Review

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Evidence-based guideline on management of status epilepticus in adult intensive care unit in resource-limited settings: a review article

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Background: Status epilepticus (SE) is a life-threatening condition associated with at least 5 min of continuous seizures or repeated seizures without regaining consciousness between episodes. It is a medical emergency with significant morbidity and mortality. The most common causes of SE are previous seizures, stroke, trauma, metabolic disorders, and central nervous system tumor. The aim of this review was to systematically review articles and ultimately develop evidence-based guidelines for the management of SE in resource-limited settings.

Methods: This review was presented under the Protocol for Systematic Reviews and Meta-Analyses (PRISMA). A literature search was performed in PubMed, Google Scholar, Cochrane, and Medline databases from 2007 to 2021. The keywords for the literature search were (SE or controlled clinical trial) AND (SE or randomized controlled trial), (SE or multicenter trial) AND (SE or meta-analysis) AND (SE or crossover study).

Conclusion: SE is an urgent medical emergency that requires early recognition and aggressive treatment. Medical treatment is initiated when seizures continue for more than 5 min after all stabilization measures have been taken. Based on the available evidence, diazepam can be used as a substitute for lorazepam in the treatment of SE. Ketamine is effective when given before other anesthetics as a third-line treatment in refractory and very refractory epilepsy. Propofol reduced the number of days of mechanical ventilation in the treatment of SE and has better seizure control than thiopental. Music has been recommended as an adjunctive therapy for epilepsy medication.

Keywords: complex partial status epilepticus, generalized convulsive status epilepticus, refractory status epilepticus, subtle status epilepticus, treatment

Introduction

Background

Status epilepticus (SE) is a life-threatening condition associated with a continuous seizure lasting at least 5 min or repeated seizures without regaining consciousness between episodes. It occurs frequently in adults and the elderly, with an incidence of 36.1 per 10 000 and an annual incidence of 12.1[1]. It is a common medical emergency with a mortality rate of 5–25%[2]. Risk factors for SE include previous seizures, stroke, infection, trauma, metabolic disorders, and central nervous system tumor. Patients with previous SE have a 30% chance of developing SE[3].

Based on the response to treatment, SE is classified into three groups; early SE, refractory, and super-refractory SE. Early SE, that lasts more than 5 min with continuous seizures without returning to baselines. Refractory SE is SE that persists after treatment of first- and second-line drug therapy. Super-refractory SE is seizure activity that lasts greater than 24 h despite treatment with anesthetic agents. It is associated with a high risk of morbidity and mortality[4].

It was difficult to determine the exact time of an epileptic seizure. Early intervention in the treatment of SE with the correct and adequate dose resolves the SE in 23% and shortens the

HIGHLIGHTS

- Status epilepticus is a medical emergency that is life-threatening if left untreated.
- Music has been recommended as an adjunctive therapy for epilepsy medication.
- Diazepam can be an alternative to lorazepam in resource-limited area.

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duration of intensive care[5]. There was a practical guide for treating SE[6]. However, the challenges of intensive care were the lack of resources in low resources. Therefore, the main purpose of this guide is to identify alternative guidelines through a systematic review of the literature.

Justification

SE is a major global health problem that requires aggressive treatment. It often occurs in adults and the elderly, with a mortality rate of 5–25 percent[2]. Most of the drugs used to treat SE are not readily available in resource-limited areas. There were practice guidelines for the treatment of patients with SE, RSE, and SRSE. According to the guidelines, lorazepam is the first-line drug, sodium valproate, and phenytoin are the second-line drugs, and thiopental sodium, propofol, and ketamine are the third-line drugs[6].

Recently, there is evidence that diazepam can be used as an alternative to lorazepam as a first-line drug in the treatment of SE[7]. Propofol shortens the duration of mechanical ventilation, shortens the length of stay in the intensive care unit, and terminates seizures more effectively than thiopental sodium in the treatment of refractory and hyperrefractory SE[8].

According to previous guidelines, ketamine was given to patients with RSE only when other anesthetics (thiopental sodium and propofol) failed. However, administration of ketamine before propofol and thiopental sodium as a third-line treatment for refractory and hyperrefractory SE is effective in seizure control, avoiding the need for intubation, and mechanical ventilation[9]. There is also evidence to support the use of Mozart (music) as a nonpharmacological aid in the treatment of epilepsy[10]. In general, this guideline aims to present evidence-based on the effectiveness of diazepam, propofol, and ketamine in the treatment of SE and their use in limited resources.

Methodology

The review presented was based on the most popular reports from the Protocol for Systematic Reviews and Meta-Analyses (PRISMA) (Fig. 1). From 2007 to 2021, a literature search was conducted from the Cochrane, PubMed, Google Scholar, and Medline databases for all English-language human studies related

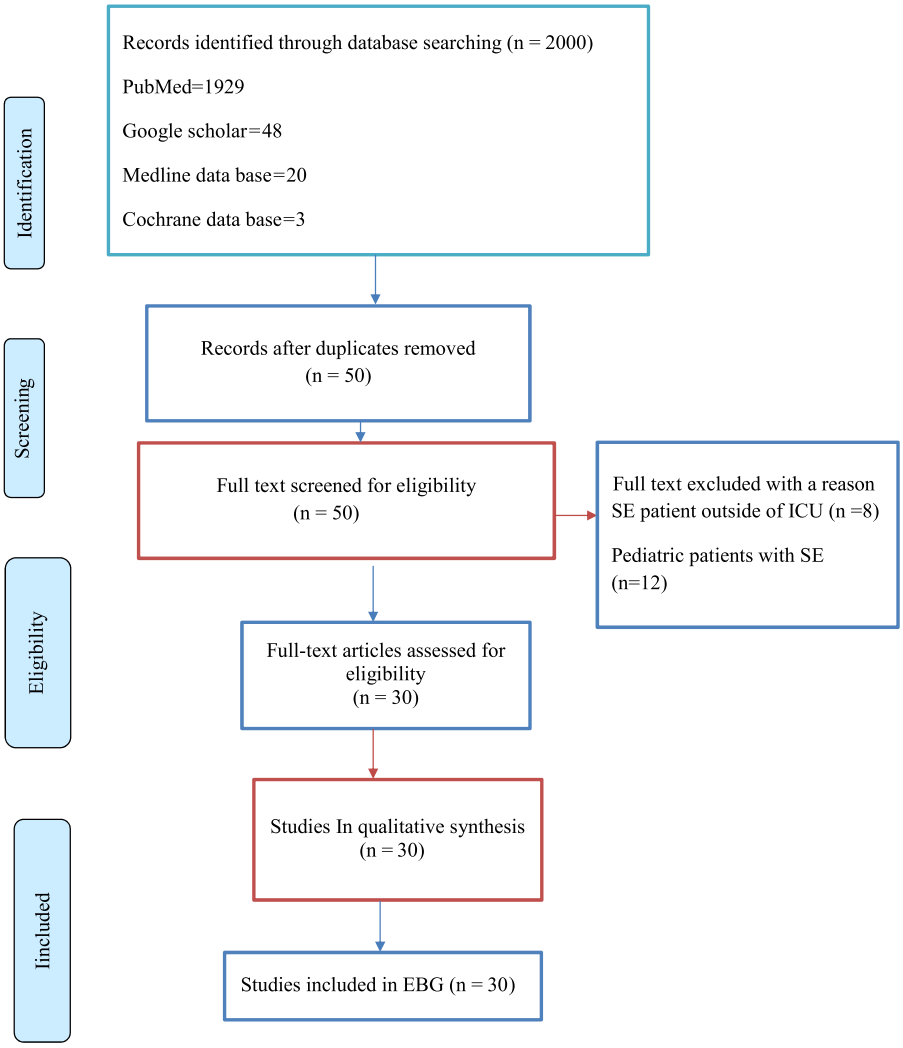

Figure 1. PRISMA flow chart.

to the treatment of SE. Several journals retrieved using the search engine were filtered based on interventions, outcomes, demographics, and methodological quality. Systematic reviews were assessed and graded according to the AMSTAR-2 review checklist[31]. Randomized controlled trials and prospective or retrospective cohort studies were also evaluated according to the Critical Appraisal Program (CASP) Checklist[32].

Overall, 2000 articles were identified using database search strategies. Finally, by filtering overlapping and unrelated articles (two RCTs, six meta-analyses and systematic reviews, two systematic reviews, six retrospective cohort studies, nine review articles, one practice guideline, and four expert opinions) on the treatment of SE were used. In the review using the following keywords: (SE or controlled clinical trial) AND (SE or randomized controlled trial), (SE or multicenter trial) AND (SE or meta-analysis) AND (SE or crossover trial). The conclusion was made based on the level of evidence and recommendations indicated by the Oxford Center for Evidence-Based Medicine (Table 1).

Discussion

General initial management

SE is a time-sensitive medical emergency associated with hypoxic brain injury that usually occurs within an hour of its onset. Respiratory failure is a major complication in 80% of patients with generalized SE and is an independent predictor of death. Early intervention, and initial stabilization by protecting the airways, providing oxygen, and opening their intravenous line is the primary therapy for the patient with SE[11].

Prolonged SE increases energy and oxygen consumption leading to metabolic acidosis. Therefore, laboratory data help in the treatment of SE. Laboratory tests required for patients with SE are; complete hematological examinations, urea, serum produces nine, electrolytes (potassium, sodium, calcium, and magnesium), and blood sugar, measurement of liver, and kidney function[12].

Patients with SE are highly risk to infection. Infection occurring in patients with SE related with increased mortality rate and prolonged duration of intensive care unit. Infections were diagnosed in 23% of critically ill SE patients. Since infection is one of the main cause of SE that should be identified urgently and treated on its own way[13].

Patients with SE associated with hypoglycemia. Glycemic disorder increases the susceptibility to the genesis of epileptic seizure. Modulation of glucose level in patients with SE and administration of 50 ml of 50% dextrose IV when glucose level is less than 60 mg/dl provide a novel and robust alternative for Treating seizure and neural damage that occurs during epileptogenesis[14].

Diazepam and lorazepam

Once a diagnosis of SE is made, appropriate antiepileptic therapy must be started immediately. Medical treatment is initiated if seizures continue for more than 5 min after all stabilization measures for patients with SE have been completed. First-line benzodiazepine therapy should be given if the attack lasts more than 5 min[5].

Lorazepam and diazepam were systematically reviewed and meta-analyzed for the treatment of SE. According to the study, there was no significant difference between the two groups in terms of cessation of clinical attacks (RR 1.09: 95% CI 1.00–2.00), continuation of SE requiring a different drug (RR 0.76: 95% CI 0.57–1.02), a single dose of medication (RR 0.96: 95% CI 0.85–1.08), and the need for mechanical ventilation was (RR 0.93: 95% CI 0.61–1.3). Even the incidence of death, hypotension, and respiratory depression was slightly higher in the lorazepam group than in the diazepam group. A loading dose of IV DZP for the treatment of SE is 0.1–0.2 mg/kg, and a maximum dose of 10 mg is recommended for the treatment of SE[7] (1a, A).

Another systematic review and meta-analysis of the effectiveness of diazepam and lorazepam in SE showed that diazepam was equally effective in controlling seizures (OR, 0.73, 95% CI 0.35–1.55; $P = 0.157$) and frequency of seizures (within 20 min) OR, 0.73, 95% CI 0.6–1.15; $I^2 = 0.0\%$, $P = 0.175$) with lorazepam. There was also no significant difference in adverse events between diazepam and lorazepam (OR, 1.13, 95% CI 0.73–1.7; $P = 0.50$)[15] (1a, A).

Phenytoin and sodium valproate

Intravenous phenytoin and sodium valproate were effective as second-line therapy for SE. The anticonvulsant effect is attributed to binding to the barbiturate site of the GABA receptor, which enhances GABA-mediated inhibition[6]. Amiri *et al.*[16] showed that there was no significant difference between sodium valproate and phenytoin in seizure control in 3 [78.18% and 39 (70.9%) patients ($P = 0.28$)]. No significant difference in mortality 12.73% VPA and 12.73% PHT: $P = 0.612$ in both groups.

The loading dose of sodium valproate for the treatment of SE is 30 mg/kg and the maintenance dose is 8 mg/kg every 8 h. Phenytoin can be given as a second-line drug. In the treatment of patients with SE, the loading dose is 20 mg/kg and 1.5 mg/kg every 8 h as a maintenance dose[16]. IV sodium valproate has been found to be as effective as IV phenytoin in SE patients. Seizures

Table 1

Level of evidence and grade of recommendation

Level of evidence	Grading criteria	Grade of recommendations
1a	Systemic review of RCT including meth-analysis	A
1b	Individual RCT with narrow CI	A
1c	All or nonrandomized control trial	B
2a	Systemic review of cohort study individual cohort including low quality RCT	B
2b	Individual cohort including low quality study	C
3b	Individual case control study	C
4	Case series poor quality cohort and case control study	C
5	Expert opinion without explicit critical appraisal	D

are controlled in 87.8% of patients treated with sodium valproate and 88% of patients treated with phenytoin[17].

There was no significant difference in efficacy and tolerability between phenytoin and sodium valproate. The effectiveness of both drugs in stopping attacks is 23.53% for VPA and 21.63% for PHT with a *P*-value of 0.13[18]. Based on their efficacy and safety profile, sodium valproate, and phenytoin are recommended as second-line treatment for patients with SE. Therefore, phenytoin can be recommended as an alternative to sodium valproate as a second-line antiepileptic for the treatment of SE in resource-limited areas[6](1a, A).

Ketamine for the treatment of status epilepticus

Ketamine is effective in the treatment of both refractory and hyperrefractory SE. In the past, ketamine was given to patients with RSE only when other anesthetics failed[19]. However, based on its potential efficacy and good safety profile, more recent studies indicate that ketamine may be more effective before other anesthetics. A systematic review showed that ketamine is effective when administered before other anesthetics, reducing the incidence of seizures from 6% in 2 patients with an RSE duration of 3 days to 32% with an average duration of 26 days. Similarly, good efficacy was observed with a response rate of 7% in 19 patients with refractory SE episodes treated after a median duration of RSE of 7 days[9] (2a, B).

Another study by Gaspard *et al.* showed that the response rate was highest when ketamine was administered before other anesthesia as third-line therapy in 60% of SE patients with seizure control. Early administration of ketamine after failure of first- and second-line AEDs controls seizures, avoiding the need for intubation and mechanical ventilation. Response rates vary between 6 and 80%[20,21] (2a, B).

Ketamine was associated with stable mean arterial pressure and reduced vasopressor requirements over time. Ketamine administration also had no effect on intracranial pressureICP (OR -0.33, 95% CI -0.32 to -0.3) and cerebral blood flow (OR -0.03, 95% CI -0.02 to -0.0) perfusion pressure (CPP) (OR - 0.13, 95% CI -0.12 -0.1)[22] (2a, B).

The study of Selam *et al.*, on 60 patients with refractory SE Showed that 57% seizure resolved, 32% seizure terminated and 11% seizure controlled with earlier administration of ketamine before propofol and thiopental sodium in the treatment of refractory and super-refractory SE. The loading dose of ketamine is 1–2 mg/kg and the maintenance dose is 1–2 mg/kg/h. for the treatment of refractory epilepsy. Therefore, ketamine is recommended over other anesthetics based on its efficacy and safety profile in the treatment of patients with RSE and SRSE[23] (2a, B).

Propofol and thiopental sodium

Propofol is a barbiturate-free intravenous anesthetic with lipid solubility and plasma protein binding of 97–98%. Propofol has a strong antiepileptic effect by inhibiting the central nervous system, increasing the effect of inhibitory GABA, reducing excitatory neurotransmitters (glutamate and aspartate), and reducing the excitability of the cerebral cortex. Propofol infusion terminates refractory and hyperrefractory SE[24].

A systematic review and meta-analysis of the effectiveness of propofol and thiopental sodium in the treatment of refractory epilepsy showed that propofol seizure control was significantly higher than thiopental sodium RSE control (Z-3.63, pandlt; 0.001). In addition, there is propofol, according to average seizure control time, average tracheal intubation time, and duration of cessation of RSE[8] (1a, A).

Prolonged intubation increases costs, so using propofol may reduce costs in the long-term. The number of days spent on a mechanical ventilator was greater in the thiopental sodium group than in the propofol group (intermediate range) ¬17 days (5–70 days) in the thiopental sodium group and four days (2–28 days) in the thiopental sodium group[25,26] (1a, A).

Propofol has good pharmacokinetic characteristics, cardiovascular tolerance, and a significant antiepileptic effect, however, prolonged infusion of propofol may cause propofol infusion syndrome[27]. The propofol loading dose in the management of RSE and SRSE is 1–3 mg/kg IV every 5 min until the seizure is controlled with a maximum dose of 10 mg/kg and the maintenance infusion rate is (5–10 mg/kg/hr)[6].

Music as an adjuvant therapy for Drug -resistance epilepsy

Music is an important part of everyday life and affects various neurological functions. Meta-analyses have shown that both short-term and long-term music therapy can improve seizures and have been used as an additional noninvasive method in the treatment of epilepsy and seizures. Analysis showed that overall, 8% (95% CI: 77.0–89.2) of patients responded to music therapy with a reduction in seizures[28] (1d, A).

The exact neural mechanisms that reduce seizures while listening to music are still not clear. However, there were several hypotheses about the antiepileptic mechanism of Mozart's music therapy. Lin *et al.* suggested that increased activity of the parasympathetic system may reduce discharge and improve seizure control in forms of epilepsy. Their results showed that most patients who responded to Mozart's music had increased parasympathetic activity. The level of dopamine, which acts as a protector of nerve cells, is reduced in most people with epilepsy. Listening to music increases dopaminergic activity in the basal ganglia by regulating dopamine receptors and stimulates dopamine release[29] (5, D).

The starting time of music therapy was not clear, but according to the result of a 6-month follow-up of epilepsy patients treated with music therapy, the longer the music therapy lasts, the more. The music used for neurological diseases can vary from classical to pop music. The patient can receive the candidate music through their smartphones and headphones without invasive material[30] (5, D). See the reviewed literature on the management of SE in the adult intensive care unit (Table 2).

Controversies and future directives

A large number of studies and, evidence-based medicine support the effectiveness of music therapy as an adjuvant antiepileptic agents. However, there has been a lack of effectively designed randomized double blind studies on music therapy as adjuvants of antiepileptic drug. There was also no clear evidence on the type of music, whether religious or language based the way how music delivered and the duration for how long music delivered. Because music therapy is simple and easy to apply large sample size, multicenter randomized double blind studies needed in the future.

Table 2

Characteristics of articles included in the guideline

References	Intervention	Study design total population	L.E	Result and conclusion
Wei wu. *et al.*2016	Lorazepam or diazepam for treatments of convulsive status epilepticus.	Meta-analysis Six RCT. Total Population = 970 DZP = 499 LZP = 471.	1a	No significance difference between the two treatment groups regarding • Seizure control [OR], 0.73, 95% CI 0.35–1.55; $I^2 = 0.0\%$, $P = 0.157$). • cessation of seizure within 20 minutes (OR, 0.73, 95% CI 0.46–1.15; $I^2 = 0.0\%$, $P = 0.175$).
Brigo. *et al.*[7]	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 Five RCT. Total population = 656 LZP = 320 and DZP = 336 patients allocated.	1a	No statistically significant differences were found between IV LZP and IV DZP • Clinical seizure cessation (RR 1.09; 95% CI 1.00–1.20), • continuation of SE requiring a different drug (RR 0.76; 95% CI 0.57–1.02), • Seizure cessation after a single dose of medication (RR 0.96; 95% CI 0.85–1.08), • Need for ventilator support (RR 0.93; 95% CI 0.61–1.43) and clinically relevant hypotension.
Amir. *et al.*[16]	Sodium valproate compared to phenytoin in treatment of status epilepticus.	RCT Total patient = 110 Phenytoin group = 55 Sodium valproate = 55.	1a	• Seizure control 43 (78.18%) with VPA and 39 (70.90%) with PHT within 7 days of drug Administration ($P = 0.428$). • mortality rate was similar in both groups (12.73 vs. 12.73%; $P = 0.612$). • There was no significant difference in adverse effects between two groups.
Tiamkao. *et al.*[18]	The efficacy of intravenous sodium valproate and phenytoin as the first-line treatment in status epilepticus:	Comparison study. Total patient = 54 Phenytoin group = 37 Sodium valproate = 17	1b	There were no significant differences between the PHT and VPA • clinically-controlled seizures, time to seizure control, • Duration of hospitalization and death. • No serious cardiovascular event such as hypotension occurred in either group. Conclusion. IV VPA is noninferior to IV PHT as the first-line treatment in SE With no significant cardiovascular compromises.
Rosati. *et al.*[9]	Ketamine for refractory status epilepticus.	Systematic review. Total population = 219.	2b	Ketamine was effective with an efficacy rate of dropping seizure from 64 to 32% in 42 patients with RSE lasting 3 days with mean duration of 26 days. Conclusion: The Study has methodological limitation and feature clinical trials will be needed to confirm the efficacy of early administration of ketamine for status epilepticus.
Alkhachroum. *et.al.* [22]	Ketamine to treat super-refractory status epilepticus.	Retrospective cohort study. Total population = 261.	2b	• Seizure burden decreased by 50% within 24 h. Of starting ketamine in 55 (81%) patients with complete seizure cessation in 43 (63%) of patients. • Ketamine was associated with stable mean arterial pressure (OR 1.39, 95% CI 1.38–1.40) and decrease vasopressor requirements. Conclusion: Ketamine treatment was associated with a decrease in seizure burden in patient with SRSE.
Gaspard. *et al.*[20]	Intravenous ketamine for refractory status epilepticus.	Multicenter retrospective study. Total population = 60.	2b	• Permanent control of refractory status epilepticus was 57% out of 60 patient who were treated with ketamine.
Zhang.*et al.*[8]	Systematic review and meta-analysis of propofol versus Thiopentone for controlling refractory status epilepticus.	Systematic review and meta-analysis. Seven RCT.	1a	Meta-analysis revealed that • The Disease control rate of propofol was higher than that of barbiturates ($P < 0.001$) and The Case fatality rate ($P = 0.382$). • Propofol also shortened the average tracheal placement time ($P < 0.001$) of RSE. • reduced the ATIPT ($P < 0.001$) of patients with RSE more extensively than did barbiturates and • Did not increase the incidence of hypotension ($P = 0.737$). Conclusions: In comparison with barbiturates, propofol can control RSE and shorten ATIPT in a more efficient and timely manner and the drug do not increase the incidence of hypotension and Case fatality.
Prapbhakar. *et al.*	Propofol versus thiopental sodium for the treatment of refractory status epilepticus.	Cochrane Database of Systematic Reviews.	1a	• The number of day of mechanical ventilator was greater in thiopental sodium group when compared with propofol group (median range) 17 days (5–70 days) with thiopental sodium and four days (2–28 days) with propofol) group.
Dastasheib *et al.*	The effect of Mozart music on interectal activity in epileptic patient.	Systemic review and metha-anlysis with 8 RCT and 4 case report.	5	• The therapeutic effect of music is effective since it is noninvasive and inexpensive adjuvant antiepileptic therapy with less side effect.

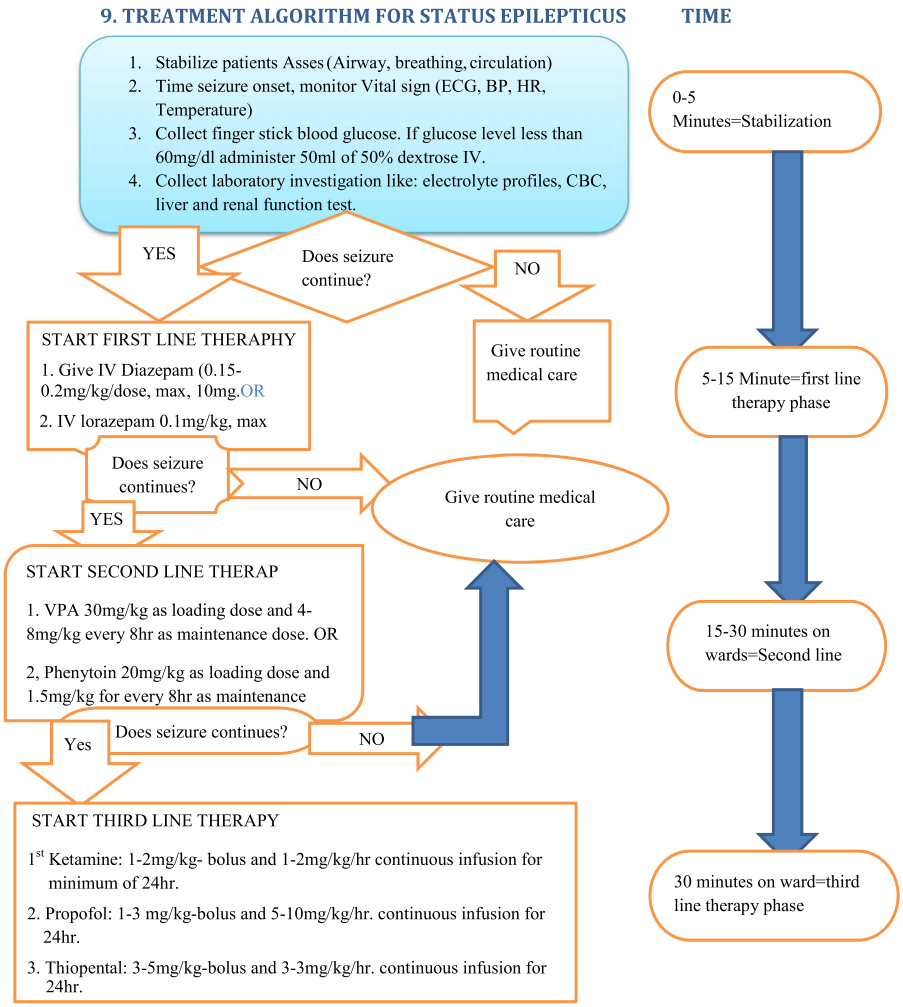

Figure 2. Management algorithm for status epilepticus in adult intensive care unit.

Conclusion

SE is a serious medical issue that needs to be treated quickly and aggressively. A significant consequence for patients with GCSEs (80%) and a standalone predictor of death is respiratory failure. The management of SE must begin with early intervention and initial stabilization. To understand the underlying reasons and to aid in the management of SE, basic laboratory studies are required. When a seizure lasts more than 5 min after all stabilization measures have been taken, pharmacological therapies are initiated. Diazepam can be utilized as an alternative to lorazepam in the treatment of SE, according to the evidence that is currently available. When used as a third-line medication for SE that is both refractory and super-refractory, ketamine is efficacious when administered before other anesthetic drugs. The number has decreased due to propofol in comparison to thiopental; propofol has a higher rate of seizure control and reduces the number of days spent on mechanical breathing when treating SE. It was advised to use music as an additional antiepileptic treatment. The recommendation has been condensed into a flow chart to make application easier (Fig. 2).

Recommendation

Recommendation 1: We recommend health professional to use 0.1–0.2 mg/kg of intravenous diazepam as loading dose and may be repeated to a maximum of 10 mg for the treatment of SE. (Strong recommendation, high quality of evidence) (1a, A).

Recommendation 2: We recommend 20 mg/kg IV phenytoin as loading dose and 1.5 mg/kg every 8 h as maintenance dose alternative to sodium valproate as second-line drug for treatments of SE. (Strong recommendation, high quality of evidence) (1a, A).

Recommendation 3: We recommend health professional to give ketamine 1-2 mg/kg as a bolus and 1-2 mg/kg/hr as continuous infusion before other anesthetic agent based on its potential efficacy and safety profile for the treatment of RSE and SRSE. (Weak recommendation, high quality of evidence) (2a, B).

Recommendation 4: We recommend health professional to give propofol 1–3 mg/kg as bolus and 5–10 mg/kg/hr as continuous infusion for treatments of refractory and super-refractory SE rather than thiopental sodium. (Strong recommendation, high quality of evidence) (1a, A).

Ethical approval

Ethical approval is not required.

Consent

Not applicable.

Conflict of interests disclosure

The authors declare that there are no conflicts of interest.

Provenance and peer review

Not commissioned, externally reviewed.

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