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Treatments for Convulsive and Nonconvulsive Status Epilepticus in Adults: An Expert Opinion Survey in South Korea

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Background and Purpose The aim of this study was to survey the expert opinions on treatments for convulsive status epilepticus (CSE) and nonconvulsive status epilepticus (NCSE) in adults.

Methods Forty-two South Korean epileptologists participated in this survey. They completed an online questionnaire regarding various patient scenarios and evaluated the appropriateness of medications used to treat CSE and NCSE.

Results Initial treatment with a benzodiazepine (BZD) followed by either a second BZD or an antiepileptic drug (AED) monotherapy was the preferred treatment strategy. More than two-thirds of the experts used a second BZD when the first one failed, and consensus was reached for 84.8% of the survey items. The preferred BZD was intravenous (IV) lorazepam for the initial treatment of status epilepticus. IV fosphenytoin and IV levetiracetam were chosen for AED monotherapy after the failure of BZD. The treatments for NCSE were similar to those for CSE. Continuous IV midazolam infusion was the treatment of choice for iatrogenic coma in refractory CSE, but other AEDs were preferred over iatrogenic coma in refractory NCSE.

Conclusions The results of this survey are consistent with previous guidelines, and can be cautiously applied in clinical practice when treating patients with CSE or NCSE.

Key Words consensus, treatment, status epilepticus, nonconvulsive status epilepticus.

INTRODUCTION

Status epilepticus (SE) is a medical and neurological emergency that requires immediate treatment.[1] The International League Against Epilepsy (ILAE) established two time points relevant for the definition of SE based a seizure duration 1) that is abnormally prolonged (t_1) and 2) that can result in significant neuronal damage (t_2).[1] The t_1 time points for convulsive status epilepticus (CSE) and nonconvulsive status epilepticus (NCSE) are 5 and 10−15 minutes, respectively, while the t_2 time point is 30 minutes for CSE but unknown for NCSE.[1]

The early recognition of SE and its prompt treatment crucially affect the outcome. All of the treatment protocols for SE use a staged approach depending on the treatment response.[2,3] A benzodiazepine (BZD) is commonly used as a first-line therapy, but approximately 40% of CSE cases do not respond to BZDs,[4,5] which is then defined as established SE. Reportedly 31−47% of cases of established SE are not controlled with conventional antiepileptic drugs (AEDs),[6,7] and so are defined as refractory SEs. Due to limited prospective randomized controlled trials, the treatment protocol and guidelines for SE are often based on an expert opinion. Several trials related to SE are being conducted, but their findings can-

not be directly applied in clinical practice. Moreover, there is insufficient evidence to make evidence-based decisions on specific situations in SE, such as the use of a second BZD or how to treat febrile infection-related epilepsy syndrome (FIRES). The choice of medication can also vary between countries, and only a few studies have been reported for Asian countries.[8]

Because NCSE can also result in poor cognitive and functional outcomes,[9] it is undisputed that this condition needs timely treatment. However, there is even less evidence relevant to NCSE, and the treatment recommendations remain controversial.[10] Only guidelines from the European Federation of Neurological Societies (EFNS) included recommendations for treating NCSE, and they state that NCSE should be treated in the same manner as CSE depending on its etiology.[11] Moreover, no expert opinion survey has been performed for NCSE.

This survey aimed to determine an expert opinion of South Korean neurologists who specialize in epilepsy about adult CSE and NCSE treatments using the same survey format as in a previous study.[12] We surveyed the preference for treatment in each clinical situation that represented a different SE stage, and evaluated the presence of consensus among the included experts.

METHODS

The experts

The 42 experts who participated in this survey represent a geographic cross section of South Korea, and all of them had participated in our previous survey related to adult epilepsy treatment.[13] This study was approved by the Kyung Hee University Hospital at Gangdong Institutional Review Board (IRB No. 2019-09-005).

The survey

The present survey was based on the expert opinion survey of SE performed in the United States in 2001.[12] The clinical scenarios and questions were translated into the Korean language and modified for different clinical situations. Members of the Drug Committee of the Korean Epilepsy Society independently checked and discussed the wording before modifying it accordingly. Treatment choices were investigated regarding the two main types of SE (CSE and NCSE), which were further divided into the following four subtypes according to the ILAE semiological classification of SE[1]: generalized convulsive status epilepticus (GCSE), myoclonic SE, focal SE, NCSE with coma, and NCSE without coma. We asked two types of questions for each SE subtype: 1) the overall approach to treatment, which allowed multiple responses for each step, and 2) the preference for specific treatment modalities on a 9-point scale (1=least appropriate and 9=extremely appropriate). Moreover, we added questions regarding FIRES, which is a refractory SE that occurs from 24 hours to 2 weeks following febrile infection,[14] which was diagnosed based on the history, neuroimaging, and blood workup. Questions on the rectal administration of BZDs were not included in this survey because this is not widely applied to adult epilepsy patients in South Korea. Moreover, questions regarding intravenous (IV) lacosamide and IV clonazepam were also not included in the survey because they were not available in South Korea when the survey was performed. The survey was performed online using the Survey Monkey website (San Mateo, CA, USA).

Statistics

Data were presented as frequencies and means, like in the previous study.[13] Each medication was categorized as the treatment of choice or the first-, second-, or third-line treatment in the same manner.[15] In short, when a medication was scored as 9 (extremely appropriate) by more than half of our experts, it was considered to be the treatment of choice. We calculated the 95% confidence interval (CI) for each medication and categorized it as first, second, or third line according to a lower CI limit of >6.5, 3.5−6.5, or <3.5, respectively. If chi-square tests indicated that the distribution of responses appeared random, we considered that there was no consensus among the experts.

RESULTS

The consensus was reached for 84.8% of the survey items. Details of the questions and responses are presented in the Supplementary Materials (in the online-only Data Supplement).

Overall treatment strategy

Our experts unanimously chose IV intramuscular (IM) BZD as the preferred treatment strategy for CSE. When the first BZD did not control SE, 71.4% of the experts chose using a second BZD. The overall initial treatment strategy for NCSE was similar to that for CSE, with 66.7% of the experts recommending using a second BZD for the NCSE (Fig. 1).

Initial treatment

IV lorazepam was considered the treatment of choice by most of our experts regardless of CSE subtype: by 95%, 88%, and 86% of them for GCSE, myoclonic SE, and focal SE, respectively. IV lorazepam was also considered the treatment of choice for NCSE patients with (76%) or without (71%) coma.

No response to benzodiazepine

For GCSE and focal SE, IV fosphenytoin (83% and 71%, respectively) and IV levetiracetam (57% and 52%) were considered the treatments of choice after the failure of BZD, while IV valproate and IV phenytoin were considered as first-line treatments. For myoclonic SE, IV valproate (83%) and IV levetiracetam (76%) were selected as the treatments of choice. For NCSE with and without coma, IV levetiracetam (79% and 81%, respectively), IV valproate (74% and 69%), and IV fosphenytoin (71% and 67%) were selected as the treatments of choice after the failure of BZD.

No response to two drugs

IV levetiracetam (62%, 74%, and 69% for GCSE, myoclonic SE, and focal SE respectively) and IV valproate (55%, 74%, and 69%, respectively) were considered as the treatments of choice regardless of the SE subtype after the failure of BZD and phenytoin. These two drugs were also considered the treatments of choice for NCSE with and without coma (81% and 86%, respectively, for IV levetiracetam, and 69% and 76% for IV valproate).

Decision to induce an iatrogenic coma

Continuous IV midazolam infusion was considered the treatment of choice for iatrogenic coma therapy for CSE regardless of the SE subtype (81%, 81%, and 69% for GCSE, myoclonic SE, and focal SE, respectively). IV propofol infusion was selected as the first-line treatment for convulsive and myoclonic SE, and IV pentobarbital was chosen as the second-line treatment regardless of the SE subtype. For refractory NCSE, the experts preferred IV or oral AEDs over iatrogenic coma therapy (Table 1, Fig. 1).

Continuous IV midazolam infusion (73%) was chosen for the treatment of choice for FIRES, while IV immunoglobulin (IVIg) and IV methylprednisolone pulse were considered as first-line treatments.

DISCUSSION

We surveyed South Korean epileptologists for their opinions

Table 1. Treatment choices for CSE and NCSE

SE type	SE subtype	Treatment of choice (%)	First-line treatment
CSE			
Initial treatment	4a. Generalized CSE	IV LZP (95)	IV DZP, IV FosPHT, IV VPA, IV LEV
	4b. Myoclonic SE	IV LZP (88)	IV VPA, IV LEV, IV DZP
	4c. Focal SE	IV LZP (86)	IV DZP, IV LEV, IV FosPHT, IV VPA
No response to BDZ	5a. Generalized CSE	IV FosPHT (83), IV LEV (57)	IV VPA, IV PHT
	5b. Myoclonic SE	IV VPA (83), IV LEV (76)	LEV, LTG
	5c. Focal SE	IV FosPHT (71), IV LEV (52)	IV VPA, IV PHT
No response to two drugs	6a. Generalized CSE	IV LEV (62), IV VPA (55)	IV PB
	6b. Myoclonic SE	IV LEV (74), IV VPA (74)	
	6c. Focal SE	IV LEV (69), IV VPA (69)	
Decision to induce an iatrogenic coma	7a. Generalized CSE	IV MDZ (81)	IV Propofol
	7b. Myoclonic SE	IV MDZ (81)	IV Propofol
	7c. Focal SE	IV MDZ (69)	
NCSE			
Initial treatment	8a. NCSE with coma	IV LZP (76)	IV LEV, IV VPA, IV FosPHT, IV DZP, IV PHT
	8b. NCSE without coma	IV LZP (71)	IV LZP, IV LEV, IV VPA, IV DZP, IV FosPHT, oral AED, IV PHT
No response to BDZ	9a. NCSE with coma	IV LEV (79), IV VPA (74), IV FosPHT (71)	IV PHT
	9b. NCSE without coma	IV LEV (81), IV VPA (69), IV FosPHT (67)	IV PHT
No response to two drugs	10a. NCSE with coma	IV LEV (81), IV VPA (69)	
	10b. NCSE without coma	IV LEV (86), IV VPA (76)	
Decision to induce an iatrogenic coma	11a. NCSE with coma	IV AED (67)	Oral AED
	11b. NCSE without coma	IV AED (74), oral AED (62)	

AED: antiepileptic drug, BDZ: benzodiazepine, CSE: convulsive status epilepticus, DZP: diazepam, FosPHT: fosphenytoin, IV: intravenous, LEV: levetiracetam, LTG: lamotrigine, LZP: lorazepam, MDZ: midazolam, NCSE: nonconvulsive status epilepticus, PB: phenobarbital, PHT: phenytoin, SE: status epilepticus, VPA: valproate.

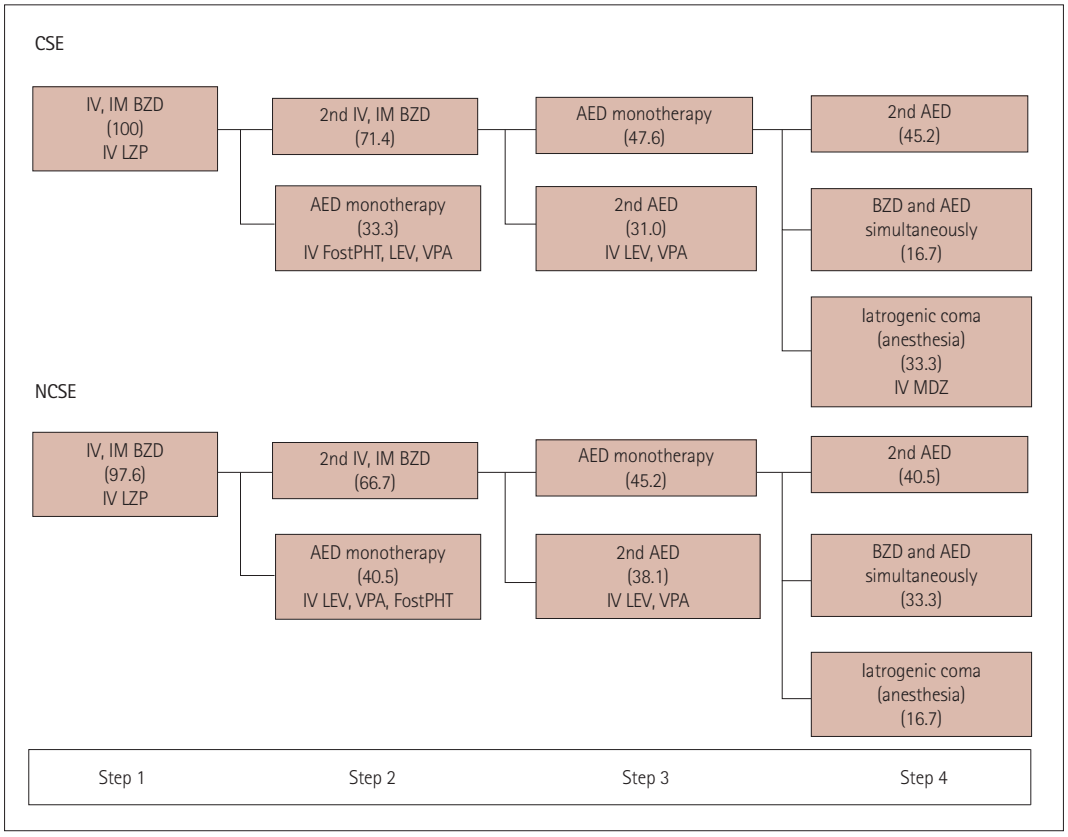

Fig. 1. Overall treatment strategy and drug of choice for patients with CSE and NCSE. Each box indicates the treatment strategy for each step (including the percentage of experts who chose the strategy for the corresponding step, with multiple responses allowed) and the medication that was chosen as the treatment of choice. AED: antiepileptic drug, BZD: benzodiazepine, CSE: convulsive status epilepticus, FosPHT: fosphenytoin, IM: intramuscular, IV: intravenous, LEV: levetiracetam, LZP: lorazepam, MDZ: midazolam, NCSE: nonconvulsive status epilepticus, VPA: valproate.

on the treatments for adult CSE and NCSE. The experts preferred treating SE first with a BZD followed by either a second BZD or an AED monotherapy. Around two-thirds of the experts (71.4% for CSE and 66.7% for NCSE) preferred using the second BZD when the first one failed. IV lorazepam was the preferred BZD. IV fosphenytoin and IV levetiracetam were chosen for AED monotherapy after the failure of BZD. For iatrogenic coma, continuous IV midazolam infusion was preferred, followed by IV propofol infusion. For patients with FIRES, immunotherapy with IVIg or IV methylprednisolone was the preferred treatment after continuous IV midazolam infusion. The treatment of choice for NCSE was similar to that for CSE: IV lorazepam followed by IV levetiracetam, valproate, and fosphenytoin. However, for those with refractory NCSE, the experts preferred IV or oral AED rather than inducing an iatrogenic coma.

BZDs were chosen as an initial therapy for both CSE and NCSE, like in the previous literature and guidelines. Our experts preferred lorazepam over diazepam due to its longer duration of action.[16] However, there is no evidence for the superiority of either particular drug.[17] IV clonazepam has also been recommended for the initial treatment of SE,[18] but its IV formulation is currently not available in South Korea. We only surveyed medications for which IV administration was possible; however, when IV access is not available, IM midazolam has been demonstrated to be equally effective.[19]

Guidelines allow the use of a second BZD when the first one fails.[2] More than two-thirds of the experts preferred using a second BZD. However, one study suggested that repeated doses of BZDs are less effective than the first dose and are associated with a higher risk of respiratory depression.[20] Underuse of BZDs may be the reason for recommending a second dose,[21] and so a second BZD might not be found to be necessary when the initial dose is sufficient.

When BZDs fail, the IV infusion of longer-acting AEDs is recommended.[3] IV phenytoin has traditionally been widely used as the second-line treatment, but there is only weak evidence for its treatment efficacy.[22,23] Our experts chose IV fosphenytoin (a prodrug of phenytoin that has better tolerability and bioavailability) and IV levetiracetam as their treatment of choice. However, there is a lack of evidence for the superiority of any particular AED. IV levetiracetam was preferred in BZD-resistant SE by several groups due to its safety and lack of drug–drug interactions.[24,25] Guidelines from Hong Kong

favored the use of medications other than phenytoin.[8] A recent randomized double-blinded trial comparing IV fosphenytoin, levetiracetam, and valproate in BZD-refractory SE found that they had similar efficacies in stopping seizures within 1 hour and similar adverse events.[7] It may be reasonable to choose from among IV fosphenytoin, levetiracetam, and valproate depending on the characteristics of individual patients, as recommended by the Neurocritical Care Society.[3]

For refractory SE, more-aggressive continuous IV infusions of coma-inducing drugs are recommended.[18] Our experts chose continuous IV midazolam infusion as the treatment of choice and propofol as the first-line treatment. This was in line with a previous survey of international experts finding that 52% chose midazolam, 32% chose propofol, and 8% chose barbiturates.[26] However, a previous survey in the United States indicated that pentobarbital was the treatment of choice.[12] Currently there is insufficient evidence for evaluating whether one drug is more effective than another for refractory SE. A systematic review of the literature suggested that pentobarbital provided better short-term treatment outcomes than did midazolam and propofol, although pentobarbital was more likely to result in hypotension.[27] A prospective clinical trial found no differences between propofol and barbiturates, although it was terminated early.[28] It might be reasonable to start with high-dose continuous IV midazolam infusion (maximum 0.4 mg/kg/hour), which produced fewer cases of breakthrough seizure and mortality than when using lower doses,[29] and add propofol in cases of superrefractory SE.

FIRES is a subcategory of new-onset refractory status epilepticus (NORSE), which is proceeded by fever or febrile infection.[14] For FIRES our experts also chose continuous IV midazolam infusion as the treatment of choice, but instead of propofol or barbiturates, they chose immunotherapy including IVIg and a methylprednisolone pulse as the first-line treatment. High-dose steroids with IVIg improved outcomes in patients with NORSE,[30] and other immunotherapies such as tocilizumab are suggested as a treatment option for patients with FIRES.[31] Immunotherapy is used in NORSE due to the possibility of underlying pathogenic or proinflammatory antibodies.[32] However, there is still controversy, since one expert survey found that 18%, 29%, and 42% of the included experts would never consider using steroids, IVIg, or steroid-sparing immunosuppressants, respectively, when treating NORSE patients.[33]

It is necessary to diagnose and manage NCSE promptly. However, most guidelines and evidence has focused on CSE, and hence there is a lack of evidence relevant to NCSE. The initial treatment strategy and medication for NCSE chosen by our experts were similar to those for CSE: IV lorazepam followed by IV levetiracetam, valproate, or fosphenytoin, which is consistent with the EFNS guidelines.[11] For refractory NCSE, our experts did not reach consensus about inducing an iatrogenic coma, which remains controversial.[34] Most experts recommended avoiding iatrogenic coma, instead using IV AEDs that have not been administered previously.[10] An observational cohort study of patients with SE, which included some with NCSE, found that the rate of complications was higher for iatrogenic coma therapy independently of other clinical cofactors.[35] This means that whether the morbidity associated with iatrogenic coma outweighs the sequelae of NCSE itself needs to be judged in individual patients.

The results obtained in this study should be interpreted while considering its limitations. This study has provided only a snapshot of expert opinion among South Koreans epileptologists in 2019, and hence does not provide definitive information for use in all scenarios. Moreover, only AEDs that were available for IV use in South Korea in 2019 were evaluated. IV lacosamide, which has shown promise in treating both CSE and NCSE,[36] was released in South Korea in June 2019 and so was not included in the present survey.

In conclusion, this study has provided the expert opinion of South Korean epileptologists about the treatments for adult CSE and NCSE. The results were in accordance with previous guidelines.[2,3,11] However, there remains discordance between the experts regarding whether to use a second BZD or induce an iatrogenic coma in NCSE. The results of this survey can be cautiously applied to patients with SE on an individualized basis.

Supplementary Materials

The online-only Data Supplement is available with this article at https://doi.org/10.3988/jcn.2021.17.1.20.

Author Contributions

Conceptualization: all authors. Data curation: all authors. Formal analysis: Jung-Ick Byun, Keun Tae Kim, Yong Won Cho. Investigation: all authors. Methodology: Jung-Ick Byun, Dong Wook Kim, Keun Tae Kim. Supervision: Dong Wook Kim, Yong Won Cho, Jae-Moon Kim. Validation: all authors. Visualization: Jung-Ick Byun. Writing—original draft: Jung-Ick Byun. Writing—review & editing: Jung-Ick Byun, Dong Wook Kim, Yong Won Cho, Jae-Moon Kim.

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Conflicts of Interest

The authors have no potential conflicts of interest to disclose.

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