Universitat de Girona
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INTRAVENOUS SODIUM VALPROATE VERSUS INTRAVENOUS PHENYTOIN IN THE TREATMENT OF CHILDREN'S STATUS EPILEPTICUS: a multicenter randomized controlled clinical trial

End of Term Project

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"Ignorance affirms or denies wholeheartedly; science doubts"
François Marie Arouet, Voltaire

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ABSTRACT

Background: Status epilepticus is a life-threatening condition and one of the most frequent neurological emergencies among pediatric population, with an increase of morbidity and mortality. It has an incidence rate of 17-23 episodes/100.000 children per year in developed countries.
The status epilepticus requires a promptly management with stabilization of vital functions and administration of antiepileptic drugs. The first-line antiepileptic drugs are the benzodiazepines, but if after two doses of benzodiazepines the status epilepticus persists, the second-line antiepileptic drugs must be administrated. Among these drugs, two of the most frequently used are intravenous sodium valproate and intravenous phenytoin. However, there is no consensus to decide which of them should be preferably used and there is a lack of standardized and universally accepted protocols. For example, valproate is preferred in Catalonia while phenytoin is preferred in United States of America (USA).

Objective: The principal objective of this study is to compare the efficacy (termination of status epilepticus) of intravenous sodium valproate and intravenous phenytoin in the treatment of benzodiazepine refractory convulsive status epilepticus in pediatric population.

Design: Multicenter, controlled, triple-blind, randomized clinical trial with the *Hospital Universitari de Girona Doctor Josep Trueta* (Girona) as the reference center. The other participating hospitals are: *Hospital Universitari Vall d'Hebron* (Barcelona), *Hospital Sant Joan de Déu* (Barcelona), *Hospital Universitari Arnau de Vilanova* (Lleida), *Hospital Universitari Parc Taulí* (Sabadell) and *Hospital Universitari Joan XXIII de Tarragona* (Tarragona).

Methods: Patients enrolled in this study will be randomized in two groups (A and B). In order to terminate the status epilepticus, the group A will receive an infusion of intravenous sodium valproate while the group B will receive an infusion of intravenous phenytoin. The efficacy and safety of these drugs of study will be evaluated and recorded and the patients will be followed-up during one month to evaluate their mortality and neurological outcome.

Participants: Children (≥ 1 years old and < 15 years old) suffering a convulsive status epilepticus refractory to two doses of a benzodiazepine (midazolam or diazepam) attended by the hospitals that will take part of this study.

Key words: status epilepticus, children, phenytoin, sodium valproate, benzodiazepine refractory

ABBREVIATIONS

AED(s): Antiepileptic Drug(s)

AEMPS: Asociación Española de Medicamentos y Productos Sanitarios

BZD(s): Benzodiazepine(s)

CNS: Central Nervous System

CSE: Convulsive Status Epilepticus

CT: Computed Tomography

ECG: Electrocardiogram

EEG: Electroencephalogram

GABA: Gamma-aminobutyric Acid

ILAE: International League Against Epilepsy

MRI: Magnetic Resonance Imaging

MTS: Mesial Temporal Sclerosis

NCSE: Non-convulsive Status Epilepticus

NHS: National Health System

NLSTEPSS: North London Convulsive Status Epilepticus in Childhood Surveillance Study

NMDA: N-methyl-D-aspartate

PAT: Pediatric Assessment Triangle

PHT: Phenytoin

PICU: Pediatric Intensive Care Unit

PRSE: Prolonged Refractory Status Epilepticus

RASS: Richmond Agitation-Sedation Scale

RCT: Randomized Controlled Trial

RSE: Refractory Status Epilepticus

SBP: Systolic Blood Pressure

SD: Standard Deviation

SE: Status Epilepticus

USA: United States of America

VPA: Sodium Valproate

1. INTRODUCTION

In order to understand the status epilepticus (SE) and its definition, we should prior understand the following concepts: seizure and epilepsy.

1.1. Seizure

The International League Against Epilepsy (ILAE) considers a seizure as "a transient occurrence of signs and/or symptoms due to abnormal excessive or synchronous neuronal activity in the brain. The term transient is used as demarcated in time, with a clear start and finish" (1).

The clinical manifestation of a seizure is variable: consciousness depression or sensitive, motor, autonomic or psychic alterations (2).

According to its etiology, a seizure can be divided in (3):

- **Acute symptomatic seizure (or provoked seizure)**: seizure that occurs in close temporal relationship with an acute central nervous system (CNS) insult such as a metabolic, infectious or structural insult. The time interval between the seizure and the CNS insult varies depending on the underlying clinical condition.
- **Unprovoked seizure**: seizure that occurs in the absence of a responsible clinical condition or beyond the time interval for the occurrence of an acute symptomatic seizure.

According to its physiopathology, a seizure can be divided in (4):

- **Focal**: seizure that is originated within a cerebral network limited to one hemisphere.
- **Generalized**: seizure that is originated within a rapidly engaging and bilaterally distributed cerebral network.

1.2. Epilepsy

Epilepsy is a cerebral disturbance that produces a long-term predisposition to generate seizures and it is characterized for its social, psychological and neurocognitive consequences. According to the ILAE (5):

"Epilepsy is a disease of the brain defined by any of the following conditions:

1. At least two unprovoked (or reflex) seizures occurring >24 h apart.
2. One unprovoked (or reflex) seizure and a probability of further seizures similar to the general recurrence risk (at least 60%) after two unprovoked seizures, occurring over the next 10 years.
3. Diagnosis of an epilepsy syndrome."

1.3. Status epilepticus

1.3.a. Definition

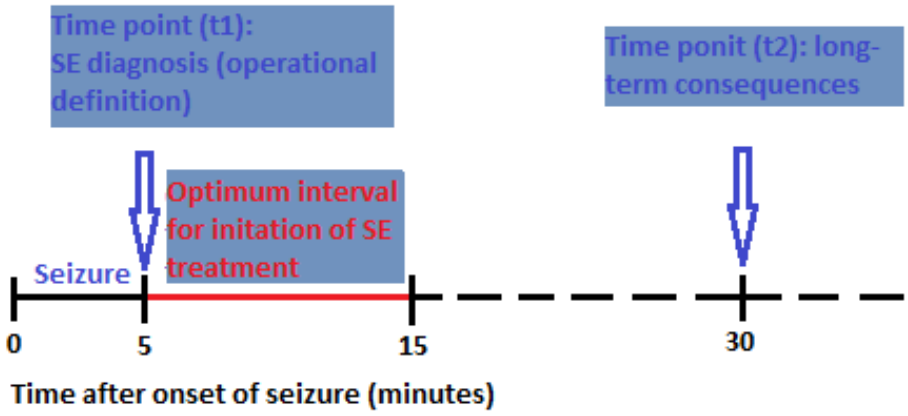
Status epilepticus (SE) is a life-threatening condition and a neurological emergency. However, during the last years, its definition has suffered important modifications. This fact seems to be related to the lack of understanding of the basic physiopathological mechanisms that underlie the SE (6).

The most accepted definition of SE until today has been: a prolonged seizure that lasts for at least 30 minutes, or 30 minutes of intermittent seizures without full recovery of

consciousness between them (7). The threshold of 30 minutes was determined because the irreversible cerebral damages appear at this time of seizure (1).
However, this definition is constantly evolving and some authors, including the ILAE, are already assuming that the SE must be diagnosed when the seizure lasts for at least 5 minutes, not 30 (1) . In fact, ILAE divides the SE in two phases (time point t1 and t2):
"SE is a condition resulting either from the failure of the mechanisms responsible for seizure termination or from the initiation of mechanisms that lead to abnormally prolonged seizures (**time point t1: ≥ 5 minutes**). It is a condition that can have long-term consequences (after **time point t2: ≥ 30 minutes**), including neuronal death, neuronal injury and alteration of neuronal networks, depending on the type and duration of seizures" (1).

This new "operational definition" is based on the work, focused with adults, done by Lowenstein et al in 1999 (6) and it has the main goal to diagnose and, then, to start the SE treatment as soon as possible. In fact, those seizures that last five minutes or more (time point t1) have a high risk of lasting 30 minutes or more (time point t2), time when long-term consequences appear (*Figure 1*). So, starting the diagnosis and the treatment of the SE at 5 minutes is basic to prevent its perpetuation. An early intervention reduces the risk of SE-induced neuronal injury and the risk of pharmacoresistance, which is time-dependent (8).

Figure 1. Duration of seizure activity and key time periods. Modified from (9)



However, this "operational definition" is used mainly for generalized convulsive status epilepticus (CSE), the most frequent type of SE. We do not have enough evidence to decide when to diagnose and start the treatment of a non-convulsive SE (NCSE) and a focal SE (1) (see **"1.3.d Classification. 3. Semiology"** to understand CSE and NCSE concepts). The lack of research done with the NCSE is justified by the necessity of an electroencephalogram (EEG), not always available, to diagnose it and because its definition criteria are not clear. So, in the *table 1* we can see the estimations that the ILAE does, regarding the lack of evidence for NCSE and focal SE.

Table 1. Operational dimensions with t1 indicating the time that emergency treatment of SE should be started and t2 indicating the time at which long-term consequences may be expected (1)

Type of SE	Time 1 (t1)	Time 2 (t2)
Convulsive SE (tonic-clonic)	5 min	30 min
Focal SE with impaired consciousness	10 min	>60 min
Absence SE (NCSE)	10-15 min *	Unknown

**Evidence for the time frame is currently limited and future data may lead to modifications*

In the case that the SE persists despite the treatment with first and second-line antiepileptic drugs (AEDs), it is considered a **refractory SE** (RSE); this situation happens in 10-40% of cases. Moreover, if the SE persists >7 days is defined as **prolonged, refractory SE** (PRSE) (10,11).

Finally, we must remark that SE does not always mean epilepsy. In fact, 62-88% of children with a first episode of convulsive SE do not suffer prior epilepsy (9). As we will see in **"1.3.d Classification. 2. Etiology"**, most of the SE among children are produced due to acute central nervous system or systemic illnesses (1,12).

1.3.b. Epidemiology

Status epilepticus has a bimodal incidence rate, with a higher rate during childhood and elderly (13). The only study addressing convulsive SE epidemiology in a wholly pediatric population, the North London Convulsive Status Epilepticus in Childhood Surveillance Study (NLSTEPSS) (14), identified a pediatric SE incidence rate of 17-23 episodes/100.000 children per year in developed countries. This incidence rate is even higher in those under 1 year old (51/100.000 per year) because there is a high proportion of acute symptomatic causes and a reduction of the seizure threshold due to the brain immaturity (14).

In fact, the age is a fundamental determinant of the SE epidemiology because SE incidence rate and etiology differ between children and adults and also between younger and older children (9).

These incidence rates also vary importantly among different geographical areas and it seems to be due to differences in the SE etiology in these different areas (15).

Moreover, there is a strong evidence that those children with previously neurological abnormalities (abnormal neurodevelopment, history of epilepsy or neurological deficits) have a higher risk of suffering seizures and CSE than those with absence of these abnormalities (14).

The NLSTEPSS (14) did not find differences in gender SE incidence rate but it found that ethnicity could influence SE incidence rate; non-white population has a higher risk of SE compared with white population (2:1). The reason of this difference is not clear and more studies must be done to evaluate the role that socioeconomic status and genetic factors may play on this ethnic difference (9).

In short, treatment facilities, gender, genetics, socioeconomic status and ethnicity may also influence the SE epidemiology but more evidence is needed to be able to develop prevention procedures.

Mortality and morbidity of SE

SE is considered one of the most frequent neurological emergencies in pediatric age (14,16) with an increase (lower than in adults) of adverse outcomes: mortality and morbidity. Nevertheless, further investigation is needed to confirm the real correlation that exists between SE and these adverse outcomes as well as to evaluate how age, duration of SE and its treatment influence in these outcomes (9). In fact, it is difficult to distinguish if this mortality and morbidity is caused by SE itself or by the underlying cause of the SE (16).

Mortality

Although, as we said before, the SE incidence rate is higher in children than in adults, the SE mortality is lower among pediatric population than in adults (14,17).

Children who suffer SE has a mortality of 3-15% (18). Studying deeply this mortality we can divide it in two groups:

a. Short-term mortality (2,7-5,2%): mortality during hospital admission or within the first 30-60 days of onset of CSE (9).

b. Long-term mortality (3%): mortality that appears up to 10 years after the SE (19).

In both types of mortality there is a principal risk factor confirmed which is the etiology of the SE; children with acute and remote symptomatic CSE (see **"1.3.d Classification. 2. Etiology"** for the explanation of these concepts) have an increased risk of death while those suffering a cryptogenic or febrile SE are unlikely to die (9,19). Younger age and longer seizure duration have been associated with more mortality but it is no clear if these effects are independent to the SE etiology (9,19). Suffering previous brain abnormalities also seem to be a risk factor of mortality (15).

Morbidity

SE also increases the risk of suffering focal neurological deficits, cognitive impairments (reduction of the intelligence quotient [IQ]) and behavioral and psychiatric problems (9). CSE is related to neurodevelopmental impairment at 6 weeks of the SE, that persists at one year of follow-up. This means that the SE seems to have a prolonged effect in cognitive abilities (20).

As happened with mortality, the etiology is the main risk factor: acute symptomatic CSE produces >20% of neurological dysfunction whereas cryptogenic or febrile CSE suffer <15% of morbidity (9).

The influence of the age and duration of SE again needs more research to be confirmed (21). In fact, longer duration of CSE has been associated with more morbidity, but the causative effect is uncertain because it is difficult to separate the effect of CSE itself from the effect of its etiology, which is a direct determinant of seizure duration and affects the resistance to treatment (21).

In children, during the 12 months after a first episode of CSE, 16% of patients have a second SE episode, a higher relapse rate than among adults. The median interval from SE to recurrence is 25 days and, although the risk of relapsing is higher during the first year, it persists high during more years (13). The etiology, again, influences this recurrence and remote symptomatic SE (44%) has a higher recurrence risk than febrile SE (17%) (9).

We said before that most children with a SE do not suffer a underlying epilepsy, however, at the same time, suffering a SE increases the risk of developing epilepsy in a 25-40%, comparing to children who do not suffer a SE (19). Again, this risk depends mainly on the etiology and those suffering a symptomatic SE have a higher risk of suffering a future epilepsy (9). SE is likely to cause some brain injuries, especially hippocampal atrophy and reduction of its growth, and the mechanisms that produce these injuries seem to be: excitotoxicity, inflammation and reduction in hippocampal blood flow (15). Singularly, there is a possible correlation between febrile SE and mesial temporal sclerosis (MTS), a specific epileptic syndrome. However, we do not know exactly the frequency at which febrile SE evolves to epilepsy and MTS, so, nowadays, we cannot strongly affirm that febrile SE increases the risk of suffering epilepsy, especially MTS, and more studies should be done (12,19).

1.3.c. Physiopathology

According to its physiopathology, SE is a prolonged epileptic condition which seizures tend to become self-perpetuating and unremitting (8).
As we said before, a seizure occurs as a consequence of an exaggerated and synchronic neuronal activity. This neuronal hyperexcitability is produced due to an imbalance between the neuronal excitatory and inhibitory mechanisms. On one hand, there is an excessive activity of NMDA (N-methyl-D-aspartate) glutamate receptor, producing an excitatory neurotransmission that depolarizes the neurons and stimulates the neuronal connections. On the other hand, there is a reduction of an inhibitory neurotransmitter, the GABA (gamma-aminobutyric acid), that affects its capacity to repolarize and inhibit the neuronal activity (22).
In most of the seizures, within the first 5 minutes, the inhibitory mechanisms (GABA) increase their activity and finish the seizure. When these mechanisms fail, the seizure becomes a SE and rarely terminates spontaneously (especially if it lasts more than 30 minutes) before exhaustion and damage of the brain occurs. (8).

Focusing our attention in this transition from seizure to SE, this imbalance between NMDA and GABA activity appears in consequence of the movement of the cell receptors. There is a reduction of inhibitory activity because GABAa receptors move from the synaptic membrane to the cytoplasm (endocytosis) where they are inactive. Furthermore, the NMDA glutamate receptors take the reverse direction and move to the synaptic membrane increasing, consequently, their activity (8).
Moreover, there are other mechanisms that intervene in the perpetuation of the seizure. In short, there is a depletion of other inhibitory peptides such as dynorphin, galanin or somatostatin and there is an increased activity of proconvulsivant peptides such as substance P and neurokinin B (8).

At the end, all the different mechanisms involved in the perpetuation of the SE converge in the same pathway: neuronal cell death. In vitro models demonstrate that the final point of SE is the excitotoxic neuronal injury due to, mainly, glutamate that increases intracellular calcium levels, leading to acute necrosis, first, and delayed apoptosis, later (18).

As a consequence of this perpetuated seizure, significant homeostatic complications appear (23):

1. Stimulation of sympathetic nervous system: hypertension, hyperthermia, tachycardia and hyperglycemia. In contrast, when the SE lasts more than 1 hour the sympathetic system becomes exhausted and hypotension and hypoglycemia appear. These events, plus hyperkalemia, acidosis and reduction of the cerebral blood flow, can produce death.
2. Systemic and cerebral hypoxia with production of lactic acidosis.
3. Increase of the neuronal metabolism with more glucose and oxygen consumption that can produce, when the compensatory mechanisms fail, neuronal death.
4. Rhabdomyolysis, as a consequence of muscular persistent contraction, that can produce myoglobinuria with the consequent risk of acute kidney failure.
5. Excessive bronchial secretions and salivation, increasing the risk of pulmonary aspirations and pneumonia.

A pathophysiological phenomenon that determines the management and treatment of the SE is the development of **pharmacoresistance**, which is time-dependent. The reason that explains this phenomenon is the same that we exposed before: the reduction of GABAa receptors. Benzodiazepines, the first line drugs used for SE treatment, increase the activity of GABAa receptors and, as a consequence, finish the SE. So, if there is a reduction of GABAa receptors, benzodiazepines cannot work and pharmacoresistance appears. This phenomenon justifies the necessity to treat SE as early as possible; more time of SE means less success of benzodiazepines (8).

Regardless we have a lot of information of the different mechanisms that underlie SE, most of it is based on the work done with animal models and, for sure, more research in humans is needed to understand and, as consequence, treat SE better.

1.3.d. Classification

SE can be classified in different axis (1,8,9):

1. Age (1)

- Neonatal (0 to 30 days)
- Infancy (1 month to 2 years)
- Childhood (2-12 years)
- Adolescence and adulthood (> 12-59)
- Elderly (≥ 60 years)

Our research will be focused in the diagnosis and treatment of, mainly, infancy and childhood status epilepticus.

2. Etiology

The etiological diagnosis of the SE is basic because it has prognostic implications and because if we want to solve the SE properly we need to eradicate its cause (24).

The causes of SE vary according to different factors, especially according to age groups (13) and, regarding its etiology, a SE can be classified as (*Table 2*):

- **"Known or symptomatic SE"** (1,25): SE caused by a known disorder. Its most severe causes are life-threatening conditions: bacterial meningitis, intoxication or brain tumor.
- **"Unknown or cryptogenic SE"** (1,25): SE caused by an unknown cause. It happens in a 8,5-47,8% of SE depending on the case series (1,24).

Furthermore, among children we find a specific type of SE that cannot be classified as neither "symptomatic" nor "cryptogenic" SE. This SE, which is the most common etiologic type of pediatric SE, is the "**febrile SE"** (33-35%): a SE in a previously neurologically normal child aged between 6 months and 5 years during a febrile (>38°C) illness not caused by a central nervous system (CNS) infection (25).

Table 2. Classification of SE etiology. Adapted from (1,25,26)

Type of SE	**Definition**	**Etiologies**
Known or symptomatic SE	SE caused by a known disorder, that can be structural, metabolic, inflammatory, infectious, toxic or genetic	
Acute symptomatic SE (26%)	SE occurring in close temporal association (<7 days) to an acute systemic, metabolic, toxic or CNS insult	CNS infection (most frequent) Electrolyte imbalance Trauma Vascular disorder Intoxication
Remote symptomatic SE (33%)	SE because of a remote CNS insult (>7 days) that is presumed to result in a static lesion	Cerebral dysgenesis Mesial temporal sclerosis Remote infection Remote vascular disorder Metabolic (Inborn error of metabolism) disorder Chromosomal disorder
Progressive symptomatic SE (3%)	Unprovoked SE related to a progressive CNS disorder	Brain tumor Degenerative disease Autoimmune disorder
Unknown or cryptogenic SE (16%)	SE caused by an unknown cause	-
Febrile SE (22%)	SE in a previously neurologically normal child aged between 6 months and 5 years during a febrile (>38°C) illness not caused by a CNS infection	Non-CNS infection

There are two specific metabolic causes that have a good response to its treatment, so, although they are not frequent, their diagnosis is really profitable. The first disorder is pyridoxine deficiency: children under 18 months with rebel SE need to be treated with pyridoxine (unique intravenous dose, 100-200 mg). The second metabolic cause is biotinidasa deficiency that must be treated with oral or intramuscular biotin (20 mg) (23).

Until this moment, we have analyzed the etiologies that could produce a **new onset SE**. However, a 16-38% of SE affects children who suffer underlying epilepsy as etiology. Particularly, between 10 and 20% of children with previous epilepsy will suffer at least one episode of CSE during the history of the disease (9), mainly during the first years. The main cause of SE among these children is the low plasma levels of the antiepileptic drugs (AEDs) that they are taking for the epilepsy treatment (bad adherence). For that reason, in front of a child with prior epilepsy who suffers a SE, an AED plasma level test must be performed (27).

3. Semiology (1)

This is the most important axis because it classifies the SE according to its symptoms and signs and, consequently, it helps us to diagnose it.

So, regarding its semiology, SE can be divided as *table 3*:

a. **Convulsive SE (CSE)**. SE with prominent and excessive motor symptoms with muscle contractions. CSE is the most common form of SE (9). In addition to these motor symptoms, some characteristic findings of CSE are mental status impairment (coma, lethargy, confusion) an focal neurological deficits after the seizure (post-ictal period) (27).
b. **Non-convulsive SE (NCSE)**. SE with absence of motor symptoms. It consists in a SE defined by an electroencephalographic seizure activity without the motor symptoms associated with the CSE. Consequently, an electroencephalogram is needed to diagnose it. This SE is also characterized by negative symptoms (aphasia, catatonia, confusion, staring) or positive symptoms (agitation, aggression, automatisms) (27).

Table 3. Semiologic classification of pediatric status epilepticus (18)

Convulsive SE (CSE)
Focal
Focal motor
Focal motor with secondary generalization
Epilepsia partialis continua
Generalized
Myoclonic
Clonic
Tonic
Tonic-clonic
Non-convulsive SE (NCSE)
Absences (typical/atypical)
Focal SE with sensorial symptoms
Autonomic or focal SE with affective symptoms
Focal SE with autonomic symptoms (Panayiotopoulos syndrome)
Complex-partial SE
Continuous spike and wave during slow sleep

Nevertheless, these symptoms and signs, as well as the electroencephalogram (EEG) pattern, are dynamic and change during the SE progression. It means that the patient must be rechecked frequently in order to reclassify the SE according to its new semiology (1).

4. Physiopathology and duration (8,16,18)

- **Early SE** (impeding SE): 5-30 minutes.
- **Established SE:** >30 minutes. Although the transition from **early SE** to **established SE** is a continuum, it is defined at 30 minutes. This is because, as we said before, at 30 minutes of SE it becomes self-perpetuated, neurological damage becomes evident and pharmacoresistance appears (1,8).
- **Subtle SE ('stuporous' stage).** It represents the late stage of SE when motor and EEG activity of seizure burnouts and becomes less evident.

1.3.e. Diagnosis

SE is a neurological emergency and its promptly diagnosis and treatment is imperative. So, when we face with a patient suffering a possible SE, the first step we must take is basic pediatric life support with airways preservation, oxygen administration and monitoring and stabilization of the vital signs (18). We will revise these actions deeply in **"1.3.e. Treatment"**.

The main goals of the SE diagnosis process are: confirm SE diagnosis as promptly as possible and identify its etiology because there are some etiologies (trauma or intoxication) that need specific treatment (23). Moreover, a differential diagnosis is needed to discard other similar processes such as psychogenic SE, prolonged syncope, tetany, dystonia or decerebrate spasms, among others (18).

In front of a patient suffering a possible SE, the diagnosis process is based in the following procedures (18):

Mandatory

1. Clinical history (18,23)

We should ask to the family (or those present at the moment of the SE) about:

- Time from the beginning of the seizure
- Seizure semiology: convulsive or non-convulsive. For sure, this will be also evaluated during the physical examination.
- Neurologic (or other) diseases that the patient or his relatives suffer o have suffered, especially we should ask about epileptic antecedents.
- Recent cranioencephalic traumatism
- Recent intoxication
- Other potential etiologies

2. Physical examination (28)**:** general and neurological physical examination with special attention to the pupils, the presence of focal neurological signs and the Glasgow Coma Scale.

3. Blood test to evaluate (18,23,29): hemogram, renal and hepatic function, electrolytes (sodium, potassium, calcium, phosphorus, ammonium, magnesium…), lactate, coagulation, amino acids and inflammatory markers (PCR, VSG). An arterial blood gas test will be also performed to evaluate the acid-base equilibrium and the partial pressure of Oxygen (PaO2) and Carbone dioxide (PaCO2). These blood tests are abnormal in 6% of cases (29).

In those patients under treatment for epilepsy, plasma levels of AEDs should be determined; they are low in 32% of cases and it reveals inadequate dosing (18,23,29).
This blood test gives us information about the SE and its etiology (18).

4. Electroencephalogram (EEG) (18,23,29) is useful to confirm the SE as well as to distinguish generalized from focal SE. Although none of the possible ictal EEG patterns is specific of any type of SE (1), epileptiform discharges are found in 43% of SE with the following proportion: 8% generalized, 16% focal and 19% focal and generalized (29). In order to not delay the beginning of the treatment, the EEG must be done always after the treatment has been started. The only situation when EEG is urgent is when we suspect that the patient is suffering a NCSE, because it appears without motor symptoms and, consequently, we need an EEG to diagnose it.
Once the SE is clinically controlled, the EEG is mandatory if the consciousness does not improve within one hour, in order to discard residual electroencephalographic activity (27).

<u>According to indication</u>
5. Lumbar puncture (18,23,29) to analyze the cerebrospinal fluid and to obtain a spinal culture. When a spinal culture is done, an infection is found in 12,8% of cases. Moreover, if we do a blood culture, it is positive in 2,5%. Nevertheless, neither lumbar puncture nor blood culture have strong evidence to be done on a routine basis in children in whom there is no clinical suspicion of a systemic or CNS infection (29). However, other authors affirm that a lumbar puncture should be done among all the children under 6 months in order to exclude CNS infection (30).

6. Toxicology studies and metabolic studies for inborn error of metabolism (serum and/or urine toxicological screening) (18,23,29) should be determined if there are clinical findings suggestive of endogenous or exogenous intoxication or if the initial evaluation cannot determine a clear etiology.

7. Neuroimaging (magnetic resonance imaging) (18,23,29)**.** The main goal is trying to identify the underlying cause of the SE, especially when it is a focal SE. The epileptogenic lesions (found in 8% of SE) are, mainly, tumors o malformations. Although there is no evidence to do routine neuroimaging, it can be considered if there is a clinical suspicious of a specific etiology or if it is unknown (29). However, if the neuroimaging is indicated, there is a lack of consensus to decide when to do it (16).

So, to sum up, to diagnose a SE we need to perform a proper clinical history, a physical examination, a blood test and an EEG. Then, depending on the suspected etiology, other tests could be done: neuroimaging, toxicology studies, blood culture and lumbar puncture.

1.3.f. Treatment

The main goal of the SE treatment is preventing CNS injuries and systemic complications that appear due to prolonged SE (24). The principal procedures that must be done to achieve this goal are (16,24):

- Stabilization of vital functions.
- Administration of antiepileptic drugs (AEDs) to stop the SE as promptly as possible. It seems to be more important an early administration of the AED than the election of one or other type of ADE (23)
- Etiologic diagnosis and treatment to solve the potentially life-threatening SE causes (meningitis, electrolyte imbalance…)
- Identification and treatment of systemic complications
- If necessary, admission to Pediatric Intensive Care Unit (PICU)

The SE management can be divided in:

1. Management of SE in the pre-hospital setting

More than three-quarters of the first episodes of CSE start in the community (9) and, as we have already said, SE is an emergency. So, the beginning of its treatment before the arrival at the hospital is highly recommendable (18,24). In order to manage a SE in the pre-hospital setting is basic:

a. Stabilization (18,24)

- Airways preservation
- Placing the patient in a safer place in supine position
- Cervical column immobilization (correct position of the head)
- Draining secretions and vomits

b. Antiepileptic drugs (AEDs)

When we face with a SE in the pre-hospital setting, an AED must be administrated. The AEDs used in this setting are the benzodiazepines (BZDs): rectal diazepam (0,5 mg/kg) has been used as the treatment of choice in pre-hospital setting (18,24). Other alternatives are buccal transmucosal midazolam (0,5 mg/kg), nasal transmucosal midazolam (0,2 mg/kg) or intramuscular midazolam that have the same (or more) efficacy and better safety than rectal diazepam (24).

The pre-hospital management achieves a reduction of the SE duration and > 80% of the cases are controlled without necessity to receive hospital management (9,23). However, if it is not well performed because, for example, the children are treated with doses below or above those suggested, pre-hospital management could be harmful (9).

2. Management of SE in the hospital setting

If the SE is not solved in the pre-hospital setting the child must be moved urgently to the hospital. There, the same basic actions must be repeated:

a. Stabilization and monitoring of vital functions (18,23,24,27)

Firstly, the "Pediatric Assessment Triangle" (PAT) must be performed. This PAT consists in evaluating, in just a few seconds, the appearance (neurological state), the work of breathing (respiratory state) and the circulation to skin (cardiovascular state), in order to obtain a rapid evaluation and impression of the patient.

After that, the ABC sequence is basic to control and monitor the vital functions of the patient and it must be repeated and revaluated frequently (23,24,28). It consists in:

A: airway preservation

- Proper head position
- Aspirate secretions and vomits
- If needed, oropharyngeal intubation

B: breathing

- Ensure effective ventilation and monitor the respiratory rate
- Control the O2 saturation and, if needed, administer oxygen
- If the ventilation is ineffective: intubation and ventilation support (16)

C: circulation

- Monitor and maintain the perfusion (control of the heart rate and blood pressure). If circulation support is needed, fluid resuscitation and administration of vasopressors (with peripheral intravenous access) are indicated (16,27). Moreover, the heart rate must be monitored with an electrocardiogram (ECG).

Moreover, in order to evaluate the neurological status of the patient, the neurological physical examination will be frequently repeated with special attention to the pupils and the Glasgow Coma Scale (28).

This ABC sequence plus the blood test are basic to identify the homeostatic and cardiovascular disruptions that can appear as a consequence of the SE or its etiology (18,24):

- Hypoglycemia (treatment with intravenous glucose 10% solution) (23). A finger stick glucose should be taken systematically (27).
- Hypovolemia and cardiovascular collapse
- Fever (body temperature must be monitored) (16)
- Electrolyte imbalance and acidosis
- Pulmonary or cerebral edema
- Cardiac arrhythmias
- Myoglobinuria and acute renal failure

At the same time, we must not forget that the etiologic treatment is basic to eradicate the SE. So, correctable causes of SE must be diagnosed and solved as fast as possible (24,27).

b. Antiepileptic drugs (AEDs)

When we attend a child suffering a SE in the hospital setting, we could face with two different situations: with a SE that has not stopped after a benzodiazepine administration in the pre-hospital setting or with a SE that has not been treated yet with any AED. Indistinctly, in both cases we must administer an AED to stop the SE.

First line of AED:

The first AEDs used in the hospital setting must be the parenteral benzodiazepines (BZDs), that eradicate the SE through the stimulation of inhibitory GABAa receptors (31).

Among these BZDs, intravenous diazepam (0,5 mg/kg; maximum dose 10 mg) or intravenous lorazepam (0,1 mg/kg; maximum dose 4 mg) are equally effective but lorazepam seems to be preferred because of its lower risk of relapse and respiratory depression (18,24,27,32). Nevertheless, intravenous lorazepam is not authorized in Spain.

Other options are intravenous midazolam (0,1-0,2 mg/kg; maximum dose 5 mg) and, if the intravenous access is not possible, intramuscular midazolam (0,2 mg/kg; maximum dose 5 mg) (24).

BZDs principal adverse reactions are: respiratory depression, hypotension and laryngospasm. So, it is basic to monitor and stabilize patients who receive BZDs (27,32).

If the first dose of BZDs (either in pre-hospital or hospital setting) does not stop the SE in five minutes, a second dose must be administrated. However, if this second dose fails, further BZD administration is forbidden due to the reduction of its therapeutic effect and the increase risk of respiratory depression and sedation (18,24,32). In fact, if after two doses of BZD the SE still persists we will define it as a **benzodiazepine refractory status epilepticus**. This situation happens in 30-40% of cases and we must use the second line antiepileptic drugs (AEDs) to solve the SE (24,33,34). Our randomized controlled trial (RCT) will try to identify the more effective and safer drug among these second line AEDs.

Second line of AEDs:

- Intravenous phenytoin (PHT) (bolus of 18-20 mg/kg, with a maximum dose of 1g, followed by a maintenance dose of 5 mg/kg/day) (18,24,27,35).

PHT has as a mechanism of action the reduction of the neuronal excitability due to the inhibition of the voltage-gated sodium channels (31).

PHT principal adverse reactions are: hypotension, cardiovascular and respiratory depression, arrhythmias, sedation, "purple glove syndrome" (pain, limb edema and discoloration 2-12 hours after the administration of phenytoin) and skin reactions (its more severe form is the Stevens-Johnson syndrome) (24,34,35).

PHT contraindications: drug hypersensitivity, sinus bradycardia, cardiac block, severe hypotension or Adams-Stokes syndrome (24,34,35).

See **"ANNEX 1. Drug relevant information"** for more information about this drug.

Fosphenytion (20 mg phenytoin equivalents/kg), a phenytoin prodrug, could be an alternative, with fewer adverse reactions and faster intravenous infusion than phenytoin (18,24,27).

- Intravenous phenobarbital (bolus of 15-20 mg/kg, with a maximum dose of 1g, followed by a maintenance dose of 5 mg/kg/day) (18,24,27).

Phenobarbital is a positive allosteric modulator of GABAa receptors and it also modulates the calcium channels (31).

Phenobarbital principal adverse reactions are: sedation, cardiorespiratory depression and hypotension (24,36). These potentially serious adverse reactions are even more frequent when intravenous phenobarbital follows a high dose of intravenous BZD, as it happens in those SE that do not respond to BZD.

- Intravenous sodium valproate (VPA) (bolus of 20-40 mg/kg followed by infusion of 1mg/kg/h) (18,24,27,37).

VPA is a broad-spectrum AED that modulates sodium and calcium channels and the metabolism of GABA (31).

VPA seems to have all the characteristics needed to be defined as an ideal AED because it (36):

- Is effective
- Has a lack of serious adverse reactions
- Has a rapid administration form; ideally available in intravenous form to reach rapidly the therapeutic serum concentrations
- Reaches the brain rapidly

Moreover, VPA has an immediate–acting antiepileptic effect and it is able to rapidly stop the seizure activity (38).

The published evidence concludes that VPA is a safe and effective therapeutic option for patients with benzodiazepine refractory SE (34). In fact, VPA is equivalent or more effective (88-90% of SE resolution) than PHT (75%) and phenobarbital (77%) in the treatment of CSE after failure of benzodiazepines, with no more adverse reactions (36,39). However, this literature has some limitations and more studies are needed.

VPA principal adverse reactions are: hypotension, dizziness, pancreatitis, hypertransaminasemia (liver dysfunction), hyperammonemia, thrombocytopenia and cardiorespiratory depression (rare) (24,34,37). In general, VPA is well tolerated with good

cardiovascular and respiratory tolerability and without significant risk of necessity to intubation and mechanical ventilation (40,41). Moreover, a lack of adverse reactions on liver function was seen in two studies: a retrospective study (41) and a randomized controlled trial (RCT) (42).

VPA contraindications: sodium valproate hypersensitivity, thrombocytopenia, pancreatic disease, chronic or acute hepatic disease or suspected metabolic disease (23,24,37).

See **"ANNEX 1. Drug relevant information"** for more information about this drug.

- Intravenous levetiracetam (15-70 mg/kg) (18,24,27)

It can be an alternative due to its good tolerability, short time of administration and absence of hemodynamic and sedative effects; its principal adverse reactions are aggression, headache, vertigo and diarrhea. Nevertheless, there are not randomized clinical trials that confirm its efficacy. So, more studies are need.

Refractory SE (RSE)

As we said before, when a SE persists after two doses of BZDs is considered a **benzodiazepine refractory status epilepticus.** We must not confuse this situation with the **refractory status epilepticus (RSE)**: a more severe situation that appears when a SE does not respond to standard doses of the two first AEDs administrated (two doses of benzodiazepine plus a second-line antiepileptic drug); it happens in 10-40% of SE cases (10,11).

RSE has a high mortality, mainly related to its etiology (14). There is not a universally accepted procedure for the RSE treatment (24,27). Nowadays, the decision to use one or other treatment is based according the patient's condition, the risk and benefit balance and the professional's experience in the use of these drugs (24,27).
Two fairly accepted sequences are (27):

- Administering a bolus of a second line AED that has not been used yet for this SE episode, and then proceeding to pharmacologic coma induction if SE persists.
- Inducing pharmacologic coma directly.

This management must be done in a Pediatric Intensive Care Unit (PICU) (24) with continuous EEG monitoring (27,32). The principal drugs used to induce coma are intravenous sodium thiopental, propofol, phenobarbital or midazolam (24,27). However, there is not enough evidence to determine which of these drugs must be used preferably.
If this drug-induced coma fails or is contraindicated we have the last line of treatment, with a significant lack of evidence and standardized protocols. This group of AED includes: topiramate, ketamine or lacosamide (24,27).

In order to show the lack of universal consensus in the SE treatment we attached two different treatment algorithms, as examples, in "**ANNEX 2. Algorithm for status epilepticus** ".

2. JUSTIFICATION

Pediatric SE is not characterized by a high incidence rate (17-23 episodes/100.000 children per year in developed countries) but it is a common neurological emergency in pediatric population (14,16) with an increase of morbidity and mortality (9).

Literature defines a general SE mortality of 3-15% (18) of cases, a not negligible proportion. Specifically, these children have a short-term SE mortality of 2,7-5,2% (9) and a long-term SE mortality of 3% (19). Talking about the morbidity, in some series it reaches a 20% of cases, suffering, mainly, focal neurological deficits and/or cognitive and neurodevelopmental impairments (9).

As an emergency, SE produces acute disturbances that are some of the underlying reasons of this morbidity and mortality. Within these disturbances, as we said before, we should remark: hypoglycemia, hypovolemia, cardiovascular collapse, cardiac arrhythmias and pulmonary or cerebral edema (18,24).

So, it is evident that SE has a significant impact among those who suffer it producing deaths and sequels that reduce their quality of life.

However, once we have revised the literature, we have identified that there is not a consensus in the pediatric SE treatment. There is a lack of standardized and universally accepted protocols due to a lack of research among pediatric population (16,18,23,24). Frequently, the recommendations are based on the protocols addressed to adult population. We guess that this lack of standardized protocols reduces the quality of the SE management and it contributes to increase or, at least, to not reduce, the SE mortality and morbidity.

The only procedure with consistent evidence and consensus in the SE treatment is the use of benzodiazepines as the first line of SE treatment (18,24,27,32). However, a 30-40% of patients do not respond to BZDs and the SE becomes a **benzodiazepine refractory SE** (33,34). Once it happens, there is a lack of evidence to select a specific second line AED. For instance, the second line AED most frequently used in Catalonia is sodium valproate while in USA is phenytoin (27,32); see "**ANNEX 2. Algorithm for status epilepticus "**.

During last years, in front of this **benzodiazepine refractory SE**, long-acting anticonvulsants have been universally used, especially phenytoin (PHT) or phenobarbital (16,36), however, there is not randomized controlled data that strongly supports the utility of these two drugs (24,39). Moreover, they have a risk of serious adverse reactions such as sedation, arrhythmias, hypotension and cardiorespiratory depression (18,24,36,39).

Nowadays, sodium valproate (VPA) has become a potential alternative to these drugs. A retrospective study (41) and a prospective study (38) that evaluated efficacy and safety of VPA among children who suffered a SE, found the VPA was safe and effective for the treatment of SE.

Consequently, we started a research through the literature to evaluate the available evidence in the treatment of the benzodiazepine refractory SE. Based on a systematic review (43) and on an evidence-based guideline (32) we found two RCT (39,44) that compared sodium valproate against phenytoin in the benzodiazepine refractory SE treatment. Nevertheless, these two studies are not useful for us because they included people from all ages and the conclusions were general, without specifying the results among children. Another RCT that wants to compare fosphenytoin, levetiracetam and VPA in the treatment of benzodiazepine refractory SE is currently recruiting participants. However, again, this study includes people from all ages (45).

In fact, we just found one RCT that studied the treatment of a benzodiazepine refractory SE among a population only composed by children. This study took place in Iran and enrolled 30 patients in one group (phenobarbital) and 30 in the other group (VPA). It concluded that, in front of a persistent CSE after intravenous diazepam, intravenous VPA was more effective (but without statistically significant difference) and better tolerated (with statistically significant difference) than intravenous phenobarbital.

However, we consider that one RCT that only enrolls 30 patients in each branch cannot provide us strong evidence to modify our clinical practice. Moreover, a specific limitation of this RCT is that Iran is a developing country and the time between the beginning of the SE and the infusion of the antiepileptic drugs is significantly longer than in developed countries. Therefore, its results cannot be properly exported to our population. This limitation also appears in the other two RCT (39,44), that were developed in India.

Moreover, these studies tried to evaluate, mainly, the proportion of SE termination and the safety of the drugs but they did not analyze properly if the different drugs of study had different rates in mortality and neurological morbidity; consequently, we will try to evaluate these variables.

To sum up, we can affirm that we cannot provide enough evidence to identify which of the principal AEDs (VPA, PHT, phenobarbital or levetiracetam) should be used as the first option in a SE when benzodiazepines fail. This lack of evidence could be explained by the fact that a SE occurs without warning and requires urgent management and it makes that clinical trials are extremely challenging to perform (34).

With the objective to fill this important gap, we decided to develop a protocol of a RCT to compare intravenous sodium valproate against intravenous phenytoin (two of the AEDs most frequently used) in order to define which of them should be considered the first line of SE treatment when benzodiazepines fail in a pediatric SE. This study will represent the second RCT worldwide that studies benzodiazepine refractory SE management among an exclusively pediatric population and, moreover, it will be the first developed in Europe.

We believe that the results of this study could provide evidence to elaborate strong treatment recommendations that could improve the management of the SE, increasing the proportion of SE resolution and reducing the appearance of adverse reactions. Consequently, these recommendations could reduce the frequency of refractory SE and the induction of coma. Then, even the mortality and morbidity would be reduced and the quality of life of our patients and their families would also improve.

3. HYPOTHESIS

3.1. Main hypothesis

Intravenous sodium valproate has a higher proportion of status epilepticus termination (efficacy) than intravenous phenytoin in the treatment of benzodiazepine refractory convulsive status epilepticus in pediatric population.

3.2. Secondary hypothesis

In the treatment of benzodiazepine refractory convulsive status epilepticus in pediatric population:

1. Intravenous sodium valproate is safer than intravenous phenytoin.
2. Intravenous sodium valproate, comparing to intravenous phenytoin, reduces the mortality.
3. Intravenous sodium valproate, comparing to intravenous phenytoin, improves the neurological outcome.
4. Intravenous sodium valproate, comparing to intravenous phenytoin, reduces the status epilepticus recurrence.
5. Intravenous sodium valproate, comparing to intravenous phenytoin, reduces the time needed to terminate the status epilepticus.

4. OBJECTIVES

4.1. Main objective

To compare the **proportion of status epilepticus termination** (efficacy) of intravenous sodium valproate versus intravenous phenytoin in the treatment of benzodiazepine refractory convulsive status epilepticus in pediatric population.

4.2. Secondary objectives

To compare, in the treatment of benzodiazepine refractory convulsive status epilepticus in pediatric population:

1. The **safety** of intravenous sodium valproate versus intravenous phenytoin.
2. The **mortality** of those who receive intravenous sodium valproate versus those who receive intravenous phenytoin.
3. The **neurological outcome** of those who receive intravenous sodium valproate versus those who receive intravenous phenytoin.
4. The **status epilepticus recurrence** of those who receive intravenous sodium valproate versus those who receive intravenous phenytoin.
5. The **time needed to terminate the status epilepticus** of those who receive intravenous sodium valproate versus those who receive intravenous phenytoin.

5. METHODOLOGY

5.1. Study design

We will carry out a randomized controlled clinical trial (RCT). This RCT will be multicentric and will take place in the following hospitals: *Hospital Universitari de Girona Doctor Josep Trueta* (Girona), *Hospital Universitari Vall d'Hebron* (Barcelona), *Hospital Sant Joan de Déu* (Barcelona), *Hospital Universitari Arnau de Vilanova* (Lleida), *Hospital Universitari Parc Taulí* (Sabadell) and *Hospital Universitari Joan XXIII de Tarragona* (Tarragona). The reference center will be the *Hospital Universitari de Girona Doctor Josep Trueta* (Girona) and a principal investigator will be assigned in each center.
This study will last 45 months.

5.1.a. Randomization and masking technique

The patients enrolled in this clinical trial will be randomly distributed in two groups:

- **Group A**: this group will receive an intravenous sodium valproate (VPA) infusion. This drug will be identified as **drug A.**
- **Group B**: this group will receive an intravenous phenytoin (PHT) infusion. This drug will be identified as **drug B.**

The randomization will be computer-generated and the investigators will not intervene in this process. When a new patient is enrolled in the study, the computerized information will show to the investigator the group where the patient belongs to (**A** or **B**) and, then, which drug will have to receive (**A** or **B**).

This RCT will be triple-blind. The information about the treatment administrated will be masked to the investigators and patients. Moreover, the professional who will analyze the results of our clinical trial will be also blinded to the drugs of study.
None of the investigators will know if they are using VPA (drug A) or PHT (drug B) because the loading dose and the maintenance dose of these drugs will be identical in appearance (consistence and color), formulation (intravenous), packing and administration (same volume and rate of infusion) (see **"5.5 Study Interventions"** for more information of the masking process). An external experimented nursing staff will prepare these medicines that will be stored at room temperature and identified with the respective letter:
- **Drug A**: sodium valproate (VPA)
- **Drug B**: phenytoin (PHT)
For sure, all the investigators will not know the meaning of "drug A" and "drug B".

5.1.b. Informed consent

A patient will be enrolled in our study only if the informed consent is available. In order to obtaining it, firstly, we will show the information sheet of our clinical trial (**"ANNEX 3. Information Sheet"**) to the parents or legal representatives of our patients and, secondly, if they agree, they will sign the informed consent document (**"ANNEX 4. Informed consent document"**). This informed consent will be granted by "parental representation" because our patients will be under-age and because, of course, they will not be physically and psychically able to decide by themselves during the status epilepticus. At the same

time, we will ensure the possibility to annul this informed consent in any time of the study, with no damages to those who annul it.

A particularity that will affect this informed consent process is that the status epilepticus is a neurological emergency, with a significant morbidity and mortality, that needs early management. So, we will need to ensure that obtaining the informed consent will not delay the beginning of the treatment of this clinical condition. In order to ensure it, while a skilled member of our team will be explaining the clinical trial to the parents or legal representatives to obtain their consent, the other investigators will start the SE treatment with one of our two drugs of study according to the group (A or B) that the patient will have been assigned randomly.
It means that we will start the treatment without knowing if the informed consent is available, however, in our situation, it is legally accepted. The current Spanish and European legislation, *"Real Decreto 1090/2015, de 24 de diciembre" and "Reglamento (UE) N° 536/2014 DEL PARLAMENTO EUROPEO Y CONSEJO de 16 de abril de 1014",* allows starting an emergency research (such as our status epilepticus research) without prior informed consent. For sure, the informed consent must be obtained, but it can be obtained after the beginning of the treatment, in order to start it as fast as possible.
Consequently, in our study, if the parents give us the consent, the treatment previously started will be continued and the patient will be formally enrolled in our RCT. On the other hand, if they do not give us the consent, the patient will not be enrolled in the study but we will have already started the status epilepticus treatment without delaying its beginning. In fact, the drugs that we will use (VPA or PHT) are also the drugs used in the clinical practice and we do not dispose of other drugs with demonstrated higher efficacy and safety in the SE treatment. Furthermore, we even do not dispose of consistent evidence to know which of our two drugs of study is safer and more effective. Consequently, administering randomly VPA or PHT will not private our patients to receive a better AED and so, we will not harm our patients with this procedure.

5.2. Population of interest

To be enrolled in this RCT the patient must be a child suffering a **benzodiazepine refractory convulsive status epilepticus**.

5.2.a. Inclusion criteria

- Patients must be ≥ 1 year old and < 15 years old.
- Patients diagnosed of **SE**: according to the ILAE recommendations, we will consider that the patient is suffering a SE when a seizure lasts 5 minutes or more.
- Patients diagnosed of **convulsive SE**: SE with prominent and excessive motor symptoms with muscle contractions.
- Patients suffering a **"benzodiazepine refractory convulsive status epilepticus"**: a **convulsive SE** is refractory to benzodiazepines when it is not controlled after 5 minutes of receiving the second adequate dose of a benzodiazepine. The first benzodiazepine (BZD) dose can be given at pre-hospital setting with a transmucosal BZD (0,5 mg/kg of buccal midazolam or 0,5 mg/kg rectal diazepam) but, at least, the second BZD dose must be given through an intravenous or intramuscular form by the emergency medical staff.

The adequate doses are:

- Intravenous diazepam (0,5 mg/kg; maximum dose 10 mg)
- Intravenous midazolam (0,1-0,2 mg/kg; maximum dose 5 mg)
- Intramuscular midazolam (0,2 mg/kg; maximum dose 5 mg)

5.2.b. Exclusion criteria

- Patients diagnosed of non-convulsive SE
- Patients diagnosed of myoclonic SE (a type of convulsive SE characterized by sudden, brief, shock-like contractions which may be generalized or confined to face and trunk or to one or more extremities; they could be rapidly repetitive or isolated)
- Patients suffering a benzodiazepine refractory convulsive status epilepticus who has received the second dose of benzodiazepine more than 30 minutes ago
- Patients who have already participated in this clinical trial
- Patients suffering underling epilepsy treated with sodium valproate or phenytoin
- Pregnancy
- Drug allergy or prior adverse reactions to sodium valproate or phenytoin
- Contraindication to sodium valproate or phenytoin:
    - Hypotension
    - Sinus bradycardia
    - Cardiac block
    - Adams-Stokes syndrome
    - Pancreatic disease
    - Thrombocytopenia (<100.000/mm^3)
    - Active hepatic disease
    - Suspected metabolic disease

5.2.c. Withdrawal criteria

- Annulation of the informed consent
- Severe or life-threatening adverse drug reactions
- Patients who do not follow the protocol of the study

The patients withdrawn from the study will not be replaced and they will be included in the statistical analysis.

5.3. Sampling and sample size

5.3.a. Sampling

Our sampling process will be a multi-staged (or conglomerate) sampling:
1st STAGE: Intentional or convenience sampling. This first stage will consist in choosing by convenience the hospitals that will participate in our study. We chose this type of sampling because of practical reasons. Although we know that the best system would be choosing the hospitals through a random sampling, it would be methodologically difficult to perform. Then, if we assume that the population that is assisted in the different Catalan hospitals is similar in medical terms, we do not think that choosing the hospitals by convenience will generate selection bias.

The hospitals that will take part of this RCT are:

- *Hospital Universitari de Girona Doctor Josep Trueta,* Girona
- *Hospital Universitari Vall d'Hebron*, Barcelona
- *Hospital Sant Joan de Déu*, Barcelona
- *Hospital Universitari Arnau de Vilanova*, Lleida
- *Hospital Universitari Parc Taulí*, Sabadell
- *Hospital Universitari Joan XXIII de Tarragona*, Tarragona

2nd STAGE. Consecutive sampling

We will use the same sampling method to choose our patients in all these hospitals.

SE is an emergent and unexpected clinical situation and we will not know our potential patients until they come to the emergency room. So, consequently, we will use a non-probabilistic consecutive sampling method: any case of a child suffering a benzodiazepine refractory SE attended in the emergency room (24 hours per day) will be considered a potential patient to be enrolled in the RCT. If the patient accomplishes the inclusion and exclusion criteria and the informed consent is accepted, he or she will be formally included in our study.

A specific circumstance that will affect our sampling process is that the most common etiologies of the SE vary depending on the period of the year; for example, febrile SE and SE due to CNS bacterial infection are more frequent during the cold months (last autumn and winter). So, in order to avoid this seasonal influence and its consequent risk of selection bias, the patient recruitment period of this clinical trial will last 3 whole years, starting and finishing at the same period of the year (March).

5.3.b. Sample size

We used the GRANMO software to calculate the sample size for our main dependent variable (termination of the SE within 20 minutes). Accepting an alfa risk of 0.05 and a beta risk of 0.2 in a bilateral contrast, we will need 195 patients in each group (390 patients in total) in order to recognize a statistically significant difference between our two independent proportions (proportion of SE termination in each group). Specifically, we defined a 10% of difference between these proportions as the minimum clinically significant difference needed to change the clinical practice.

The group ratio will be 1:1 and, as our main dependent variable is measured immediately (20 minutes at maximum), we assume no follow up loses.

5.3.c. Time of recruitment

According to non-published data, the *Hospital Universitari de Girona Doctor Josep Trueta* (Girona) attends around 20 children suffering a benzodiazepine refractory status epilepticus per year. Then, in accordance with the potential pediatric population attended in our 6 hospitals, we estimate that they attend together approximately 160 pediatric patients with a benzodiazepine refractory status epilepticus per year. If our sample size is 390 patients and we hypothesize that a 10% of patients who accomplish the inclusion and exclusion criteria may not accept to be enrolled in this clinical trial (response rate of 90%), we estimate that the time of recruitment will last 36 months (3 whole years).

5.4. Variables

5.4.a. Independent variable

The independent variable of this study will be the administration of an antiepileptic drug in each group of study: one group will receive an intravenous sodium valproate (VPA) infusion (identified as the **drug A)** and the other group will receive an intravenous phenytoin (PHT) infusion (identified as the **drug B**). This is considered a dichotomous qualitative variable.
See **"ANNEX 1. Drug relevant information"** for more information about our drugs of study.

5.4.b. Dependent variables

The **main dependent variable** of this study is**:**
Termination of the SE within 20 minutes since the beginning of the VPA or PHT infusion. This is a dichotomous qualitative variable (treatment success or treatment failure).
We define the "SE termination" when the convulsive seizure (motor symptoms) is finished and the consciousness is recovered (we accept a light reduction of this consciousness due to the post-critic seizure state only if the patient shows a good response to our stimuli and orders, according to his or her age). This clinical seizure activity will be evaluated with a general and neurological physical examination performed by an experimented and previously taught pediatrician.
It would be ideal to evaluate the termination of the SE with the performance of an EEG (in addition to the physical examination) as soon as possible, however, immediate EEG investigation is not universally available in the hospitals that will take part of this RCT. Consequently, we will define our "termination of the SE" as a "clinical SE termination", not as an "EEG SE termination".
If this "termination of the SE" appears within the first 20 minutes after the antiepileptic drug infusion (VPA or PHT), it will be considered a treatment success. However, if the SE has not terminated after 20 minutes since the beginning of the AED infusion we will consider this situation a treatment failure.
We will explain the monitoring controls to evaluate this variable in **"5.6 Data collection"**.

The **secondary dependent variables** of this study are:
a. Appearance of adverse drug reactions
b. Mortality
c. Neurological outcome
d. Recurrence of the SE
e. Time to termination of the SE

a. Appearance of adverse drug reactions due to sodium valproate or phenytoin. This is a dichotomous qualitative variable (presence or absence of adverse drug reactions).
The main adverse drug reactions are:

- Hypotension, cardiovascular failure and necessity of its management: intravenous fluids (crystalloids) and inotropic treatment. We define this adverse drug reaction and its treatment is indicated if any of the following items appear:

- Hypotension:
  - 1-3 years: Systolic Blood Pressure (SBP) < 70 mmHg
  - 4-6 years: SBP < 75 mmHg
  - 6-11 years: SBP < 80 mmHg
  - 12-14 years: SBP < 90 mmHg
- Heart rate:

  Bradycardia:
  - 1-3 years: < 90 bpm (beats per minute)
  - 4-6 years: < 80 bpm
  - 6-11 years: < 70 bpm
  - 12-14 years: < 60 bpm

  Tachycardia (it will be only treated with crystalloids if it appears at the same time as hypotension):
  - 1-3 years: > 150 bpm (beats per minute)
  - 4-6 years: > 140 bpm
  - 6-11 years: >120 bpm
  - 12-14 years: >100 bpm

- Respiratory dysfunction and necessity of its management: oxygen and/or intubation and mechanic ventilation. We define this adverse drug reaction and its treatment is indicated if any of the following items appear:
  - Respiratory rate:

    Bradypnea:
    - 1-3 years: < 24 bpm (breaths per minute)
    - 4-6 years: < 22 bpm
    - 6-11 years: < 18 bpm
    - 12-14: < 12 bpm

    Tachypnea:
    - 1-3 years: > 40 bpm (breaths per minute)
    - 4-6 years: > 34 bpm
    - 6-11 years: > 30 bpm
    - 12-14: > 16 bpm

    According to the previous data and in order to facilitate the urgent management of the SE, we define the respiratory rate "unacceptable" if:
    - < 6 years: < 20 or >60 bpm
    - >6 years: < 12 bpm > 40 bpm
  - Oxygen saturation:
    - Dangerous: <94% (especially if it goes with excessive respiratory work)
    - Unacceptable: <90%
  - Partial pressure of Oxygen (PaO_2) and Carbone dioxide ($PaCO_2$)
    - We define the respiratory failure if PaO_2 < 60 mmHg with a Fraction of inspired Oxygen (FiO_2) of 60% or $PaCO_2$ > 60 mmHg without previous disease that could justify this value.

Both cardiovascular and respiratory dysfunction will be evaluated with vital signs monitors properly standardized.

- Life-threatening cardiac arrhythmia. It is defined as an arrhythmia that persists despite reduction or finalization of the study drug infusion and, consequently, it requires defibrillation or administration of an antiarrhythmic agent. In order to discard this complication the patient must be monitored with a continuous electrocardiogram (ECG).

- Sedation. The reduction degree of responsiveness will be evaluated with the Richmond Agitation-Sedation Scale (RASS) (**"ANNEX 5. Richmond Agitation-Sedation Scale (RASS)**). We will consider as "unacceptable sedation" a score of ≤ -2.

Other adverse drug reactions:

- Transaminase or ammonia elevations. We will perform a blood test in order to define as "unacceptable" elevation those levels greater than 3 times the upper limit of normal levels. We will also consider an "unacceptable" elevation of transaminase or ammonia levels if it produces clinical manifestations.
- Purple glove syndrome. It is defined as the presence of pain, limb edema and discoloration 2-12 hours after the administration of phenytoin and if there is no other possible etiology.
- Anaphylaxis. It is defined as a clinical condition that appears shortly after the infusion of the drug and it is characterized by the presence of, at least, 2 of the following:
    - Urticaria.
    - Respiratory compromise: dyspnea, stridor, hypoxemia, wheeze-bronchospasm or reduction of peak expiratory flow.
    - Cardiovascular compromise: vasodilation, reduction of blood pressure, syncope.
    - Persistent gastrointestinal symptoms: vomiting, crampy abdominal pain, diarrhea.

All these adverse drug reactions will be recorded and they will be appropriately managed, as it is done in the clinical practice. Moreover, if the adverse drug reaction is considered **severe** (medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated) or **life-threatening** (urgent intervention indicated), the drug infusion will be stopped.
The monitoring controls to evaluate this dependent variable are also explained in **"5.6 Data collection"**.

However, we would like to remark something important related to this variable. Among these expected adverse drug reactions, we find some of them that can only be produced by our drugs of study, such as anaphylaxis or transaminase or ammonia elevations. Nevertheless, among them we also find others, such as cardiorespiratory depression or cardiac arrhythmia, that could also appear as a complication of the SE itself or its etiology. This situation could lead us to misinterpretations and we could identity a SE complication as an adverse drug reaction. In order to prevent this misinterpretation, we will classify all the potential **adverse events** (SE complications or adverse drug reactions) that appear throughout our study according to their possibility to be related to the drug of study.

This classification will consist in 4 categories (**"ANNEX 6. Adverse events"**):

- Not related adverse event to study agent
- Unlikely adverse event to study agent
- Reasonably possible adverse event to study agent
- Definitive adverse event to study agent

We will consider that the first two categories (not related and unlikely adverse event to study agent) will not be related to the drug infusion and they will identified as a **"Status Epilepticus complication"** while the last two categories (reasonably possible and definitive adverse event to study agent) will be related to the drug infusion and, then, they will be identified as the real "**adverse drug reactions**".
Consequently, in order to evaluate this dependent variable (appearance of adverse drug reactions) we will only statistically analyze those adverse events classified as "adverse drug reactions".

b. Mortality. We will record all the deaths that appear during our follow up (30 days) and all causes of mortality will be included. This is a dichotomous qualitative variable because we will define our patients as "alive" or "dead".

c. Neurological outcome at 30 days after the study drug infusion.
The neurological outcome will be evaluated by a neuropediatrician and a neuropsychologist, blinded to the study drug used, at 30 days after the clinical trial enrolment. We will evaluate the presence of cognitive neurodevelopmental impairments using equivalent scales of cognitive development, according to the age of the patient:

- Children < 3 years: Bayley Scales of Infant and Toddler Development, Third Edition (Bayley-III)
- Children 3 - 7 years: Wechsler Preschool and Primary Scale of Intelligence IV (WPPSI-IV)
- Children 8-14 years: Wechsler Intelligence Scale for Children V (WISC-V).

Moreover, the neuropediatrician will also evaluate the presence of focal neurological deficits with the neurological examination.
We will define two categories of neurological outcome according to these results:

- Acceptable neurological outcome: patient with a cognitive development equivalent to children of the same age and with absence of focal neurological deficits.
- Unacceptable neurological outcome: patient with a lower cognitive development than children of the same age or with presence of focal neurological deficits.

This is a dichotomous qualitative variable.

d. Recurrence of the SE occurring between 20 minutes and 30 days after the beginning of the VPA or PHT infusion. This is a dichotomous qualitative variable. The SE recurrence will be defined as the appearance of a seizure that lasts ≥ 5 minutes (operational definition of status epilepticus). It will be evaluated with a general and neurological physical examination performed by an experimented and previously taught pediatrician. Moreover, this variable will be controlled with the same monitoring controls used to analyze the main dependent variable, that we explain in **"5.6 Data collection"**.

e. Time to termination of the SE. If the SE treatment achieves a treatment success (termination of the SE within, at maximum, 20 minutes), then we will define how many minutes (0 to 20 min) will have passed since the beginning of the VPA or PHT infusion. This is a continuous quantitative variable (minutes).

5.4.c. Covariables

- **Age**: years; a discrete quantitative variable.
- **Gender**: male/female; a dichotomous qualitative variable
- **Socioeconomic level:** MEDEA Index. A quantitative variable.
- **Convulsive SE type**: generalized or focal CSE; a dichotomous qualitative variable.
- **SE Etiology** (a qualitative variable):
  - Febrile SE
  - Known or symptomatic SE
    - Acute symptomatic SE
    - Remote symptomatic SE
    - Progressive symptomatic SE
  - Unknown or cryptogenic SE
  - SE due to prior epilepsy
- **Type of benzodiazepines received before admission to the RCT**: diazepam or midazolam: a qualitative variable.
- **Dose of the benzodiazepines received before admission to the RCT**: mg/kg; a continuous quantitative variable.
- **Time from the beginning of the SE until the infusion of our AED of study:** minutes; a continuous quantitative variable.
- **Time from the administration of the second dose of benzodiazepines until the infusion of our AED of study:** minutes; a continuous quantitative variable.

5.5. Study interventions

The patients enrolled in this clinical trial will be randomly distributed in two groups:
Group A: this group will receive the **drug A**: an intravenous sodium valproate (VPA) infusion. The loading dose will be 20 mg/kg infused with a rate of 1 mg/kg/min (maximum rate of 50 mg/min).
If this drug terminates the status epilepticus (treatment success), the maintenance dose will be started 30 minutes after the loading dose, using a continuous valproate infusion of 1 mg/kg/hour.

Group B: this group will receive the **drug B**: an intravenous phenytoin (PHT) infusion. The loading dose will be 20 mg/kg infused with a rate of 1 mg/kg/min (maximum rate of 50 mg/min).
If this drug terminates the status epilepticus (treatment success), the maintenance dose will be started 12 hours after the loading dose, using a phenytoin infusion of 5 mg/kg/day divided in two doses per day.

Both drugs will be diluted with saline (0,9% sodium chloride) solution to a concentration of 1 mg/ml. Then, the corresponding drug will be administrated by an experimented nurse

(supervised by an experimented pediatrician) using an independent venous access. Before and after this drug infusion, a sterile saline solution will be administrated through the venous access to prevent the appearance of phlebitis. See **"ANNEX 1. Drug relevant information"** for more information about our drugs of study.

In both groups of study, we need to know the patient weight to calculate the dose of the AED used. As measuring the patient weight in this emergent situation will not be possible, we will obtain it from reliable caregivers or records. If these options are not available, we will estimate the weight with the Broselow Pediatric Emergency Tape.

As we said before, our study will be triple-blind for both loading dose and maintenance dose. Firstly, the loading doses of VPA (drug A) and PHT (drug B) will be masked because they will be identical in appearance (consistence and color), formulation (intravenous), packing and administration (same volume and rate of infusion). Secondly, although the maintenance dose posology of our drugs of study is different, we will mask it using the following procedure (*Table 4*):
Maintenance dose 1: at 30 minutes after the loading dose we will start an infusion of sodium valproate (1mg/ml) in group A (maintenance dose A1) and an infusion of saline solution (as a placebo) in group B (maintenance dose B1). We will use the same rate of infusion (1 ml/kg/hour) with the same appearance and packing in both groups.

Maintenance dose 2: at 12 hours after the loading dose we will infuse 2,5 mg/kg of phenytoin (1mg/ml) in group B (maintenance dose B2) and 2,5 ml/kg of saline solution (as a placebo) in group A (maintenance dose A2). This infusion will be repeated twice per day (every 12 hours). Again, we will use the same appearance and packing in both groups.

TABLE 4. Study interventions

GROUP OF STUDY	**LOADING DOSE**	**MAINTENANCE DOSE 1** (at 30 minutes)	**MAINTENANCE DOSE 2** (at 12 hours)
GROUP A	Drug A (VPA)	Maintenance dose A1 (VPA)	Maintenance dose A2 (saline solution)
GROUP B	Drug B (PHT)	Maintenance dose B1 (saline solution)	Maintenance dose B2 (PHT)

These maintenance doses (and its respective placebo) will be infused during the hospitalization period.

If the SE persists after 20 minutes of the loading dose of VPA (drug A) or PHT (drug B), we will consider this situation, as we said before, as a treatment failure and we will not start the maintenance dose (we only start it if the loading dose has succeed). In this situation, we will keep trying to solve the SE and the patient will receive immediately the loading dose of the other AED of study (**group A → drug B** and **group B → drug A**). Finally, if the SE still persists 20 minutes after the second study drug infusion, the patient will receive the standard protocol for the **refractory SE** management of each hospital. All this process will be recorded.
In the statistical analysis, the patients who suffer this treatment failure will be included in the group of study to which they were randomly assigned (group A or B if the first drug

that they received was VPA (drug A) or PHT (drug B), respectively), regardless of the necessity to receive the second drug of study and regardless of deviation from the study protocol. This statistical method is known as "intention to treat" (ITT) analysis (46).

5.6. Data collection

A specific number will be assigned to each patient who participates in this RCT in order to prevent his or her anonymity and to keep the blind during the study. All his or her information will be collected in the "Data collection sheet" (**"ANNEX 7. Data collection Sheet"**) and it will be introduced into our database.

Emergency room

Any case of benzodiazepine refractory SE attended in the emergency room will be considered a potential patient to be included in the RCT. If the patient accomplishes the inclusion and exclusion criteria and the informed consent is obtained, he or she will be formally enrolled in our study.

As soon as possible, the investigators will try to stabilize and monitor the vital signs of the patient and, at the same time, they will begin the treatment of the SE with one of our drugs of study according to the group (A or B) that the patient will have been randomly assigned.

General hospitalization area or PICU (Pediatric Intensive Care Unit)

Once VPA or PHT will have been infused, if the SE is finished (treatment success) and the vital signs are stabilized, he or she will be moved to the general hospitalization area where will be controlled for, at least, 24 hours. However, if the stabilization of the vital signs is not reached and the SE persists more than 20 minutes (treatment failure), the patient will be moved to the Pediatric Intensive Care Unit (PICU) where he or she will receive vital support management and, as we have already said, the infusion of the other antiepileptic drug of study. In addition, if we are able to diagnose the SE etiology, the etiologic treatment will be started.

In order to evaluate our main dependent variable (termination of the SE), the SE recurrence and the appearance of adverse drug reactions, the same experimented and previously taught pediatricians and nurses will control and recheck the patients both in the emergency room and in the general hospitalization area (or in the PICU if the SE still persists). These controls will be done periodically:

- First 2 hours of the study: before and after the AED infusion and then, every 5 minutes
- 2-12 hours: controls every 30 minutes
- 12-24 hours: controls every 1 hour
- >24 hours (if needed): controls every 2 hours
- Or whenever it is needed

In these controls, we will check:

- Clinical seizure activity to evaluate the resolution of the SE. It will be evaluated with a general and neurological physical examination and we will use a chronometer to

calculate its duration. Once the SE will have been solved, these clinical controls will be performed to evaluate the SE recurrence.

- Vital signs: blood pressure and pulses, temperature, respiratory rate and oxygen saturation; a continuous ECG will be also performed. These vitals signs will be evaluated with standardized vital signs monitors. The evaluation of the vitals signs will be basic to evaluate the appearance of the principal adverse drug reactions (cardiovascular and respiratory dysfunction and cardiac arrhythmias).
- Consciousness and sedation degree. As we said before, it will be evaluated with the Richmond Agitation-Sedation Scale (RASS) (**"ANNEX 5. Richmond Agitation-Sedation Scale (RASS)**).
- Appearance of other adverse drug reactions (purple glove syndrome and anaphylaxis). It will be evaluated with the general physical examination and the standardized vital signs monitors.

Moreover, additional tests will be performed:

- At least one EEG will be required before hospital discharge. If the patient is in the general hospitalization area, the EEG will be realized during the first 24 hours after the beginning of the clinical trial, while if he or she is in the PICU, a continuous EEG will be used to monitor the electroclinical seizure activity.
  The EEG will be especially mandatory and urgent if the consciousness does not improve within one hour after clinical resolution of the SE, in order to discard a prolonged electrical SE.
  The patients who are in the general hospitalization area will be moved to the neurophysiology room where the neurophysiologist will realize the EEG. These patients will lie on their backs on a bed and they will wear a cap with fixed electrodes that will follow the 10-20 International System of Electrode Placement. We will perform a Standard EEG and, according to the age, the clinical situation and the cooperation of the patient, we will add to this standard procedure the following interventions: intermittent photic stimulation, hyperventilation and EEG sleep registration.

- A blood test will be periodically performed (the first one done urgently and then, once per day during the hospital stay) to evaluate: complete blood count, glucose levels, electrolytes, ammonium, amino acids, lactate, renal function (urea and creatinine) and liver function (transaminases, coagulation). Moreover, in those patients under treatment for previous epilepsy, plasma levels of antiepileptic drugs will be also determined.
  After disinfecting the sampling site with 70% alcohol, the blood sample will be collected from the median cubital or basilic vein, preferently. It will be performed by a nurse with a needle and a syringe.
  An arterial blood gas test will be also performed to evaluate the acid-base equilibrium and the PaO2 and PaCO2. In this case, we will collect the arterial blood sample from the radial artery of the patient.
  Then, both arterial and venous blood samples will be carried to the laboratory of each hospital where they will be properly analyzed.

- In order to identify the etiology of the SE, if indicated, a magnetic resonance imaging (MRI), a Computed Tomography (CT) a lumbar puncture or a blood culture will be performed.

Follow-up

After these first and exhaustive controls, the patient will be followed up (until 30 days from the RCT enrolment) in the out-patient setting (or in the inpatient setting if the patient is still in the hospital) by a neuropediatrician and a neuropsychologist in order to promptly identify adverse neurological outcome or the presence of a seizure or SE recurrence.

The follow-up will last one month:

- First visit: 15 days after RCT enrolment. The neuropediatrician will evaluate the clinical and neurological state of the patient performing an anamnesis and a general and neurological physical examination.
- Second visit: 30 days after the RCT enrolment. The same neuropediatrician will recheck the clinical and neurological state of the patient and the neuropsychologist will use the adequate scale of cognitive development, according to the age of the patient, to evaluate the presence of neurodevelopment impairments.

Pilot test

We will dedicate the first two months of the RCT to analyze the viability of the protocol timing (diagnosis, treatment and data collection sequence) and the reliability of our data collection. This procedure will let us know the principal practical weaknesses and unexpected complications of our study and, consequently, we will be able to solve them.

6. STATISTICAL ANALYSIS

This statistical analysis will be done using the Statistical Package for the Social Sciences (SPSS Windows©). The statistician who will perform it will be blinded to the study groups and the statistical analysis method used will be the "intention to treat" (ITT) analysis.

6.1. Univariate analysis

The result of our variables in each group of study will be expressed according to if they are qualitative or quantitative:

Qualitative variables:

- Antiepileptic drug of study: drug A (sodium valproate) or drug B (phenytoin)
- Termination of the SE within 20 minutes
- Appearance of adverse drug reactions
- Mortality
- Neurological outcome at 30 days after the study drug infusion
- SE recurrence between 20 minutes and 30 days after the study drug infusion
- Gender
- SE etiology
- Convulsive SE type
- Type of benzodiazepine received prior the RCT

These variables will be expressed as a proportion (percentage). We will use a table of frequencies and a sector diagram to represent these proportions.

Quantitative variables:

- Time to termination of the SE
- Age
- Socioeconomic level
- Dose of benzodiazepine received prior the RCT
- Time from the beginning of the SE until the infusion of the AED of study
- Time from the administration of the second dose of benzodiazepines until the infusion of our AED of study.

These variables will be expressed as a mean +/- standard deviation (SD) if we assume a normal distribution of them. If is not possible to assume a normal distribution, median and quartiles will be estimated. We will use a bar chart (discrete variable) and histogram (continuous variable) to represent these variables.

6.2. Bivariate analysis

We will use different tests to analyze the association between the independent variable with the dependent variables. Our independent variable (antiepileptic drug of study: sodium valproate or phenytoin) is a dichotomous qualitative variable. So, the tests used to evaluate the association between this variable with a dependent variable will be:

- Chi-square (x^2) test if the dependent variable is qualitative.

- Student's t-test if the dependent variable is quantitative with a normal distribution. If it is not possible to assume a normal distribution, a Mann-Whitney U test will be performed.

We will consider the results statistically significant at a value of p <0,05 defining a confidence interval of 95%.

6.3. Multivariate analysis

In order to detect and inform a possible confusion produced by the covariables, that could influence the relationship between our dependent and independent variables, we will perform a multivariate analysis. As our dependent variable is a dichotomous qualitative variable (VPA or PHT), we will use a Logistic Regression Model to perform this multivariate analysis.

7. WORK PLAN AND SCHEDULE OF EVENTS

Principal investigators: pediatricians of the hospitals that participate in this study. In each of our 6 hospitals, these pediatricians will compose the "hospital investigation team" with one "coordinator" in each team. The 6 coordinators from each "hospital investigation team" will compose the "Trial Coordination Team" that will meet periodically (once a year) at the *Hospital Universitari de Girona Doctor Josep Trueta* (Girona). Furthermore, the coordinator of the "hospital investigation team" of this hospital will be the "Principal Coordinator" of this randomized controlled trial (RCT).

Co-investigators:

- An emergency staff from each hospital
- A nursing staff from each hospital
- A pharmacist from each hospital
- A neurophysiologist from each hospital
- A neuropsychologist from each hospital
- A statistician

7.1. STAGE 1. Coordination and formation

Duration: 4 months

Responsible: Principal investigators and co-investigators.

Tasks:

- Scientific research. A scientific research will be performed in order to make sure that there is a lack of information about the topic of study that will justify the necessity to perform this clinical trial.

- Protocol redaction

- Definition of the objectives, hypothesis and variables of the study.
- Definition of the methodology of the study

- Coordination meetings. Definition of the investigators and hospitals roles and determination of the schedule and work plan.

- Investigators formation. All the investigators that will take part of this RCT will have been taught prior the beginning of it. They will receive formation about the study protocol (diagnosis, treatment and data collection techniques) in order to ensure that all the researchers from all the hospitals will act in the same way. That will ensure the homogeneity required to get representative conclusions.

- Presentation to Clinical Research Ethics Committee. Prior the beginning of the next stage, the protocol will have to be ethically accepted.

7.2. STAGE 2. Field research

Duration: According to the time needed to recruit the 390 patients, this stage will last 36 months.

Responsible: Principal investigators and co-investigators

Tasks:

- **Patient recruitment and informed consent.** A non-probabilistic consecutive sampling will identify those patients that, if accomplish the inclusion and exclusion criteria and the informed consent is available, will be enrolled in this study. This process will be done in the emergency room of the participating hospitals.

- Study intervention. The patients will be randomly distributed in two groups of study and the pediatricians will administer the drug of study according to the group that the patient will have been assigned.

- Follow up. Once the study intervention will have been administrated, the patient will be followed in the hospital and out-hospital setting. The last follow up visit will be performed 30 days after the RCT enrolment.

- Data collection. Collection of the clinical information of every patient enrolled in this RCT. An individual data collection sheet (**"ANNEX 7. Data collection Sheet"**) will be used and stored in our database. This database will be frequently revised to guarantee its functioning.

The "Trial Coordination Team" will meet twice to evaluate if the protocol is well executed and to determine the necessity to modify specific procedures that do not work. The first meeting will take place one year after the beginning of the "field research" stage and the second meeting will take place the following year. For the same reasons, each "hospital investigation team" will meet every two months.

7.3. STAGE 3. Data analysis and result interpretation

Duration: 3 months
Responsible: Coordinators and statistician
Tasks:

- Statistical analysis. The statistician will analyze the collected data. Different statistical tests will be used according to the different variables of study.

- Result interpretation. The coordinators will interpret the results of the study to obtain the pertinent conclusions. From these conclusions new clinical recommendations will be defined.

This Stage 3 will be performed twice. The first analysis will be done in the middle of the "field research" stage with the mission to identify unethical results; if these results are identified the study will be stopped. The second analysis will be performed once the "field research" stage will be finished.

7.4. STAGE 4. Publication

Duration: 2 months
Responsible: Coordinators
Tasks:

According to the previous stage, a paper will be redacted to show the study results and conclusions. This paper will be sent to the principal pediatrics journals. Moreover, these results will be also exposed in a congress of the *Asociación Española de Pediatría (AEP)*.

7.5. CHRONOGRAM

STAGE	2016		2017			2018	2019	2020			
	Nov	Des	Jan	Feb	Mar-Des	Jan-Des	Jan-Des	Jan-Feb	Mar	Apr-May	Jun-Jul
Stage 1: Coordination and formation											
Scientific research											
Protocol redaction											
Coordination meetings						*	*				
Investigators formation											
Presentation to Clinical Research Ethics Committee											
Stage 2: Field research											
Patient recruitment and informed consent											
Study intervention and follow-up											
Data collection											
Stage 3: Data analysis and result interpretation											
Statistical analysis						**					
Result interpretation						**					
Stage 4: Publication											
Paper redaction											
Dissemination											

**March*

*** September*

8. LEGAL AND ETHICAL ASPECTS

Once this protocol will be finished, it will be sent to the Clinical Research Ethics Committee of the hospitals that are pretended to take part of this study. According to the *"Real Decreto 1090/2015, de 24 de diciembre, ensayos clínicos con medicamentos"* the approbation of this protocol by this committee is mandatory to start the clinical research. In addition, we will ask permission to perform this study to the direction of our hospitals and the protocol will be also sent to the *Asociación Española de Medicamentos y Productos Sanitarios* (AEMPS) to receive its authorization. After its approval, this RCT will be submitted to the European Clinical Trials Database (EudraCT).

According to the same Spanish legislation, *"Real Decreto 1090/2015, de 24 de diciembre, ensayos clínicos con medicamentos"* and the European legislation *"Reglamento (UE) N° 536/2014 DEL PARLAMENTO EUROPEO Y CONSEJO de 16 de abril de 1014"*, the parents or legal representatives of our patients will receive information about the study **("Annex 3. Information Sheet")** and, if they agree, they will give us the informed consent **("Annex 4. Informed consent document")** to enroll the patients in the RCT. This legislation also rules the obligation to compensate economically the patients if they get injured due to the clinical trial and an insurance is needed to face with these adverse events.

According to the Spanish legislation, *"Ley Orgánica 15/1999, 13 de Diciembre, Protección de Datos de Carácter Personal",* the confidentiality of the personal information of the patient (name, surname, clinical history) will be guaranteed. Moreover, the patient (and his or her parents) will have the possibility to access, erase or modify this information.

In addition, this RCT will respect the principals of human experimentation according to the World Medical Association Declaration of Helsinki - Ethical Principles for Medical Research Involving Humans Subjects (64th WMA General Assembly, Fortaleza, Brazil, October 2013).

Regarding the ethical aspects, we decided to not using placebo in our study because status epilepticus is an emergency that needs a promptly treatment. So, we could not administer to half of our patients a placebo while we have different available medicines that seem to be effective for the treatment of this emergent situation.

Our RCT does not imply many ethical conflicts. Both sodium valproate and phenytoin are used in the clinical practice to treat the SE and there is not evidence to decide which must be used preferently. Although our hypothesis says that sodium valproate is more effective and safer than phenytoin, it has not been proved yet, so none of our patients will receive a drug that is demonstrated to be less effective and less safe than the other. Moreover, taking part of this study will not private our patients to receive a better available treatment because we do not dispose of other antiepileptic drugs with demonstrated higher efficacy and safety than our drugs of study.

Furthermore, as we explained in **"5.1.b. Informed Consent"**, we will make sure that participating in this RCT will not delay the beginning of the SE treatment. Regarding this aspect, although starting the randomization and treatment before obtaining the informed consent is legal, we accept that the parents could not understand it. If it happened, we would explain to them the legislation and we would also show them that taking part in this clinical trial does not modify the treatment that the patient would receive if he or she were not enrolled in the trial. Moreover, we will show them the utility and necessity of the research in emergent situations, in order to justify our conduct.

9. LIMITATIONS

The principal limitations of our study are:

1. From our point of view, the principal objective of our study should have been: to compare the **neurological outcome** of children who suffer a benzodiazepine refractory convulsive status epilepticus that receive intravenous valproate versus those who receive intravenous phenytoin. However, it is very difficult to compare a variable (neurological outcome) characterized by a significant variability among those who suffer the SE, even prior the beginning of its treatment. In fact, the neurological outcome of children who suffer a SE depends on the SE etiology and on their previous neurological state. For example, children who suffer a febrile SE tends to have a better neurological outcome after the SE than those who suffer SE produced due to a degenerative neurological disease because the first SE type affects a child with a perfect neurological functioning while a the second SE type affects a child with a prior reduction of his or her neurological functioning.

For sure, our randomization process could reduce this previous variability ensuring that our two groups of study could include children with a similar average of prior neurological state and a similar proportion of the different etiologies. However, despite this randomization process, we would not be able to strongly affirm that the neurological outcome difference found between our two groups of study after the treatment would not be influenced by the SE etiology and the previous neurological state of the patients.

A possible alternative to avoid this risk of bias could be performing a consecutive stratified sampling with a stratus composed by patients suffering a febrile SE (with a good prior neurological state) and another stratus composed by patients suffering a non-febrile SE (with a worse prior neurological state) and, then, analyzing the neurological outcome in each stratus separately. However, we are not able to stratify our sampling by etiology because when we enroll the patients in our study we cannot know the SE etiology; it is diagnosed later, when the etiologic diagnosis is performed.

Moreover, we found another difficulty to develop this objective. There is not a specific scale that analyses the neurological functioning of a patient who suffered a SE. Therefore, we would have to use unspecific scales that evaluate general cognitive development. In addition, these scales are different depending on the age, so it would be difficult to unify the results to obtain general and equivalent conclusions.

So, all these difficulties made almost impossible to evaluate the neurological outcome properly. As we think it is an important endpoint, we decided to analyze it as a secondary objective assuming that the risk of bias is important and the conclusions obtained about this topic will not be definitive; they should be confirmed in further researches addressed specifically to study it.

We guess that these limitations are the reasons why most of the clinical trials previously developed to analyze the SE management decided that their principal objective had to be evaluating the proportion of status epilepticus termination. This objective is easier to develop and it is also relevant, for that reason, we chose it as our main objective.

2. However, choosing the proportion of status epilepticus termination as our main objective has also a limitation. It is known that the SE morbidity and mortality increases as the duration of the SE increases, especially if there is an absence of SE termination with the second-line antiepileptic drugs (our drugs of study). Therefore, we could assume that if the drug of study (VPA or PHT) had a higher proportion of SE cessation it would reduce the SE mortality and morbidity. Nevertheless, this assumption could be biased because it is true that the duration and the treatment of the SE are related to this morbidity and mortality but remains unclear if this relationship is independent or if it is confused by the etiology of the SE.

We will try to avoid this confusion with the randomization process and the multivariate analysis but, at the same time, we remark the necessity to analyze deeper the relationship between etiology, duration and treatment of SE and its consequences (morbidity and mortality); a long-term prospective follow-up of children who suffered a SE could be a proper study method.

At the same time, we assume that we should define the "SE termination" with the clinical examination and the EEG simultaneously. However, as we said before, the immediate EEG investigation is not universally available in the hospitals that will take part of this clinical trial so we will only use the clinical examination. Consequently, we will define our "SE termination" as a "clinical SE termination", not as an "EEG SE termination".

3. We will evaluate only two antiepileptic drugs, although we know that there are other possible options. In fact, we could also evaluate one of these AEDs, the levetiracetam, which is an emergent drug. However, if we had included levetiracetam in our study it would have implied a significant increase of our sample size. Therefore, it would have represented an unacceptable duration of our study and, moreover, an increase of our budget. For that reason, we thought that evaluating the two most used AEDs (valproate and phenytoin) was enough relevant.

4. As we said in **"5.2 Population of interest. Inclusion criteria"**, we will accept in our study patients who will have received, prior to their study enrolment, two different types of benzodiazepines (diazepam or midazolam). These two drugs have the same pharmacodynamics and mechanism of action but they have different pharmacokinetics (diazepam has a greater half-life than midazolam and, then, it lasts more time in the blood). This difference, of course, could affect our study; the efficacy and safety of sodium valproate or phenytoin could vary depending on the plasma benzodiazepine levels.
Despite this fact, we decided to include patients who had received any of the two benzodiazepines. If we just accepted patients who had received only diazepam (or only midazolam) the potential patients to enroll in our RCT would have been significant less. Then, our study would have been much longer and unfeasible. Furthermore, the randomization process and multivariate analysis will control this covariable.

5. We assume that the SE complications, such as cardiorespiratory depression and cardiac arrhythmias, could be similar to the adverse reactions produced by our study drugs. This fact could lead us to identify a SE complication as an adverse drug reaction. We will

prevent this misinterpretation classifying the adverse events (SE complications or adverse drug reactions) according to their possibility to be related to the drug of study (see **"ANNEX 6. Adverse events"**). This classification will let us identify those adverse events not related to the drug of study (**SE complications**) and those adverse events related to the drug of study (**adverse drug reactions**). This second type of adverse events will be the one that we will statistically analyze to evaluate one of our dependent variables (appearance of adverse drug reactions).

Another limitation related to these adverse drug reactions is that some of them are specific to one of our drugs of study (hyperammonemia is related to sodium valproate and purple glove syndrome to phenytoin). Consequently, its appearance could make us lose the blind. However, these specific adverse reactions are not very common and they occur after the appearance of our main variable. Then, we assume that they will not affect significantly the quality of our study.

6. We will carry out a multicentric study and it could imply unacceptable variability in the study procedures developed in each hospital. Nevertheless, we defined a standardized protocol and a formation course to ensure that all investigators will act in the same way. Moreover, we will avoid coordination problems with periodic coordination meetings.

7. Our randomized controlled trial does do not dispose of a control group (administration of placebo). However, as we said before, we think that we cannot administrate to half of our patients a placebo while we dispose of medicines that seem to be effective for SE treatment.

8. We suspect that a significant percentage of the potential patients could not accept to take part in this RCT. We assume that children will be in a critical situation and some of their parents could not accept and sign the informed consent document. However, we will try to reduce this percentage by explaining to them that our study does not modify at all the routine management of the SE. Moreover we will remark to them that this study is basic to improve the SE management that, nowadays, lacks of consistent evidence.

9. We assume that the results of our secondary variables could not be definitive because of a lack of study power (due to small sample size or methodological disparities). Consequently, we recommend new studies to confirm these results.

10. FEASIBILITY AND BUDGET

Hospitals. This randomized controlled trial (RCT) will be developed in six Catalan hospitals: *Hospital Universitari de Girona Doctor Josep Trueta* (Girona), *Hospital Universitari Vall d'Hebron* (Barcelona), *Hospital Sant Joan de Déu* (Barcelona), *Hospital Universitari Arnau de Vilanova* (Lleida), *Hospital Universitari Part Taulí* (Sabadell) and *Hospital Universitari Joan XXIII de Tarragona* (Tarragona). All these hospitals are included in the National Health System (NHS).

Investigators. The investigators of this study will be workers (physicians and nurses) of these hospitals and our clinical trial will be performed during their working hours so, no extra budget is needed to hire them. However, we will need to hire a neuropsychologist, in each hospital, to assess the child neurological outcome at 30 days after the status epilepticus and we will also need to hire a statistician to analyze the data collected (see **"BUDGET"**).
All the physicians participating in this trial have enough knowledge and experience in the status epilepticus management. The nursing staff is also prepared to develop its role in this RCT. Moreover, all the investigators will receive the same formation course. Therefore, we believe that our staff is prepared to develop properly this study.

Medical resources. Each patient will be attended at the hospital emergency room, which is operating 24 hours per day during all the year. After this first management, if the patient is stabilized and the SE solved, he or she will be moved to the general hospitalization area but, if not, the patient will be moved to the Pediatric Intensive Care Unit (PICU). In both areas, the patient will be attended by pediatricians and nurses that are taking part of this study. It will be important to make sure, prior the enrolment of the patient in the study, that these areas have available beds. After the hospital discharge, the patient will be followed up in the outpatient setting of the same hospitals.

Among the material used in this study we include the intravenous sodium valproate and phenytoin medicines, as well as other medical devices (syringes, needles, stabilization and monitoring materials). All these materials are available in our hospitals because they are already used for the SE management in the routinely clinical practice. In fact, they are funded by the National Health System so, we will not need to use extra budget to pay for them. Moreover, it will not represent an important expenditure to the NHS because our drugs of study are not expensive:

- Intravenous phenytoin: 1,872 €*/patient x 195 patients = 365,04 €
- Intravenous valproate: 25 €*/patient x 195 patients = 4.875 €

  ** This cost has been calculated assuming the maximum dose possible. We consulted the price with the hospital pharmacy.*

In addition, during our study we will perform the following additional tests: blood tests, an electroencephalogram and, if indicated, neuroimaging, blood culture or lumbar puncture. These tests are also performed in the routine management of the SE so no extra budget will be needed, again.

Nevertheless, the insurance policy, as well as the publication, travelling and accommodation expenditures, will imply a significant increase of our budget (see **"BUDGET"**).

Patient recruitment. We assume that our 6 hospitals together will approximately attend 160 patients suffering a benzodiazepine refractory status epilepticus per year. If we need to enroll 390 patients and we hypothesize that a 10% of patients will not accept to be enrolled in this clinical trial, we estimate that the time of patient recruitment will last 36 months (3 whole years).

If we add to these months the time needed for the formation and coordination as well as the time needed to analyze and publish the results, we estimate that this RCT will last approximately 45 months.

10.1. BUDGET

		QUANTITY	COST	SUBTOTAL
Personnel cost	Statistician	2 times/50 hours	35 €/hour	3.500 €
	Neuropsychologist	390 hours (one hour per patient)	50€/hour	19.500
Insurance policy	Insurance policy	1	15.000 €	15.000 €
Publication cost	Publication in a pediatric neurology journal	1	2.500 €	2.500 €
	AEP * presentation			
	Inscription	2	500 €	1.000 €
	Travel and accommodation	2	300 €	600 €
Coordination meeting expenses	Travel and subsistence allowance	5 meetings / 5 investigators	50 €	1.250 €
Printing	Information sheet	390	0,04 €/page (x3 pages)	46,8 €
	Informed consent	390	0,04 €/page	15,6 €
				TOTAL
				43.412,4 €

* AEP*: Asociación Española de Pediatría*

11. IMPACT ON THE NATIONAL HEALTH SYSTEM

Pediatric status epilepticus is a common neurological emergency in children and it implies a significant mortality and morbidity among those who suffer it.

The SE short-term complications, such as cardiorespiratory depression or cerebral edema, imply an increase of time of hospitalization and consumption of public resources. In fact, more duration of SE implies lower spontaneous termination of it, more risk of complications and more necessity to hospitalization, especially in the Pediatric Intensive Care Unit (PICU).

Moreover, the long-term morbidity, such as neurodevelopment impairments and focal neurological deficits, also implies an increase of the consumption of the National Health System (NHS) resources because these patients need to be followed up regularly to attend their special necessities. In addition, the reduction of the children cognitive skills may reduce their ability to learn and, consequently, it may reduce their quality of life and productivity, as well as it may also reduce the quality of life of their families.

Despite these evident bad consequences, the current management of the SE is not sustained by confirmed scientific evidence. Therefore, when the first line drugs for SE treatment (benzodiazepines) fail, the different hospitals and doctors vary their procedures depending on not standardized protocols. We guess that this lack of proper protocols reduces the quality of the current SE management and, consequently, it may contribute to increase or, at least, to not reduce, the SE mortality and morbidity.

Therefore, with our study, we would like to be able to define which is the best medicine (sodium valproate or phenytoin) that should be used to solve the status epilepticus when benzodiazepines fail. We guess that, if strong evidence is found, the management of this clinical condition will improve. Consequently, it may reduce the mortality and morbidity related to SE and, therefore, it could also reduce the NHS resources used to solve this clinical condition and its consequences. Even we expect that it may also improve the quality of life of the patients and their families.

12. BIBLIOGRAPHY

1. Trinka E, Cock H, Hesdorffer D, Rossetti AO, Scheffer IE, Shinnar S, et al. A definition and classification of status epilepticus - Report of the ILAE Task Force on Classification of Status Epilepticus. Epilepsia [Internet]. 2015 [cited 2016 Nov 25];56(10):1515–23. Available from: http://onlinelibrary.wiley.com/doi/10.1111/epi.13121/epdf
2. Carreño M, Donaire A, Falip M, Fossas P, Molins A, Raspall M. Diagnòstic i tractament de les epilèpsies [Internet]. 2nd ed. Barcelona: Societat Catalana de Neurologia; 2011 [cited 2016 Nov 25]. Available from: http://www.scn.cat/docs/guies_protoc/3_Epilepsia.pdf
3. Beghi E, Carpio A, Forsgren L, Hesdorffer DC, Malmgren K, Sander JW, et al. Recommendation for a definition of acute symptomatic seizure. Epilepsia [Internet]. 2010 [cited 2016 Dec 5];51(4):671–5. Available from: http://onlinelibrary.wiley.com/doi/10.1111/j.1528-1167.2009.02285.x/full
4. Fisher R. Operational Classification of Seizure Types by the International League Against Epilepsy. J Chem Inf Model [Internet]. 2013 [cited 2016 Dec 5];53(9):1689–99. Available from: http://www.ilae.org/visitors/centre/documents/ClassificationSeizureILAE-2016.pdf
5. Fisher RS, Acevedo C, Arzimanoglou A, Bogacz A, Cross JH, Elger CE, et al. ILAE Official Report: A practical clinical definition of epilepsy. Epilepsia [Internet]. 2014 [cited 2016 Nov 24];55(4):475–82. Available from: http://onlinelibrary.wiley.com/doi/10.1111/epi.12550/epdf
6. Lowenstein DH, Bleck T MR. It's time to revise the definition fo status epilepticus. Epilepsia [Internet]. 1999 [cited 2016 Nov 25];40(0):120–2. Available from: http://onlinelibrary.wiley.com/doi/10.1111/j.1528-1157.1999.tb02000.x/epdf
7. Commission on Epidemiology and Prognosis ILAE. Guidelines for Epidemiologic Studies on Epilepsy. Epilepsia. 1993;34(4):592–6.
8. Chen JWY, Naylor DE, Wasterlain CG. Advances in the pathophysiology of status epilepticus. Acta Neurol Scand. 2007;115(Suppl.186):7–15.
9. Raspall-Chaure M, Chin RFM, Neville BG, Bedford H, Scott RC. The epidemiology of convulsive status epilepticus in children: A critical review. Epilepsia [Internet]. 2007 [cited 2016 Nov 27];48(9):1652–63. Available from: http://onlinelibrary.wiley.com/doi/10.1111/j.1528-1167.2007.01175.x/epdf
10. Shiloh-Malawsky Y, Fan Z, Greenwood R, Tennison M. Successful treatment of childhood prolonged refractory status epilepticus with lacosamide. Seizure [Internet]. 2011 Sep [cited 2016 Nov 23];20(7):586–8. Available from: http://www.ncbi.nlm.nih.gov/pubmed/21474342
11. Lowenstein DH. The management of refractory status epilepticus: An update. Epilepsia [Internet]. 2006 [cited 2016 Nov 23];47(SUPPL. 1):35–40. Available from: http://onlinelibrary.wiley.com/doi/10.1111/j.1528-1167.2006.00658.x/epdf
12. Neville BG, Chin RF, Scott RC. Childhood convulsive status epilepticus: epidemiology, management and outcome. Acta Neurol Scand Suppl [Internet]. 2007 [cited 2016 Nov 27];186(6):21–4. Available from: http://www.ncbi.nlm.nih.gov/pubmed/17784533

13. Chin RFM, Neville BGR, Scott RC. A systematic review of the epidemiology of status epilepticus. Eur J Neurol. 2004;11(12):800–10.
14. Chin RF, Neville BG, Peckham C, Bedford H, Wade A, Scott RC. Incidence, cause, and short-term outcome of convulsive status epilepticus in childhood: prospective population-based study. Lancet. 2006;368(9531):222–9.
15. Scott RC. Prolonged Epileptic Seizures : What are the effects of prolonged seizures in the brain? Epileptic Disord [Internet]. 2014 [cited 2016 Nov 27];16(October):6–11. Available from: http://www.jle.com/download/epd-302577-what_are_the_effects_of_prolonged_seizures_in_the_brain_--WID-Pn8AAQEAAB-w9MUAAAAK-a.pdf
16. Smith D, McGinnis E, Walleigh D, Abend N. Management of Status Epilepticus in Children. J Clin Med [Internet]. 2016 [cited 2016 Dec 7];5(4):47. Available from: http://www.mdpi.com/2077-0383/5/4/47
17. Dham BS, Hunter K, Rincon F. The epidemiology of status epilepticus in the United States. Neurocrit Care. 2014;20(3):476–83.
18. Mastrangelo M, Celato A. Diagnostic work-up and therapeutic options in management of pediatric status epilepticus. World J Pediatr [Internet]. 2012 May 10 [cited 2016 Nov 23];8(2):109–15. Available from: http://link.springer.com/10.1007/s12519-012-0348-2
19. Scott RC. Status epilepticus in the developing brain: Long-term effects seen in humans. Epilepsia [Internet]. 2009 [cited 2016 Nov 26];50:32–3. Available from: http://onlinelibrary.wiley.com/doi/10.1111/j.1528-1167.2009.02374.x/pdf
20. Martinos MM, Yoong M, Patil S, Chong WK, Mardari R, Chin RFM, et al. Early developmental outcomes in children following convulsive status epilepticus: A longitudinal study. Epilepsia [Internet]. 2013 [cited 2016 Dec 20];54(6):1012–9. Available from: http://onlinelibrary.wiley.com/doi/10.1111/epi.12136/epdf
21. Raspall-Chaure M, Chin RF, Neville BG, Scott RC. Outcome of paediatric convulsive status epilepticus: a systematic review. Lancet Neurol. 2006;5(9):769–79.
22. Herranz J. Epilepsias. An Pediatr Contin [Internet]. 2006 [cited 2016 Nov 25];4(1):1–11. Available from: http://www.apcontinuada.com/es/epilepsias/articulo/80000162/
23. Palencia Luaces R. Estado de mal convulsivo: protocolo de actuación. In: Protocolos Diagnóstico Terapéuticos de la AEP: Neurologia Pediátrica [Internet]. Madrid: Asociación Española de Pediatría; 2008 [cited 2016 Nov 28]. p. 46–51. Available from: http://www.aeped.es/sites/default/files/documentos/6-malconvulsivo.pdf
24. Capovilla G, Beccaria F, Beghi E, Minicucci F, Sartori S, Vecchi M. Treatment of convulsive status epilepticus in childhood: recommendations of the Italian League Against Epilepsy. Epilepsia [Internet]. 2013 Oct [cited 2016 Nov 23];54 Suppl 7:23–34. Available from: http://www.ncbi.nlm.nih.gov/pubmed/24099053
25. Freilich ER, Zelleke T, Gaillard WD. Identification and Evaluation of the Child in Status Epilepticus. Semin Pediatr Neurol [Internet]. 2010 [cited 2016 Dec 7];17(3):144–9. Available from: http://dx.doi.org/10.1016/j.spen.2010.06.003
26. Singh R, Stephens S, Berl M, Chang T, Brown K, Vezina L, et al. Prospective Study of new onset seizures presenting as status epilepticus in childhood. Neurology. 2010;74:636–42.

27. Brophy GM, Bell R, Claassen J, Alldredge B, Bleck TP, Glauser T, et al. Guidelines for the evaluation and management of status epilepticus. Neurocrit Care. 2012;17(1):3–23.

28. Fernández Carrión F, Gómez de Quero Masía P. Protocolo Estado Epiléptico. Salamanca: SECIP; 2013. 22 p.

29. Riviello JJ, Ashwal S, Hirtz D, Glauser T, Ballaban-Gill K. Practice Parameter : Diagnostic assessment of the child with Report of the Quality Standards Subcommittee of the American Academy of Neurology and the Practice Committee of the Child Neurology Society. Am Acad Neurol [Internet]. 2006 [cited 2016 Nov 30];67:1542–50. Available from: http://www.neurology.org/content/67/9/1542.full.pdf+html

30. Chin RFM, Neville BGR, Scott RC. Meningitis is a common cause of convulsive status epilepticus with fever. Arch Dis Child [Internet]. 2005 [cited 2017 Jan 2];90(1):66–9. Available from: http://adc.bmj.com/cgi/doi/10.1136/adc.2003.038844

31. Rogawski MA, Löscher W. The neurobiology of antiepileptic drugs. Nat Rev Neurosci. 2004;5(7):553–64.

32. Glauser T, Shinnar S, Gloss D, Alldredge B, Arya R, Bainbridge J, 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 [Internet]. 2016 [cited 2016 Dec 6];16(1):48–61. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4749120/

33. Niquet J, Baldwin R, Suchomelova L, Lumley L, Naylor D, Eavey R, et al. Benzodiazepine-refractory status epilepticus: pathophysiology and principles of treatment. Ann N Y Acad Sci. 2016;1378(1):166–73.

34. Trinka E, Höfler J, Zerbs A, Brigo F. Efficacy and safety of intravenous valproate for status epilepticus: A systematic review. CNS Drugs [Internet]. 2014 [cited 2016 Nov 30];28(7):623–39. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4078236/

35. Agencia española de medicamentos y productos sanitarios. Ficha técnica Fenitoína G.E.S. [Internet]. Madrid: AEMPS; 2014 [cited 2016 Nov 30]. p. 1–8. Available from: https://www.aemps.gob.es/cima/pdfs/es/ft/65372/65372_ft.pdf

36. Malamiri RA, Ghaempanah M, Khosroshahi N, Nikkhah A, Bavarian B, Ashrafi MR. Efficacy and safety of intravenous sodium valproate versus phenobarbital in controlling convulsive status epilepticus and acute prolonged convulsive seizures in children: A randomised trial. Eur J Paediatr Neurol [Internet]. 2012 [cited 2016 Nov 30];16(5):536–41. Available from: http://dx.doi.org/10.1016/j.ejpn.2012.01.012

37. Agencia española de medicamentos y productos sanitarios. Ficha técnica Depakine [Internet]. Madrid: AEMPS; 2016 [cited 2016 Nov 30]. 1-16 p. Available from: https://www.aemps.gob.es/cima/pdfs/es/ft/60352/60352_ft.pdf

38. Uberall M, Trollmann R, Wunsiedler U, Wenzel D. Intravenous valproate in pediatric epilepsy patients with refractory status epilepticus. Neurology. 2000;4:1–2.

39. Agarwal P, Kumar N, Chandra R, Gupta G, Antony AR, Garg N. Randomized study of intravenous valproate and phenytoin in status epilepticus. Seizure [Internet]. 2007 [cited 2016 Dec 2];16(6):527–32. Available from: http://www.seizure-journal.com/article/S1059-1311(07)00088-X/pdf

40. Waterhouse E. Intravenous Valproate For Pediatric Status Epilepticus. Epilepsia Curr [Internet]. 2003 [cited 2016 Nov 29];3(6):208–9. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC321226/pdf/epc_03612.pdf

41. Yu KT, Mills S, Thompson N, Cunanan C. Safety and efficacy of intravenous valproate in pediatric status epilepticus and acute repetitive seizures. Epilepsia [Internet]. 2003 [cited 2016 Nov 29];44(5):724–6. Available from: http://onlinelibrary.wiley.com/doi/10.1046/j.1528-1157.2003.41302.x/epdf

42. Mehta V, Singhi P, Singhi S. Intravenous Sodium Valproate Versus Diazepam Infusion for the Control of Refractory Status Epilepticus in Children : A Randomized Controlled Trial. J Child Neurol [Internet]. 2007 [cited 2016 Dec 2];22:1191–7. Available from: http://journals.sagepub.com/doi/pdf/10.1177/0883073807306248

43. Brigo F, Bragazzi N, Nardone R, Trinka E. Direct and indirect comparison meta-analysis of levetiracetam versus phenytoin or valproate for convulsive status epilepticus. Epilepsy Behav. 2016;64:110–5.

44. Misra UK, Kalita J, Patel R. Sodium valproate vs phenytoin in status epilepticus: A pilot study. Neurology. 2006;67(2):340–2.

45. Kapur J. Established Status Epilepticus Treatment Trial (ESETT) [Internet]. Michigan: Neurological Emergencies Treatment Trials; 2016 [cited 2016 Dec 21]. 1-72 p. Available from: https://nett.umich.edu/sites/default/files/docs/esettprotocolversion1final.pdf

46. Lewis J, Machin D. Intention to treat - who should use ITT? Br J Cancer [Internet]. 1993 [cited 2017 Jan 10];68(4):647–50. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC1968589/pdf/brjcancer00200-0003.pdf

47. Sessler CN, Gosnell MS, Grap MJ, Brophy GM, O'Neal PV, Keane KA, et al. The Richmond Agitation-Sedation Scale: Validity and reliability in adult intensive care unit patients. Am J Respir Crit Care Med [Internet]. 2002 [cited 2016 Dec 14];166(10):1338–44. Available from: http://www.atsjournals.org/doi/pdf/10.1164/rccm.2107138

48. Kerson AG, Demaria R, Mauer E, Joyce C, Gerber LM, Greenwald BM, et al. Validity of the Richmond Agitation- Sedation Scale (RASS) in critically ill children. J Intensive Care [Internet]. 2016 [cited 2016 Dec 14];1–6. Available from: http://dx.doi.org/10.1186/s40560-016-0189-5

49. Kapur J. ESETT Safety monitoring plan. Michigan: Neurological Emergencies Treatment Trials; 2016. 1-18 p.

13. ANNEXES

ANNEX 1. Drug relevant information

Relevant information about intravenous phenytoin (35)

Name of the product: FENITOÍNA G.E.S. 50 mg/ml Solución inyectable

Presentation: type I glass ampoule of 5 ml that contains 250 mg of sodium phenytoin (50 mg/ml)

Qualitative and quantitative composition

- **Active ingredient:** sodium phenytoin
- **Excipients:** sodium hydroxide, propylene glycol, ethyl alcohol

No special storage conditions required.

Pharmaceutical form: injectable solution.

Indications:

- Treatment of convulsive status epilepticus (tonic-clonic)
- Treatment of tonic-clonic generalized seizures and partial seizures
- Treatment and prevention of seizures in neurosurgery
- Treatment of ventricular and auricular arrhythmias

Pediatric status epilepticus posology and instructions for its administration

Loading dose: intravenous perfusion of 15-20 mg/kg, diluted in saline (0,9% sodium chloride) solution to a concentration of 1-10 mg/ml. It must be administrated slowly with an infusion rate of no more than 1-3 mg/kg/min (maximum rate of 50 mg/min).
Maintenance dose: it will be started 12-24 hours after the loading dose with an infusion of 5 mg/kg/day divided in two doses per day. Maximum dose of 15000 mg/day.

Before and after the phenytoin infusion, a sterile saline infusion will be administrated through the venous access to prevent the appearance of phlebitis.
It is recommended to determine the plasma phenytoin levels.

General advertences and precautions:

- Intramuscular administration is not recommended because the drug absorption through this route of administration is erratic.
- Acute alcohol consumption can increase plasma phenytoin levels while chronic alcohol consumption can reduce plasma phenytoin levels.
- Phenytoin infusion can produce life-threatening skin reactions, such as Stevens Johnson Syndrome (SJS) or Toxic Epidermal Necrolysis (TEN). When these reactions appear, the phenytoin infusion must be stopped.
- Phenytoin is metabolized in the liver so, its toxicity can appear early among patients with hepatic insufficiency.
- Phenytoin can produce tissue inflammation in the injection site. This inflammation varies from a light erythema to extensive necrosis.

- Phenytoin can produce hyperglycemia, especially among diabetic population.

Fertility, pregnancy and breastfeeding

- Pregnancy: Phenytoin administration during pregnancy is related to congenital malformations. Then, it should not be used as a first line drug during pregnancy, especially during the first trimester.
- Breastfeeding: Phenytoin is excreted in low concentrations through breast milk. Then, breastfeeding is not recommended during phenytoin consumption.

Contraindications:

- Phenytoin or excipient hypersensitivity
- Sinus bradycardia
- Sinoatrial block
- Second and third-degree atrioventricular block
- Adams-Stokes syndrome

Interactions:

- **Drugs that can increase the plasma phenytoin levels:**
  Chloramphenicol, dicoumarol, ethosuximide, amiodarone, isoniazid, salicylates…
- **Drugs that can reduce the plasma phenytoin levels:**
  Carbamazepine, reserpine, diazoxide, folic acid and sucralfate.
- **Drugs that can increase or reduce the plasma phenytoin levels:**
  Phenobarbital, sodium valproate.
- **Phenytoin can reduce the efficacy of:**
  Corticosteroids, coumarin anticoagulants, oral contraceptives, vitamin D, digoxin…

Adverse reactions

- Cardiovascular and respiratory collapse (principal adverse reactions).
- Cardiac disorders: atrial and ventricular conduction depression and ventricular fibrillation.
- Nervous system disorders: most of these adverse reactions are produced in the central nervous system (CNS) and are dose-dependent. Among them we find CNS depression (mental confusion), nystagmus, ataxia, headache…
- Gastrointestinal disorders: nausea, vomiting, constipation, hepatic injury…
- Skin and subcutaneous tissue disorders: morbilliform rash, purple glove syndrome, Stevens-Johnson Syndrome (SJS), Toxic Epidermal Necrolysis (TEN)…
- Hematologic disorders: thrombocytopenia, leukocytopenia, granulocytopenia, pancytopenia, lymphadenopathy…
- Musculoskeletal and connective tissue disorders: gingival hyperplasia, Peyronie's disease…
- General and injection site disorders: local irritation and vein inflammation (phlebitis), hypersensitivity, necrosis…
- Others: systemic lupus erythematosus, toxic hepatitis, osteoporosis…

Relevant information about intravenous sodium valproate (37)

Name of the product: DEPAKINE 100 mg/ml polvo y disolvente para solucion inyectable

Presentation:

- Vial: type I colorless glass with rubber stopper made of chlorobutyl and an aluminum capsule
- Ampoule: type I colorless glass

Qualitative and quantitative composition

Each vial of DEPAKINE 100 mg/ml contains:

- **Active ingredient:** 400 mg of sodium valproate
- **Excipients:** None

Each solvent ampoule contains:

- 4 ml of water for injectable preparations

It must be stored at room temperature. The solutions that contain sodium valproate will need to be used in the following 24 hours.

Pharmaceutical form: powder and solvent for injectable solution.

Indications:

- Treatment of partial and generalized epilepsies:
  - Generalized: convulsive, non-convulsive or absence and myoclonic
  - Partial: with elemental or complex symptomatology
  - Secondarily Generalized
  - Mixed forms (West and Lennox-Gastaut)
- Treatment of urgent situations where rapid therapeutic induction is needed. *After consulting with a pharmacologist, we consider that this indication includes status epilepticus.*

Pediatric Posology

Loading dose: intravenous perfusion of 20-30 mg/kg, diluted with saline (0,9% sodium chloride) solution to a concentration of 0,8 mg/ml. *Infusion rate not specified.*

Maintenance dose: it will be started 30 minutes after the loading dose with a continuous intravenous infusion of 1 mg/kg/h (*not specified for children)*.

General advertences and precautions:

- "*DEPAKINE 100 mg/ml polvo y disolvente para solucion inyectable*" will not be used through a route of administration different from the intravenous route.
- Sodium valproate can worsen the clinical signs of mitochondrial diseases produced by mitochondrial DNA mutations.
- Although it is rare, sodium valproate can produce lethal hepatic and pancreatic dysfunction. We must control the hepatic and pancreatic function periodically.

Fertility, pregnancy and breastfeeding

- Sodium valproate should not be used among girls, women of childbearing age and pregnant women, if there are other effective options.
- There is a high risk of congenital malformations and development disorders if sodium valproate is consumed during pregnancy.
- Breastfeeding: Sodium valproate is excreted through the breast milk. Then, breastfeeding is not recommended during sodium valproate consumption.

Contraindications:

- Sodium valproate or excipient hypersensitivity
- Acute and chronic hepatitis (or personal or familiar antecedents of sever hepatitis)
- Hepatic porphyria
- Acute severe pancreatic dysfunction
- Branched-chain amino acid metabolism disorder
- Urea cycle disorder
- Confirmed mitochondrial disorders (or suspected mitochondrial disorders among children under 2 years old)

Interactions:

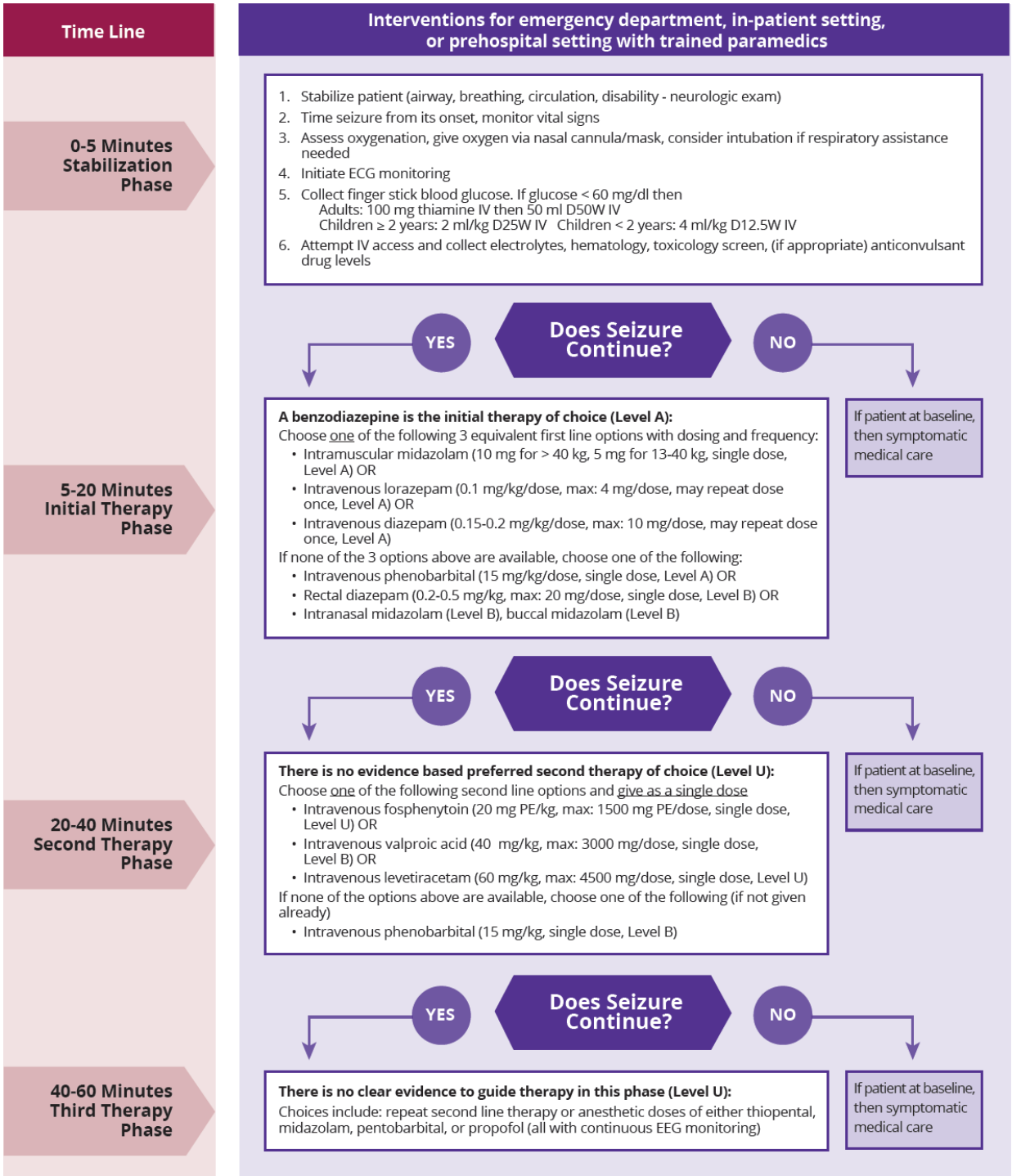
- **Drugs that can increase the plasma sodium valproate levels:**
  Felbamate, fluoxetine, erythromycin.
- **Drugs that can reduce the plasma sodium valproate levels:**
  Carbapenems, rifampicin, phenobarbital, phenytoin and carbamazepine. The last three drugs can also increase the risk of hyperammonemia and hypertransaminasemia.
- **Sodium valproate can increase the plasma levels of:**
  Benzodiazepines, neuroleptic, antidepressants, phenobarbital, primidone, carbamazepine, lamotrigine, zidovudine, nimodipine, ethosuximide, propofol…
- **Sodium valproate can reduce the plasma levels of:**
  Phenytoin (more risk of toxicity), olanzapine.

Adverse reactions

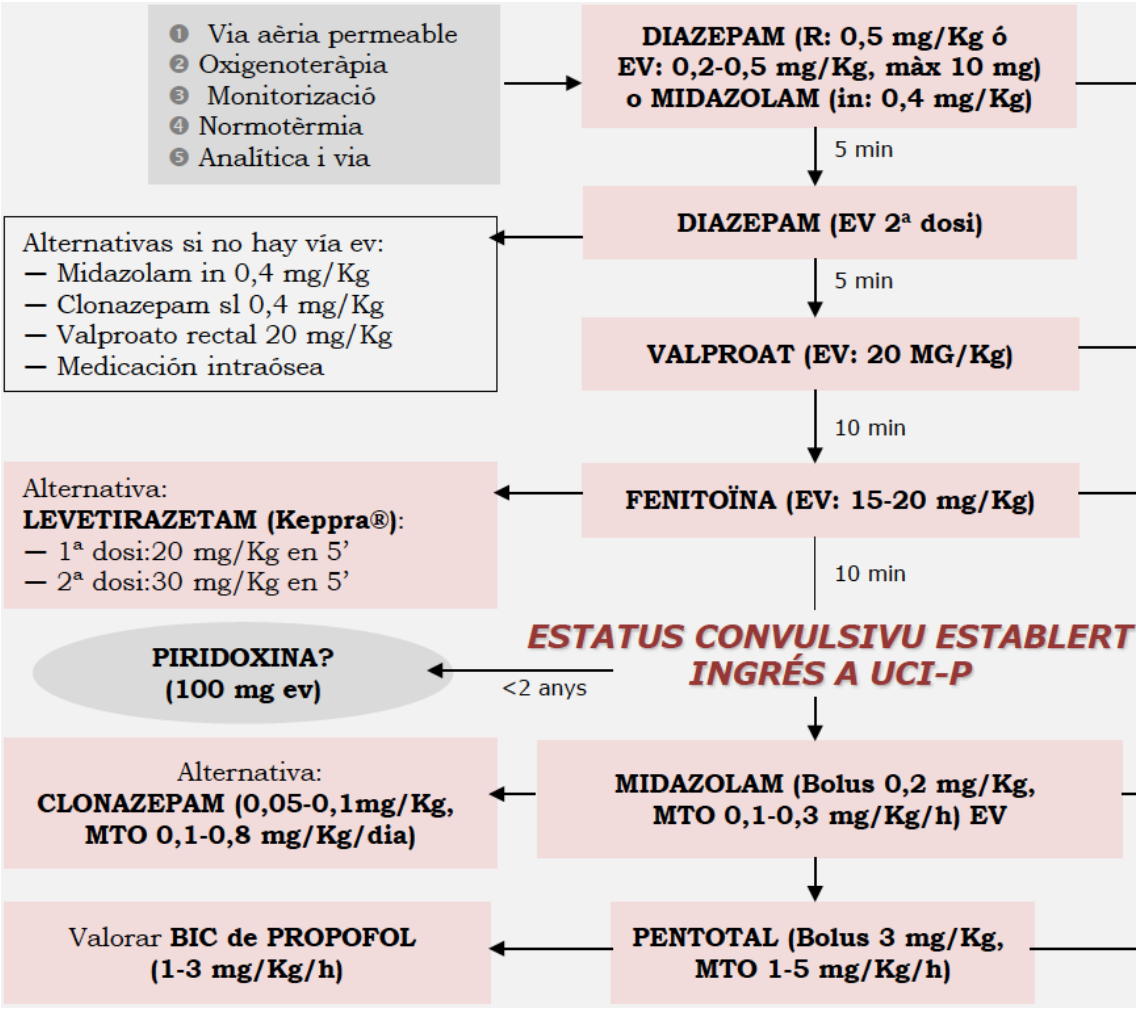
- Congenital disorders: congenital malformations and development disorders.
- Hematologic disorders: anemia, thrombocytopenia (frequent), pancytopenia…
- Nervous system disorders: trembling (very frequent), extrapyramidal disorders, somnolence, seizures, stupor, lethargy, coma…
- Hearing disorders: deafness
- Respiratory and thoracic disorders: pleural effusion
- Gastrointestinal and hepatobiliary disorders: nausea (very frequent), vomiting, gingival hyperplasia, diarrhea, pancreatitis, hepatic dysfunction…
- Skin and subcutaneous tissue disorders: hypersensitivity, transient alopecia…
- Metabolism and nutritional disorders: hyponatremia, weight gain, hyperammonemia…
- Vascular disorders: hemorrhage
- Reproductive system disorders: dysmenorrhea
- Psychiatric disorders: hallucinations, aggressiveness, agitation, inattention…

ANNEX 2. Algorithm for status epilepticus

Algorithm for convulsive status epilepticus in children and adults from American Society Epilepsy Guideline (32)



Algorithm for status epilepticus in children from *Hospital Sant Joan de Déu*, Catalonia, 2016



ANNEX 3. Information sheet

FULL D'INFORMACIÓ SOBRE L'ASSAIG CLÍNIC:

VALPROAT SÒDIC INTRAVENÓS VERSUS FENITOINA INTRAVENOSA EN EL TRACTAMENT DE L'ESTATUS EPILÈPTIC EN LA POBLACIÓ PEDIÀTRICA

Investigador principal:
Centre:

Introducció

Ens dirigim a vostè per informar-lo sobre un estudi d'investigació en el qual es convida a participar al seu fill/a o representat legal. L'estudi ha estat apropat per el Comitè d'Ètica d'Investigació Clínica d'aquest hospital i per l'Agència Espanyola del Medicament i Productes Sanitaris, d'acord amb la legislació vigent, el *Real Decret 1090/2015, del 24 de desembre*, pel qual es regulen els assajos clínics amb medicaments.

La nostra intenció és que vostè rebi la informació correcta i suficient perquè pugui avaluar i jutjar si vol o no que el seu fill/a o representat participi en aquest estudi. Per això, llegeixi aquesta fulla informativa amb atenció i nosaltres li aclarirem els dubtes que li puguin sorgir després de l'explicació. A més a més, pot consultar a les persones que consideri oportunes.

Participació voluntària

Ha de saber que la participació del seu fill/a o representat en aquest estudi és voluntària i que pot decidir no participar o canviar la seva decisió i retirar el consentiment en qualsevol moment, sense que per això s'alteri la relació amb el seu metge o metgessa ni es produeixi cap perjudici en el seu tractament.

Descripció general de l'estudi

L'estatus epilèptic, que s'ha definit com una crisi convulsiva de com a mínim 30 minuts de durada, tot i que en l'actualitat també s'accepta el diagnòstic d'estatus epilèptic si la crisi convulsiva dura com a mínim 5 minuts, és una emergència clínica que afecta anualment uns 20 de cada 100.000 nens i representa un augment de la mortalitat i de les seqüeles entre aquells qui el pateixen.

Actualment es disposa d'un ventall de medicaments per tractar aquesta condició clínica. Malauradament, no es disposa de la informació suficient per decidir quin és el millor d'aquest fàrmacs. El nostre estudi, doncs, busca estudiar dos fàrmacs usats en el tractament de l'estatus epilèptics per intentar definir quin hauríem d'usar en primer lloc quan ens enfrontem a aquesta situació clínica.

Metodologia

El nostre estudi inclourà aquells nens i nenes (≥ 1 any i <15 anys) que pateixin un estatus epilèptic convulsiu que no respongui a les benzodiazepines.

Mentre se us estigui demanant el consentiment informat, tal i com permet la legislació espanyola (*Real Decret 1090/2015, del 24 de desembre*), es distribuirà als pacients de forma aleatòria en dos grups i s'iniciarà el tractament. Cada grup rebrà un medicament diferent: un grup rebrà el vaporat sòdic intravenós i l'altre rebrà la fenitoïna intravenosa;

aquests dos fàrmacs s'utilitzen en la pràctica clínica habitual i tenen una efectivitat i seguretat almenys tan bones com les altres alternatives de tractament.
En el cas que no se'ns doni el consentiment informat, no podrem incloure el pacient en el nostre assaig clínic. Nogensmenys, el pacient ja haurà rebut (i seguirà rebent) el tractament adequat per resoldre l'estat epilèptic sense ser sotmès a cap perjudici.
En canvi, en el cas que se'ns doni el consentiment informat, el pacient passarà a formar part de l'assaig clínic al llarg del qual es continuarà amb la infusió del fàrmac d'estudi i es realitzarà un seguiment detallat de l'estat del pacient. En el cas que l'estatus epilèptic no finalitzi als 20 minuts amb el fàrmac d'estudi utilitzat es considerarà un fracàs del tractament i s'utilitzarà l'altra fàrmac d'estudi. Si en aquest cas tampoc es resol l'estatus (en 20 minuts més) es seguirà tractant al pacient tal i com es fa en la pràctica clínica.
Durant l'ingrés del pacient s'avaluarà, de forma periòdica, les seves constants vitals i estat neurològic i, a més a més, inicialment s'obtindran les següents proves complementàries: anàlisi de sang i electroencefalograma. Més endavant, si s'escau, es realitzaran més proves diagnòstiques per identificar la causa d'aquest estatus epilèptic: ressonància magnètica, tomografia computeritzada i cultiu de sang o de líquid cefaloraquidi. Cal remarcar que totes les proves prèviament esmentades es realitzen a la pràctica clínica i, per tant, no se sotmetrà al pacient a cap prova que no rebria si no s'inclogués en l'assaig clínic.
A més a més, un cop el pacient sigui donat d'alta serà seguit de forma ambulatòria als 15 i 30 dies de l'estatus epilèptic. En aquestes dues visites s'avaluarà l'estat neurològic del pacient així com l'aparició de noves crisis convulsives o estatus epilèptics.
És important comentar que, en cap moment, ni el nen/a, ni els investigadors, ni els professionals que avaluaran els resultats de l'estudi sabran quin fàrmac haurà rebut el pacient. Aquesta tècnica, coneguda com a triple-cec, garanteix que els resultats que s'obtinguin no es vegin influenciats per raons que no siguin estrictament relacionades amb les variables d'estudi.
Objectiu
El nostre principal objectiu és analitzar quin dels dos fàrmacs d'estudi permet una major proporció de resolució de l'estatus epilèptic en menys de 20 minuts. A més a més, també analitzarem quin dels dos fàrmacs té menys reaccions adverses, quin mostra una menor mortalitat i quin mostra un millor estat neurològic als 30 dies.

Beneficis i riscos derivats de la participació en l'estudi
Els dos fàrmacs que s'estudien en aquest assaig clínic (valproat sòdic intravenós i fenitoïna intravenosa) estan comercialitzats i utilitzats per el tractament de l'estatus epilèptic en edat pediàtrica quan les benzodiazepines fracassen.
Així doncs, aquest assaig clínic no privarà en cap moment al vostre fill/a o representat de rebre un medicament que s'hagi demostrat amb una millor efectivitat i seguretat que els dos fàrmacs d'estudi. De fet, tan si participa en aquest estudi com si no ho fa, rebrà els mateixos medicaments, ja que el valproat sòdic i la fenitoïna són dos del fàrmacs usats per aquesta condició a la pràctica clínica assistencial.
De fet, la participació en aquest estudi permetrà conèixer quin d'aquests fàrmacs és el que s'hauria d'utilitzar en primer lloc si el vostre fill/a o representat, o qualsevol altre nen o nena, patís un estat epilèptic en el futur.
No obstant això, malgrat hi ha certa evidència que confirma l'efectivitat d'aquests dos fàrmacs, no podem assegurar que sempre s'obtinguin els resultats esperats. A més a més,

els medicaments que s'usaran en aquest assaig clínic no estan exemptes de reaccions adverses com ara hipotensió, depressió respiratòria, mareig, alteracions hepàtiques i reaccions cutànies. Per tal d'identificar i tractar aquestes reaccions adverses es farà un seguiment periòdic del seu fill/a o representat. Si es detecta l'aparició d'un reacció adversa es prendran les mesures pertinents per resoldre'l.

Tractaments alternatius

Ha de saber que per el tractament de l'estatus epilèptic en edat pediàtrica, un cop les benzodiazepines han fracassat, es disposa de diferents fàrmacs, entre els quals cap ha demostrat una millor efectivitat ni seguretat amb suficient evidència científica per ser definit com a tractament de primera elecció. Entre aquests tractaments hi trobem: levetirazepam, fenobarbital, fenitoïna i valproat sòdic.

Assegurança

El promotor de l'estudi disposa d'una pòlissa d'assegurança que s'ajusta a la legislació vigent i que li proporcionarà la compensació i indemnització en el cas de detriment de la salut del seu fill/a o representat que pugui produir-se al participar en l'estudi.

Confidencialitat

El tractament, la comunicació i la cessió de les dades de caràcter personal de tots els subjectes participants s'ajustarà allò determinat a la *Llei Orgànica 15/1999, del 13 de desembre de protecció de dades de caràcter personal*. D'acord al que s'estableix a la legislació esmentada, vostè podrà exercir els drets d'accés, modificació, oposició i cancel·lació d'aquestes dades.

Les dades recollides per l'estudi estaran identificades mitjançant un codi i només els investigadors podran relacionar aquestes dades amb el seu fill/a o representat. En cap cas, el nom de seu fill/a o representat apareixerà en la publicació dels resultats.

L'accés a la informació personal del seu fill/a o representat quedarà restringit als investigadors, autoritats sanitàries i al Comitè d'Ètica d'Investigació Clínica sempre mantenint la confidencialitat d'acord amb la legislació vigent.

Compensació econòmica

Els investigadors no obtindran cap benefici econòmic amb aquest assaig clínic. A més a més, ni el seu fill/a o representat ni vostè serà remunerat per participar en aquest assaig clínic però tampoc els hi suposarà cap despesa i se'ls hi reintegraran les despeses extraordinàries. A més a més, no hauran de pagar els medicaments de l'assaig clínic.

Altra informació rellevant

Si vostè decideix retirar el consentiment perquè el seu fill/a o representat participi en aquest assaig clínic, cap dada s'afegirà a la base de dades i podrà exigir la destrucció de totes les mostres identificables per evitar la realització de noves anàlisis.

També ha de saber que el seu fill/a o representat podrà ser exclòs de l'estudi si els investigadors ho consideren oportú, ja sigui per motius de seguretat, per qualsevol esdeveniment advers que es produeixi per la medicació d'estudi, o perquè es consideri que no s'està complint amb els procediments establerts.

ANNEX 4. Informed consent document

DOCUMENT DE CONSENTIMENT INFORMAT PER PARTICIPAR EN L'ASSAIG CLÍNIC:

VALPROAT SÒDIC INTRAVENÓS VERSUS FENITOINA INTRAVENOSA EN EL TRACTAMENT DE L'ESTATUS EPILÈPTIC EN LA POBLACIÓ PEDIÀTRICA

Jo ……, amb DNI ……, com a pare, mare o representant legal del nen/nena …… confirmo que:

- He llegit tota la informació que se m'ha facilitat sobre aquest projecte: SÍ / NO
- He rebut suficient informació sobre aquest projecte: SÍ / NO
- He tingut la possibilitat de preguntar i comentar qüestions sobre el projecte: SÍ / NO
- He rebut respostes satisfactòries a totes les preguntes: SÍ / NO
- He comprés que el meu fill/filla/representat pot abandonar aquest projecte sense que aquesta decisió li ocasioni cap perjudici: SÍ / NO
- He comprés els possibles riscos associats a la participació del meu fill/filla/representat en aquest projecte: SÍ / NO
- Rebré una compensació econòmica: SÍ / NO
- L'investigador que m'ha parlat sobre aquest projectes és (nom i cognoms):

……

Per tant,

- Estic d'acord en què el meu fill/filla/representat participi en aquest assaig clínic:

SÍ / NO

- Estic d'acord en què la informació obtinguda amb aquest assaig clínic pugui ser utilitzada en investigacions futures sobre el maneig de l'estatus epilèptic en el nen:

SÍ / NO

- Permeto que la informació sigui introduïda a la base de dades de l'hospital en què ha estat atès:

SÍ / NO

Signatura del pare/mare o representant legal

Nom de l'investigador

……

DNI

……

Signatura

Data: ___ de _____ 20___

ANNEX 5. Richmond Agitation-Sedation Scale (RASS)

Score	Term	Description
+4	Combative	Overtly combative or violent; immediate danger to staff
+3	Very agitation	Pulls on or removes tube(s) or catheter(s) or has aggressive behavior toward staff
+2	Agitated	Frequent nonpurposeful movement or patient-ventilator dyssynchrony
+1	Restless	Anxious or apprehensive but movements not aggressive or vigorous
0	Alert and calm	
-1	Drowsy	Not fully alert, but has sustained (more than 10 seconds) awakening, with eye contact, to voice
-2	Light sedation	Briefly (less than 10 seconds) awakens with eye contact to voice
-3	Moderate sedation	Any movement (but no eye contact) to voice
-4	Deep sedation	No response to voice, but any movement to physical stimulation
-5	Unarousable	No response to voice or physical stimulation

Table obtained from (47)

The RASS was created to evaluate sedation and agitation in adult intensive care unit patients (47) but it is also a valid tool for use in critically ill children (48).

ANNEX 6. Adverse events

Algorithm to Determine Relatedness of Adverse Event to Study Agent	
Not Related	The temporal relationship between treatment exposure and the adverse event is unreasonable or incompatible and/or adverse event is clearly due to extraneous causes (e.g., underlying disease, environment)
Unlikely	**Must have both of the following 2 conditions**, but may have reasonable or only tenuous temporal relationship to intervention: 1. Could readily have been produced by the subject's clinical state, or environmental or other interventions. 2. Does not follow known pattern of response to intervention.
Reasonable Possibility	**Must have at least 2 of the following 3 conditions:** 1. Has a reasonable temporal relationship to intervention. 2. Could not readily have been produced by the subject's clinical state or environmental or other interventions. 3. Follows a known pattern of response to intervention.
Definitely	**Must have all 3 of the following conditions:** 1. Has a reasonable temporal relationship to intervention. 2. Could not possibly have been produced by the subject's clinical state or have been due to environmental or other interventions. 3. Follows a known pattern of response to intervention.

Table obtained from (49)

ANNEX 7. Data collection sheet

PATIENT INFORMATION	
Patient's code number	
Date of birth (age)	
Gender	
Telephone (parents)	
Address	
Socioeconomic level	
Date of enrolment to the RCT	
Hospital	

CLINCIAL HISTORY	
Personal History	
Allergies	
Pathologies	
Previous SE (number of episodes)	
Etiology of previous SE	
Family History	

STUDY INFORMATION (INTERVENTIONS and VARIABLES)	
Type and dose of benzodiazepine prior to the clinical trial	
Time from the beginning of the SE until the infusion of our AED of study (minutes)	
Time from the second dose of BZD until the infusion of our AED of study (minutes)	
Type of SE	*(see the following table*)*
Antiepileptic drug (AED) of study	Drug A / Drug B
Resolution of the SE within 20 minutes	YES / NO
If the previous answer is YES:	
Time needed to solve the SE (minutes)	
If the previous answer is NO:	
Resolution of the SE adding the other AED of study	YES / NO
Coma induction	YES / NO
Recurrence of SE	YES / NO
Adverse drug reactions	
Hypotension and cardiovascular collapse	YES / NO
Respiratory depression	YES / NO
Cardiac arrhythmia	YES / NO
RASS ≤ -2	YES / NO
Other	
Neurological outcome	
At 30 days	Acceptable / Unacceptable
Death	DEAD / ALIVE

* TYPE OF SE (choose the correct option for category 1 and 2)
1. Etiology
Known or symptomatic SE
Acute symptomatic SE
Remote symptomatic SE
Progressive symptomatic SE
Unknown or cryptogenic SE
Febrile SE
SE due to prior epilepsy
2. Semiology
Generalized convulsive SE
Focal convulsive SE

MONITORING CONTROLS (during hospitalization)	
Clinical seizure activity	YES / NO
Vital signs	
Blood pressure (mmHg)	
Heart rate (bpm)	
Temperature (°C)	
Respiratory rate (bpm)	
Oxygen saturation (%)	
Electrocardiogram	
Richmond Agitation-Sedation Scale (RASS)	

COMPLEMENTARY TESTS	RESULT
Electroencephalogram	
Blood test	
Computed tomography (CT) (if required)	
Magnetic resonance imaging (MRI) (if required)	
Blood culture (if required)	
Lumbar puncture (if required)	