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Status Epilepticus in Critically Ill Children

Kritik Çocuk Hastada Status Epileptikus

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Introduction

1.1. Definition

A seizure is a paroxysmal disorder of the central nervous system and consists of abnormal excessive hypersynchronous discharges of cortical neurons and may be accompanied by changes in behavior, movement and/or consciousness. Status epilepticus (SE) is a common pediatric neurological emergency that requires prompt recognition and intervention. SE was described thousands of years ago by the people of that period in Mesopotamian inscriptions as "...his neck turning left, hands and feet are tense, and his eyes wide open and from his mouth froth is flowing without him having any consciousness".[1] SE annually affects 25,000-50,000 children, 40% of whom are children under 2 years of age. In 2015, the International League Against Epilepsy, which published seizure classification and SE reports in 1970 and 1981, defined two operational time dimensions at the meeting to evaluate the definition of SE. Time point "t1" indicates when treatment should be initiated, because if the seizure has not stopped after this point, it is characterized by sustained seizure activity. Time point "t2" defines the time point at which the risk of long-term consequences increases. In the new definition, SE is defined as seizures that are prolonged as a result of activation of seizure termination mechanisms (after time point t1). Depending on the type and duration of the seizure (after time point t2), SE can lead to long-term consequences such as neuronal death, neuronal damage and disruption of neuronal

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connections. The International League Against Epilepsy has determined the duration of abnormally prolonged seizure in convulsive SE to be 5 minutes for t1 and 30 minutes for t2 when the risk of long-term effects increases.[2,3] These time points are used to decide when and how to start treatment in SE, to reduce long-term adverse outcomes and to determine clinical effects (Table 1).

Refractory SE (RSE) is seizure activity that persists despite the administration of initial benzodiazepine group (first-line treatments) and non-benzodiazepine group (second-line treatments) therapies, although there is no one hundred percent consensus on the definition.[4] In these patients, clinical and electroconvulsive seizures may continue for hours. These patients should be followed up together with pediatric neurology and pediatric intensive care unit specialists in pediatric intensive care units where continuous electroencephalography (EEG) monitoring can be performed 24 hours a day. Treatment should be titrated to provide seizure suppression or burst-suppression with continuous EEG monitoring.[5]

Super RSE (SRSE) has been defined as SE that persists for 24 hours or longer. Seizures occurring during reduction or withdrawal of anesthesia should also be considered as SRSE.[4]

Non-convulsive SE is an occult, clinical or non-convulsive seizure disorder and is mostly detected during intensive care follow-up of patients with convulsive SE. Without continuous EEG monitoring, it is not possible to distinguish post-ictal stupor or coma due to sedative effects of treatments from non-convulsive seizures. Electroencephalographic seizures have been observed in approximately 15% of patients with controlled seizures.[5]

1.2. Morbidity and Mortality in Status Epilepticus:

Although the mortality rate related to SE varies between countries, it has been reported to be 3% in developed countries. In studies reported from different countries, mortality was found to be between 1% and 28%. In a study conducted in our country, in which 100 SE patients followed up in pediatric intensive care unit were evaluated, mortality was found to be 10%.[6] Although the risk of epilepsy can be observed with a rate of 13-74% in children followed up because of SE, the rate of a new SE may develop up to 20% during the 4 years following SE. The recurrence rate is highest in patients with structural or metabolic disorders.[5]

1.3. Febrile Seizures and Febrile Status Epilepticus:

Febrile seizures are seizures that occur in children between the age of 6 months and 60 months (most commonly between 12-18 months) with a body temperature of 38 ˚C and higher. Central nervous system infection or metabolic disorders should be excluded especially in children with no previous history of seizures. Simple febrile seizure is a type of febrile seizure that occurs in generalized tonic-clonic form in the patient and does not exceed 15 minutes. Simple febrile seizures usually do not recur in the first 24 hours. Complex febrile seizures are defined as seizures that last longer than 15 minutes and/or have focal findings and/or recur in the first 24 hours. Febrile SE refers to febrile seizures lasting longer than 30 minutes. The postictal period of most simple febrile seizures is short and the child's behavior and consciousness return to normal in a short time.[7]

2.1. Management of Status Epilepticus:

SE is a neurologic emergency that should be managed rapidly and accurately. It may be observed for various reasons (Table 2).[8] Although the outcome of SE depends on the underlying cause, seizure duration is important. Timely and appropriate intervention is more important than pharmacologic intervention.[8]

The following goals should be achieved in the treatment of acute convulsive SE:

1.Ensuring airway, respiration and circulation

2.Stopping the seizure and prevent its recurrence

3.Management of RSE in patients with RSE

4.Recognizing life-threatening lesions and taking necessary interventions (hypoglycemia, meningitis, intracranial space-occupying lesions, etc.)

Although most seizures (approximately 75%) stop within the first 5 minutes, a patient with an ongoing seizure on admission to the emergency or intensive care unit should be considered to have had a seizure for more than 5 minutes.

2.2. Ensuring Airway, Respiration and Circulation:

In patients admitted to a health center for SE, ABC should be reviewed, vital signs should be checked and the patient should be monitored. Hypoxemia is often present in these

Table 1. Conceptual definition of status epilepticus

SE type	Time point 1 (t1) (point at which the seizure is likely to be prolonged)	Time point 2 (t2) (the point at which the seizure is likely to cause long-term damage)
Tonic-clonic	5 minutes	30 minutes
Focal seizure with impaired consciousness	10 minutes	>60 minutes
Absence	10-15 minutes	Insufficient data

SE: Status epilepticus

Table 2. Common causes of convulsive status epilepticus in pediatric patients

Acute pathology
◦ Acute symptomatic
• Acute central nervous system infection (meningitis, encephalitis)
• Anoxic damage
• Metabolic imbalance (hypoglycemia, hyperglycemia, hyponatremia, hypocalcemia)
• Traumatic brain injury
• Drug-related
- Antiepileptic non-compliance or withdrawal
- Antiepileptic overdose
- Non-antiepileptic overdose
◦ Prolonged febrile seizure
Indirect pathology
Cerebral dysgenesis
Perinatal hypoxic ischemic encephalopathy
Progressive neurodegenerative diseases
Previous brain damage (meningitis, stroke, trauma)
Idiopathic/cryptogenic

patients, and administration of antiepileptics by family members or 112 before hospitalization increases the risk of respiratory depression. Airway patency and respiration should be assessed first, and 100% oxygen therapy with an irreversible mask should be started. The patient should be given an appropriate sniffing position and easily accessible secretions should be aspirated. After aspiration, the patient should be repositioned and the airway should be opened with head tilt-chin lift or jaw-thrust maneuvers if necessary. In patients with acute disturbance of consciousness or severe neuromuscular weakness, the airway may be closed because adequate glossopharyngeal muscle tone cannot be maintained. In these patients, an appropriately sized oropharyngeal or nasopharyngeal airway should be used. If the patient has signs of respiratory depression (decreased air intake and outflow, superficial breathing, inadequate respiratory effort, apnea, central cyanosis) or if oxygen saturation is below 90% despite 100% oxygen therapy, ventilation with a balloon mask should be started and rapid sequential intubation should be considered if the findings persist or the status is prolonged. Some patients may require neuromuscular muscle blockade during intubation. Short half-life neuromuscular blocking agents should be used in these patients. In patients receiving neuromuscular blocking agents, electroencephalographic seizure activity in the brain persists even if the motor component of the seizure disappears. In cases where continuous infusion of neuromuscular blocking agents is required, the patient should be followed up with continuous EEG monitoring.

Patients with seizures should be monitored tachycardia and hypertension are observed in patients with seizures. After the seizure stops, blood pressure and pulse rate return to the normal range for age. Bradycardia, signs of low perfusion and hypotension are poor signs of impaired tissue perfusion and oxygenation. Findings may be due to hypoxia and therefore ventilation with a balloon mask should be started and the patient should be endotracheally intubated. Blood glucose should be checked rapidly in a patient having a seizure. If the patient's blood sugar is <60 mg/dL, dextrose at 0.5 g/kg should be administered intravenously. If there is a central route, 2 mL/kg of 25% dextrose can be given or 10% dextrose 5 mL/kg should be administered peripherally. Blood glucose should be checked every 5 minutes and if hypoglycemia persists, the bolus dose of dextrose should be repeated.

Tachycardia, cold extremities, prolonged capillary refill, weak pulses and decreased urine output are signs of low cardiac output. At least two vascular accesses should be established. In patients with signs of circulatory disorders, appropriate isotonic fluid replacement should be administered intravenously or intraosseously at 20 mL/kg. If the patient's fever is high, intervention should be made. Paracetamol 10-15 mg/kg max: 500 mg intravenous can be administered rectally.[9]

2.3. First-line treatments:

First-line treatments can be administered in the pre-hospital period and in the emergency department. Benzodiazepines are the first group of drugs to be used in the first step. Benzodiazepines can be administered intravenously, or if there is no vascular access and it will take a long time to open, they can be administered by other routes until the vascular access is opened. Treatment options in patients without intravenous access include intramuscular, intranasal and buccal midazolam and rectal diazepam (Table 3).[8] Intramuscular midazolam is the first-line treatment for a pediatric patient older than one year and/or over 13 kg with convulsions without intravenous access. Rectal diazepam is the first-line treatment for convulsions in a patient younger than one year or weighing less than 13 kg, who has no vascular access. Intravenous diazepam is the first-line treatment option in the patient with an intravenous access. If the seizure does not stop within 5 minutes after benzodiazepine is administered to the patient, a second dose of intravenous diazepam should be administered to the patient with intravenous access.[10]

All benzodiazepines act by potentiating the neuroinhibitory effect of gamma amino butyric acid (GABA). The main difference between midazolam, lorezepam and diazepam is due to their different pharmacokinetic properties. All three benzodiazepines are metabolized via cytochrome p450-dependent isoenzymes. Midazolam, which has a half-life of 1-4 hours, is the most rapidly metabolized one. While enzyme activity is at the lowest level in the newborn, enzyme activity above normal is observed at 2-3 years of age and enzyme activity decreases back to adult level at 4 years of

Table 3. Anticonvulsants used in the first-line treatment of status epilepticus

Drug and route of administration	Dose	Maximum dose	Administration rate	Repeated dose	Risks
Midazolam					
Intramuscular	0.2 mg/kg	10 mg		In a seizure that continues 5 minutes after the first dose	Hypotension, respiratory depression, sedation
Buccal	0.5 mg/kg	10 mg			
Intranasal	0.2 mg/kg	10 mg (5 mg for each nostril)			
Diazepam					
IV, IO	0.3 mg/kg	5 mg (<5 years) 10 mg (≥5 years)	Longer than 2 minutes	In a seizure that continues 5 minutes after the first dose	Hypotension, respiratory depression, sedation
Rectal	0.5 mg/kg	20 mg			

IV: Intravenous, IO: Intraosseous

age. Repeated doses should be administered with caution in children in the infant age group.

2.4. Second-line treatments:

If the first-line treatments are applied twice with 5-minute intervals but seizures do not stop, second-line treatment is started. Phenobarbital therapy for those under 1 year of age and phenytoin therapy for those over 1 year of age, traditionally used in secondary line, have changed with the introduction of new drugs. Levetiracetam, valproic acid and lacosamide are more frequently used new generation drugs.[1] However, in a randomized blind study in the United States, there was no difference between groups in terms of levetiracetam, phenytoin and valproic acid efficacy levels and side effects in 384 patients with benzodiazepine resistant seizures.[11] In the ConCEPT study published in Australia and New Zealand and the EcLIPSE study published in the United Kingdom, no significant difference was observed in terms of clinical seizure cessation in both groups when two groups treated with phenytoin and levetiracetam were compared in pediatric patients with benzodiazepine-resistant SE. In another multi-centered study comparing levetiracetam, fosphenytoin and valproic acid treatments, which was performed in the United States, similar results were found for all three treatments for the treatment of benzodiazepine resistant SE, and each of the three drugs could be applied as the first option in the second-line treatment of SE.[12,13] Drugs used in the second line treatment of SE are given in Table 4.[8])

Phenytoin is one of the frequently used antiepileptics in the treatment of SE. Phenytoin affects the neuronal membrane by stabilizing it. Therapeutic effect occurs in about 20 minutes. Phenytoin is not effective in stopping drug-related seizures despite its frequent use and increases the risk of arrhythmia in these poisoning.

Phenobarbital is often an antiepileptic used for the seizure of the newborn and SE. Its potential side effects include respiratory depression, hypotension, bradycardia and prolonged sedation. When used with benzodiazepines, it may have an intubation requirement due to respiratory depression. Phenytoin is more in the background because it disrupts neurological evaluation due to prolonged sedation effect. Phenobarbital has no intravenous form in our country. Therefore, its use is limited.

Levetiracetam is a 2nd line agent preferred for its efficacy on all types of seizures, low side effect profile, low protein binding rate and limited metabolism from the liver. Although its oral and intravenous use is common, intramuscular route is applied safely and with high bioavailability. Intramuscular peak effect occurs in 2 hours. In patients with SE, it is thought that the application of levetiracetam may have a role in pre-hospital treatment due to its safe use and effectiveness.

Sodium is effective by regulating valproate sodium channels, potassium channels and GABA activity. Rare but severe side effects of valproic acid use are liver failure due to hepatotoxicity, pancytopenia and hyperammoniemia. It should not be used in patients with mitochondrial disease.

Pyridoxine (Vitamin B6) is the cofactor of glutamic acid decarboxylase and GABA transaminase enzymes, used in GABA synthesis and metabolism in the brain. Pyridoxine deficiency is a rare disease. Although it is mostly seen in the newborn and infant period, it can also be seen in children up to the age of 30 months. In patients with pyridoxine deficiency, seizures resistant to other conventional antiepileptics can be seen. These patients respond quickly and dramatically to pyridoxine. After other causes of seizure are ruled out, pyridoxine 100 mg can be administered intravenously. Pyridoxine should be administered by EEG monitoring if possible. The improvement in EEG brings to mind the deficiency of pyridoxine.[14]

2.5. Third-line treatments:

One definition of RSE implies seizures that have been going on for more than 1 hour despite anticonvulsive treatment. In another definition, it is emphasized as the condition that seizure continues despite the administration of two groups of anticonvulsive treatment-one of which is non-benzodiazepine

Table 4. Anticonvulsants used in the second-line treatment of status epilepticus

Drug and administration route	Dose	Maximum dose	Administration rate	Repeated dose	Risks	Suggestions
Phenytoin						
IV, IO, IM	20 mg/kg	1000 mg	It should be administered above 1 mg/kg/min dose. (It should be prepared only with 0.9% NaCl.)	If the dose is insufficient, repeat at 5 mg/kg	Hypotension, bradycardia, arrhythmia, extravasation injury if developed	Should not be given with fosphenytoin, should not be given in drug-induced seizures
Phenobarbital						
IV, IO	20 mg/kg	1000 mg	It should be administered above a dose of 1 mg/kg/min. (It should be prepared with 0.9% NaCl or 5% dextrose)		Respiratory depression, Hypotension, prolonged sedation	2nd best option in a patient <6 months, with febrile status and maintenance therapy with phenytoin
Levetiracetam						
IV, IO, IM	60 mg/kg	3000 mg	It should be given over 5-15 minutes (it should be prepared with 0.9% NaCl or 5% dextrose and should have a concentration of 15-50 mg/mL).		Psychosis	
Valproic acid						
IV, IO	30 mg/kg	3000 mg	It should be given over 5 min. (It should be prepared with 0.9% NaCl or 5% dextrose)	An additional dose of 10 mg/kg can be administered.	Liver failure, presence of mitochondrial disease, <2 years of age	

IV: Intravenous, IO: Intraosseous, IM: Intramuscular

group. These patients are at risk for complications, long hospitalization and mortality.

Although conventional antiepileptics has a low efficacy in the treatment of RSE, drugs such as topiramate, levetiracetam and carbamazepine should be continued during attacks. Higher doses or more potent agents should be used in RSE treatment. Treatment options are high-dose benzodiazepine, short-acting barbiturates, valproic acid, ketamine, lidocaine and inhalation anesthetic agents. The patients in induced coma may have cardiopulmonary insufficiency and metabolic imbalances. Multidisciplinary study is required here. Pediatric neurology specialist should lead the patient management in a diagnostic sense and should be a guide for the treatment selection and drug interactions. Pediatric intensive care specialist should provide the necessary respiratory and circulatory support treatments, management of metabolic disorders, safe induction of coma and anesthesia.

Nowadays, high-quality studies required to determine optimum RSE management are limited. Therefore, differences occur in management and treatment goals. Partly for this reason, treatment response of 15-35% of patients receiving RSE treatment is not sufficient and SRSE develops in these patients. SRSE is an ongoing seizure activity in which seizure continues more than 24 hours despite the use of anesthetic agent or in the stage of anesthetic agent cessation (15).

The definition of new-onset RSE (NORSE) is used for the patients with RSE developing without epilepsy or associated neurological disease, and without an identifiable acute structural, toxic and metabolic disorder. Febril infection-related epilepsy syndrome (FIRES), which is defined in a sub-category of the NORSE, is defined in school-age children. These patients usually have a history of feverish infection until 24 hours to 2 weeks before the SE. The SE seen in these patients may occur with fever or without fever. The etiology of these syndromes is unknown.

Its clinical presentation is mostly focal SE with convulsive SE or impaired consciousness. Another presentation is non-convulsive SE. Although the convulsive SE often evolves into non-convulsive SE, it is very important to distinguish the difference between these two phenotypes because the therapeutic approaches have different consequences. The development of non-convulsive SE in the patient is more often associated with resistance to treatment and delayed recognition of the clinic.

Most patients who are monitored due to RSE have structural brain damage, metabolic disorder and/or cerebral hypoxemia. Diagnostic studies during the evaluation of the patient who was followed due to RSE are given in Table 5.

Continuous electroencephalographic monitoring (CEEG) is the basis for the diagnosis and management of RSE and SRSE.

Table 5. Diagnostic studies that should be performed in patients followed up for RSE-FIRES

Clinical evaluation
• Evaluation for pathologies not previously considered; meningoencephalitis, sepsis, FIRES, demyelinating disease, toxicology • Detailed examination for cortical malformations, neurocutaneous syndromes, autoimmune diseases, monogenic epileptic encephalopathies, metabolic diseases, chromosomal anomalies • Ophthalmic evaluation
Laboratory parameters not previously evaluated
• Inflammatory markers: CRP, erythrocyte sedimentation rate, von Willebrand factor antigen • Infectious agents: bacterial, fungal or viral cultures and serology tests • Oligoclonal band • Autoantibody tests, neuronal or ion channel antibodies
Cranial imaging
• Gadolinium-based diffusion cranial magnetic resonance imaging, MR angiography
CSF analysis
• CSF: glucose, protein level and cell count • Bacterial, fungal or viral cultures and serology tests • Oligoclonal band • Autoantibody tests, neuronal or ion channel antibodies
Brain biopsy
• In the detection of microvascular vasculitis findings on MR angiography

CSF: Cerebrospinal fluid, FIRES: Febrile infection-related epilepsy syndrome, RSE: Refractory status epilepticus

Continuous EEG monitoring helps to stop non-convulsive seizures and to ensure burst-suppression. It is also useful in the induction of pharmacologic coma and in the detection of unrecognized seizures during drug withdrawal. Although continuous EEG monitoring plays an important role in the initial management and diagnosis of RSE/SRSE, not all pediatric studies have included CEEG monitoring in the management of RSE/SRSE. This situation greatly limits the generalization of clinical results and comparison of study results since CEEG cannot be applied in all pediatric studies on CEEG monitoring.

The therapeutic goal in patients with RSE, SRSE, NORSE and FIRES is to control clinical and electrographic seizures. In this respect, four parallel therapeutic strategies need to be addressed:

1.Is there an indication for immunotherapy? What is the hierarchy of escalation of antiepileptic therapies and anesthetic agents given as infusions?

2.Is there an indication for immunotherapy?

3.Should a ketogenic diet be started?

4.Does the patient have an indication for surgical treatment?

Pharmacotherapy in the treatment of RSE is possible with additional dose boluses of level 2 therapies (phenytoin, levetiracetam, phenobarbital, valproic acid) or medically induced coma with continuous infusion of anesthetic agents with continuous EEG monitoring. Some patients benefit from additional boluses of level 2 drugs while others benefit from continuous infusion of anesthetic agents. In the treatment management of RSE, there are no definite patient criteria to guide treatment. Since no standard treatment protocol has been established, the treatment dose should be titrated until electroencephalographic seizure arrest or burst-suppression is achieved in continuous EEG monitoring and seizure control is achieved for 24-48 hours. After that, the drug dose should be gradually decreased.[15] Drugs to be used in the treatment of RSE and SRSE are shown in Table 6.

In a patient who will receive infusion therapy for SE, midazolam infusion is usually started in the first stage. If midazolam fails, ketamine or pentobarbital infusion is administered. The elimination half-life of midazolam varies between 1.5 and 3.5 hours. This pharmacodynamic allows for repeated bolus administration and aggressive titration of the infusion, leading to relatively faster recovery. Midazolam has anxiolytic, muscle relaxant, hypnotic and anticonvulsant effects like other benzodiazepines. The exact clinical or electroencephalographic target point of midazolam has not been clearly defined. Seizure control and infusion administration time were found to be longer in patients with continuous EEG monitoring compared to patients without continuous EEG monitoring. Early burst-suppression is rarely achieved with midazolam infusion in continuous EEG monitoring, so it should not be a treatment target in patients receiving midazolam infusion. In patients receiving midazolam infusion, the goal should be to achieve 12 hours of seizure-free time followed by dose reduction. Titration of midazolam infusion is shown in Table 7.[5] There are studies in which midazolam infusion was administered up to a dose of 1.92 mg/kg/hour. Midazolam is soluble below pH 4.5 and a patient receiving 1.5 mg/kg/hour infusion receives as much ion as the hydrogen ion present in the whole body. Therefore, unexplained metabolic acidosis may be observed in patients receiving high doses, especially in patients with hepatic and renal insufficiency. Other infusion

Table 6. Pharmacological agents used in the treatment of RSE/SRSE

Drug	Action mechanism	Dose	Side effects	Clinically important points
Midazolam	Positive allosteric modulation of GABA-A receptors, increased chlorine channel opening frequency	Initial loading dose 0.2 mg/kg, Infusion rate: 0.05-2 mg/kg/h. Existence of sudden seizures under infusion: 0.1-0.2 mg/kg bolus, infusion is increased by 0.05-0.1 mg/kg/h.	Hypotension, respiratory depression	Prolonged use tachyphylaxis and drug accumulation
Thiopental	GABA receptor activation, increased chlorine channel opening, NMDA receptor inhibition, variability in chlorine, calcium, potassium ion channel conductivity	2-7 mg/kg, infusion rate ≤50 mg/min. Infusion rate: 0.5-5 mg/kg/h. Existence of sudden seizures under infusion: 1-2 mg/kg bolus, infusion is increased by 0.5-1 mg/kg/h.	Hypotension, cardiac and respiratory depression	The need for mechanical ventilation, burst-suppression should be provided in infusion EEG.
Propofol	Chlorine canal conductivity, GABA-A receptor activation	Initial loading dose 1-2 mg/kg, Infusion rate: 20 mcg/kg/min. Titrated in 5-10 mcg/kg/min doses. Should be carefully used over the dose of >65 mcg/kg/min. Existence of sudden seizures under infusion: every 5 minutes Infusion is increased by 5-10 mcg/kg/min.	Propofol infusion syndrome, hypotension, cardiac and respiratory depression	The need for mechanical ventilation, In the child, the extended infusion is relative contraindication in the presence of metabolic acidosis, the presence of hypertriglyceridemia, and the presence of mitochondrial disease. ICP decreases, It should be used carefully with steroid and catecholamine.
Ketamine	Non-competitive NMDA is glutamate receptor antagonist, it decreases neuron inducibility.	Bolus: 0,5 -3 mg/kg Infusion dose: 1-10 mg/kg/h	Tachycardia, hypertension,	It is relative contraindication in patient with increased ICP. Ketamine is an enzyme stimulant and inhibitor.
Inhaled anesthetic-Isoflurane-	Increases GABA-A receptor activity. Non-competitive NMDA is glutamate receptor antagonist.	Should be applied in the concentration of 1-5%. Burst-suppression should be provided in EEG monitorization.	Hypotension, atelectasis, paralytical ileus, infection, deep vein thrombosis in need of vasopressor	High rate of repeated seizure

ICP: Intracranial Pressure, GABA: Gamma amino butyric acid, NMDA: N-methyl D-aspartate, RSE: refractory status epilepticus, SRSE: Super refractory status epilepticus

Table 7. High dose midazolam titration in refractory status epilepticus treatment

Time after treatment starts	Midazolam dose	Step
0th min; Initial bolus	0.5 mg/kg	A
0th min; Start continuous infusion	Start 2 mcg/kg/min (0.12 mg/kg/hour)	B
5th min; Seizure continues after the 5th minutes (Step A)	Bolus repeated 0.5 mg/kg Infusion: Increase 4 mcg/kg/min (0.24 mg/kg/hour)	C
10th min; Seizure continues after the 10th minutes following Step C	Bolus 0.1 mg/kg Infusion: Increase 4 mcg/kg/min (0.24 mg/kg/hour)	D
15th min; Seizure continues after the 15th minutes following Step D	Bolus 0.1 mg/kg Infusion: Increase 4 mcg/kg/min (0.24 mg/kg/hour)	E
20th-45th min: If the seizure persists or repeats after step E, the step D is repeated every 5 minutes until the maximum dose is reached.	Maximum infusion rate 36 mcg/kg/min (1,92 mg/kg/hour)	F (5 cycle can be repeated from D to E)
45th min: Following the completion of the step F, it should be confirmed that the seizure stops with EEG. If the seizure or seizure activity continues, treatment should be considered as unsuccessful and step into H.	After the seizure control is provided with clinical monitorization and EEG, begin step I after 12 hours.	G
45th-60th min: Failed treatment	Reducing midazolam infusion and providing general anesthesia with ketamine or pentobarbital	H
Patient without clinical and electrographic seizures for 12 hours, infusion dose is decreased.	Decrease by 2 mcg/kg/min every 30 minutes.	I
EEG monitorization is continued for seizure observation of 12 hours.	Other antiepileptic treatment plan should be made and infusion should be discontinued. If there is seizure during the reduction, go to the K step. The patient is likely to have a SRSE.	J
Failure in decreasing	Bolus repeat 0.1 mg/kg Infusion: Increase 4 mcg/kg/min (0.24 mg/kg/hour) Evaluate alternatives.	K

EEG: Electroencephalography, SRSE: Super refractory status epilepticus, min: Minute

therapies should be considered in these patients. In the KETASER study, doses above 0.36 mg/kg/h (>6 mcg/kg/min) were defined as midazolam infusion failure. This dose was also defined in other studies.[16]

In patients for whom midazolam infusion has failed, clinicians usually use barbiturates as secondary agents. Pentobarbital and thiopental are barbiturates that, like midazolam, act by increasing GABA activity. In addition, they cause glutamate N-methyl D-aspartate (NMDA) receptor inhibition and restriction of ion conduction in the axonal membrane. Although pentobarbital is commonly used in clinics abroad, thiopental is available in Türkiye. Thiopental can be used as an infusion at a dose of 0.5-5 mg/kg/hour following a bolus of 2-7 mg/kg. In studies, its efficacy in stopping seizures was found to be less than propofol. It takes a long time to be excreted from the body due to its long half-life. It may cause hypotension, cardiopulmonary depression, infection, anemia and prolonged intensive care unit stay. SE cessation rates of barbiturates vary between 64-69%.[15] Since seizures persist despite midazolam infusion in patients who will be started on barbiturate infusion, it should be kept in mind that seizures may recur with barbiturate infusion and a more careful clinical follow-up should be applied in these patients in terms of the risk of SRSE development.

Propofol is a non-barbiturate anesthetic agent (GABA agonist) used for rapid induction and maintenance of anesthesia. It stops seizures within minutes after initiation of administration and provides burst-suppression. Long-term propofol infusion is not recommended in the United States and other countries. Bradycardia, apnea, hypotension and propofol infusion syndrome (metabolic acidosis, rhabdomyolysis and cardiovascular collapse, arrhythmia, renal failure) may occur. Propofol infusion syndrome may occur when the drug is administered in excess of 4 mg/kg/hour or for longer than 48 hours.

Ketamine is a typical NMDA antagonist. It has anti-convulsant and neuroprotective properties. With its unique mechanism of action, it is an alternative treatment alternative in patients receiving high dose midazolam infusion. If ketamine will be administered to patients whose seizures persist while receiving midazolam infusion under the treatment of RSE, the dose of midazolam should be reduced from 0.36 mg/kg/hour to 0.12 mg/kg/hour in patients receiving midazolam for less than 5 days to prevent anesthetic reactions. In patients receiving midazolam infusion for more than five days, the midazolam dose should be reduced from 0.36 mg/kg/hour to 0.24 mg/kg/hour in order to prevent seizures that may develop due to sudden benzodiazepine withdrawal and to prevent reactions that may develop due to sudden discontinuation of benzodiazepine. Recently published adult and pediatric studies have shown that ketamine may cause metabolic acidosis, hemodynamic disorder, sepsis and pneumonia due to prolonged use.[15]

In the ongoing KETASER01 study protocol reported from Italy, which was conducted in pediatric patients followed up due to multicenter RSE, ketamine dose was started at a dose of 10 mcg/kg/min following a bolus at a dose of 2-3 mg/kg, and the infusion dose was increased by 5-10 mcg/kg/min every 10 minutes until the seizure was under control. A bolus of 1-2 mg/kg was repeated before each increase. The maximum dose was set as 100 mcg/kg/min. After the seizure was under control, the infusion was planned to continue for 48 hours-7 days. When the seizure continued and adverse events developed, ketamine was discontinued and defined as failure. Ketamine dose was reduced by 25% every 12 hours at doses of 50-100 mcg/kg/min and by 25% every 6 hours at doses below 50 mcg/kg/min. In patients receiving ketamine infusion, the goal of continuous EEG burst-suppression like midazolam is rarely achieved. The aim is to stop seizures for 48 hours.[16]

As a last-line treatment, inhaled anesthetics can be used in the treatment of RSE. Among inhaled anesthetics, isoflurane is most commonly used in pediatric patients. Since the efficacy of inhaled anesthetics is temporary, it saves time for diagnostic studies to be performed and adjunctive therapies to be arranged. However, since they are short-acting, seizure activity relapses at a high rate as soon as they are discontinued.[15]

If a seizure recurs in a patient who is in the period of tapering continuous anesthetic infusion therapy due to RSE, this is called super-resistant SE. From this point, treatment is continued with higher doses, additional infusions or oral antiepileptics that cannot be given intravenously.

Immune modulatory therapies should be considered when autoinflammatory, autoimmune processes or cryptogenic NORSE are considered in the etiology of RSE. The most commonly used treatments are corticosteroids, intravenous immunoglobulin (IVIG) and plasmapheresis. However, their efficacy is controversial. In a publication reporting the treatment of five young adults followed up for NORSE, early immunomodulatory treatment (steroid, IVIG and azothioprine) helped to achieve seizure control in 3 patients and reduced anticonvulsive treatment to a reasonable level.[15] In a study in which twenty-one RSE/SRSE patients were evaluated, the treatment response rate with additional immune modulator therapy was only 5%.[15] Immune modulator therapies used in the treatment of RSE are shown in Table 8.

Plasmapheresis is mostly used in parallel with other immune therapies in the presence of FIRES, anti-NMDA encephalitis and RSE/SRSE due to paraneoplastic autoimmune encephalitis.

Table 8. Immune modulator agents used in the treatment of RSE/SRSE

Drug/Treatment	Action mechanism	Dose	Side effects	Clinically important points
IVIG	Change in expression and function of Ig-G specific receptors (decrease in cytokine release), decrease in complement-related cell damage	Total dose of 1-2 g/kg is given in 3-5 days	Hypersensitivity reactions, transfusion associated lung damage, thromboembolic events, renal damage due to the concentration of solution, aseptic meningitis	It should be used in the treatment of crypogenic or autoimmune RSE/SRSE.
Methylprednisolone Prednisone	Inhibition of inflammation -related proteins (cytokine, chemokine) and immune -suppressive effect	Methylprednisolone :1 gr/day,3-5 days Prednisone: 60 mg/day	Glucose intolerance, psychiatric disorders, reduced immune functions, adrenal insufficiency	
Plasmapheresis	Cleaning of autoantibodies, immune factors and high -weight proteins participating in the possible inflammatory process	5 sessions		

IVIG: Intravenous immune globulin, RSE: Refractory status epilepticus, SRSE: Super refractory status epilepticus

Although there are previous studies showing that patients with FIRES who receive early plasmapheresis treatment have better outcomes, there are also case series in which plasmapheresis is administered for FIRES and no benefit was seen.

Immune therapies targeting inflammatory cytokines thought to be involved in the etiology of refractory epilepsies may be used instead of conventional immunotherapy. Recently, anakinra has been a treatment of interest in the treatment of FIRES. Anakinra is an Interleukin type 1 receptor antagonist. It prevents the biological activation of IL-1β. In animal experiments for IL-1β-resistant seizures, IL-1β overexpression was observed in microglia and astrocytes of subjects. This suggests anakinra as a potential therapeutic agent.

Ketogenic Diet:

Ketogenic diet is a safe and effective form of treatment containing high fat, low carbohydrate and sufficient protein used as a treatment alternative in treatment-resistant epilepsies. Due to its anti-inflammatory and antiepileptic properties, it has gained value as adjunctive therapy in recent years. In pediatric case series, the success rate was found to be 54%. Ketogenic diet is contraindicated in carnitine deficiency, beta oxidation defects, beta carboxylase deficiency and porphyria. Ketogenic diet should be started with a 4:1 or 3:1 ratio (ratio of fat to protein and carbohydrate in grams), with glucose completely excluded from the diet. It may cause hypoglycemia, acidosis, weight loss and gastroesophageal reflux in the early period. Blood glucose should be checked every 3 hours for the first 3 days. If blood glucose falls below <45 mg/dL, glucose should be given. Urine and serum ketones should be checked daily. Steroids should be avoided because they inhibit ketosis.

Hypothermia:

Therapeutic hypothermia is mainly used in the treatment of traumatic brain injury. Nowadays, it can also be used in the treatment of RSE and SRSE as adjunctive therapy due to its neuroprotective and antiepileptic properties as shown in animal experiments. It has been reported in case series that RSE was controlled with hypothermia used as adjunctive therapy in the childhood age group. In a multicenter series evaluating 270 patients with convulsive SE, hypothermia did not prevent progression to RSE and did not provide positive results compared to standard treatments.[17]

Epilepsy Surgery:

Resistant cases with persistent seizures despite multiple medical treatment may be evaluated for surgical treatment by centers performing epilepsy surgery. When a focal epileptic focus is detected on neuroimaging, it can be evaluated for focal resection. Neuroimaging alone is not sufficient to determine the potential surgical resection site. At least, it should be shown that the ictal and interictal discharges of the region with structural lesion are compatible. In clinically stable patients, flurodeoxyglucose positron emission tomography should be performed to show interictal and ictal hypermettabolism of the epileptogenic focus. Special patient groups such as cortical dysplasia, tuberous sclerosis complex, polymicrogyria, hypothalamic hamartoma, hemispheric syndromes, Sturge-Weber syndrome, Rasmussen syndrome and Landau-Kleffner syndrome can be treated with epilepsy surgery. Surgical procedures may include vagal nerve stimulator, resection of the cortical lesion, temporal lobectomy, hemispherectomy, corpus callosotomy or multiple subpial resection.

Footnotes

Authorship Contributions

Concept: S.Ö., M.U.Y., F.K., F.İ.G., P.Y.Ö., Ç.K., R.Y., E.U.S., A.Ç., Design: S.Ö., M.U.Y., F.K., F.İ.G., P.Y.Ö., Ç.K., R.Y., E.U.S., A.Ç., Data Collection or Processing: S.Ö., M.U.Y., F.K., F.İ.G., P.Y.Ö., Ç.K., R.Y., E.U.S., A.Ç., Analysis or Interpretation: S.Ö., M.U.Y., F.K., F.İ.G., P.Y.Ö., Ç.K., R.Y., E.U.S., A.Ç., Literature Search: S.Ö., M.U.Y., F.K., E.U.S., A.Ç., Writing: S.Ö., M.U.Y., E.U.S., A.Ç.

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