rescue?: a 6-year cohort study. Neurology 2014;83:866.
43. De Stefano P, Baumann SM, Semmlack S, et al. Safety and efficacy of coma induction following first-line treatment in status epilepticus: a 2-center study. Neurology 2021;97:e564–e576.
44. Sperling MR, Klein P, Tsai J. Randomized, double-blind, placebo-controlled phase 2 study of ganaxolone as add-on therapy in adults with uncontrolled partial-onset seizures. Epilepsia 2017;58:558–564.
45. Vaitkevicius H, Ramsay RE, Swisher CB, Husain AM, Aimetti A, Gasior M. Intravenous ganaxolone for the treatment of refractory status epilepticus: results from an open-label, dose-finding, phase 2 trial. Epilepsia 2022;63:2381–2391.