Electroconvulsive Therapy for Super Refractory Status Epilepticus: A Scoping Review Protocol

Delaney Dowd, Denise Nunes, Pooja Shah, Andrea Pardo

Abstract

Introduction

Status epilepticus (SE), a condition characterized by abnormally prolonged seizures, is associated with significant morbidity and mortality. It is a neurologic emergency that needs to be promptly recognized and treated. Refractory status epilepticus (RSE) is defined as “status epilepticus persisting despite administration of at least two appropriately selected and dosed parenteral medications including a benzodiazepine.” Super refractory status epilepticus (SRSE) is defined as “status epilepticus persisting at least 24 hours after onset of anesthesia, either without interruption despite appropriate treatment with anesthesia, recurring while on appropriate anesthetic treatment, or recurring after withdrawal of anesthesia and requiring anesthetic reintroduction.”

Electroconvulsive therapy (ECT) was initially proposed in psychiatry in the 1930s and is still in widespread use to treat refractory psychiatric disorders. ECT has medically documented safety and efficacy in this setting. Seizure reduction or control attributed to ECT in the setting of SRSE has been reported in several case reports and small case series. The mechanism by which ECT aborts SE is poorly understood. Better understanding of the impact of ECT for patients who develop SRSE on seizure burden and outcomes is still needed.

Methods and Analysis

This scoping review protocol is based on guidelines from the Joanna Briggs Institute (JBI) and follows guidelines from the Preferred Reporting Items Checklist for Systematic Reviews and Meta-analyses (PRISMA) extension for Scoping Reviews checklist. Electronic databases (Medline [Ovid], The Cochrane Library [Wiley], Embase [Elsevier], Web of Science, and CINAHL [EBSCO]), will be searched to identify relevant papers, which will be independently appraised by two independent reviewers. Data relevant to patient population, clinical course, and outcomes will be collated in a prespecified proforma.

Ethics and Dissemination

Results will be disseminated through a peer-reviewed academic journal. The review itself will deal exclusively with secondary data and thus will not require ethical approval.

Introduction

Status epilepticus (SE) is a neurologic emergency that needs to be promptly recognized and treated to reduce associated morbidity and mortality. SE is defined by the International League Against Epilepsy (ILAE) as “a condition resulting from either the failure of the mechanisms responsible for seizure termination or from the initiation of mechanisms, which lead to abnormally prolonged seizures (after time point t1). It is a condition, which can have long-term consequences (after time point t2), including neuronal death, neuronal injury, and alteration of neuronal networks, depending on the type and duration of seizures” (Trinka et al., 2015).

This definition of SE is an operational definition that gives guidance as to when emergency treatment should be considered. Time point t1 represents the time after which seizures are unlikely to stop on their own, and time point t2 represents the time after which neuronal damage and alteration of epileptogenic neuronal networks are suspected to begin. Time points t1 and t2 vary depending on the type of SE. Treatment of SE is recommended at time point t1 and ideally, seizures are controlled prior to reaching time point t2.

Refractory status epilepticus (RSE) is defined as “status epilepticus persisting despite administration of at least two appropriately selected and dosed parenteral medications including a benzodiazepine” (Hirsch et al., 2018). Super refractory status epilepticus (SRSE) is defined as “status epilepticus persisting at least 24 hours after onset of anesthesia, either without interruption despite appropriate treatment with anesthesia, recurring while on appropriate anesthetic treatment, or recurring after withdrawal of anesthesia and requiring anesthetic reintroduction.”

The epidemiology of SE is influenced by the time criterion used to define SE and the patient population included. In a recent systematic review including 61 studies from high-income countries, mortality rate at 30 days attributed to SE in adults was estimated to be 15.9% (95% CI, 12.7% to 19.2%) and 3.6% (95% CI, 2.0% to 5.2%) for children (Neligan et al., 2019). The same review found that mortality was 17.3% (95% CI, 9.8% to 24.7%) for allcomers with RSE. Mortality of SE is likely attributable to a combination of the underlying etiology as well as the impact of ongoing epileptic activity, which increases metabolic demand and results in deleterious consequences on neuronal tissue and networks (Leitinger et al., 2015, Giovannini et al., 2017).

Prompt treatment of SE is crucial to prevent detrimental consequences of ongoing, uncontrolled seizures, and robust evidence exists supporting benzodiazepine administration after time point t1 (Glauser et al., 2016). When benzodiazepines fail to abort seizures, patients develop benzodiazepine-refractory SE. Evidence-based protocols recommend prompt treatment with a non-benzodiazepine IV anti-seizure

medication (ASM) as the next step. Three multicenter randomized controlled trials failed to demonstrate statistical differences in efficacy of seizure cessation and tolerability between levetiracetam, fosphenytoin, and valproic acid when used to treat benzodiazepine-refractory SE in adults and children (Dalziel et al., 2019, Kapur et al., 2019, Lyttle et al., 2019).

Unfortunately, seizures remain uncontrolled in about 50% of cases after non-benzodiazepine IV ASM administration, and these patients go on to develop RSE. Contrary to SE, treatment of RSE and SRSE is considered an “evidence-free” area of medicine. Continuous anesthetics are used with continuous electroencephalogram (EEG) to treat RSE. Current guidelines recommend titrating to achieve either seizure suppression or burst suppression for at least 24-48 hours prior to attempting to wean anesthetics (Brophy et al., 2012, Glauser et al., 2016). When seizures continue beyond this time point, patients develop SRSE. Neither guidelines nor strong evidence supports the use of any unique therapy beyond this point.

Despite advances in understanding and early recognition of SE, mortality in patients who progress to SRSE remains quite high (Neligan et al., 2019). Electroconvulsive therapy (ECT) was initially proposed in psychiatry in the 1930s and is still in widespread use to treat refractory psychiatric disorders. ECT has medically documented safety and efficacy in this setting.

Seizure reduction or control attributed to ECT in the setting of SRSE has been reported in several case reports and small case series. The mechanism by which ECT aborts SE is poorly understood. In 2016, a systematic review was published that appraised the existing body of literature regarding the efficacy of ECT in treating SRSE (Ziler et al., 2015). This review concluded that although low-level (Oxford level 4, grade D) evidence exists that ECT could be associated with improved seizure control for individuals who develop SRSE, there was not sufficient evidence to recommend routine use of ECT in this setting.

Since 2016, as noted previously, formal consensus definitions for RSE and SRSE have been updated (Hirsch et al., 2018). Consensus definitions have also been established for new onset refractory status epilepticus (NORSE) and febrile illness related epilepsy syndrome (FIRES) (Hirsch et al., 2018). Several slightly larger case reports and case series have been published since 2016 that suggest that ECT could be an effective therapy for both adult and pediatric patients who develop SRSE (Ahmed et al., 2018, Garcia-Lopez et al., 2020, Nath et al., 2021, Woodward et al., 2023). Case reports also suggest a possible role for ECT in the treatment of seizures in the specific contexts of NORSE and FIRES (Miras Viega et al., 2017, Nath et al., 2021).

Although most cases of SRSE can be aborted with anesthetic agents by targeting burst suppression, weaning off anesthetic agents without recurrence of SE is an additional challenge. Recent literature also suggests that in addition to seizure

control, an additional benefit of ECT could be facilitating weaning off anesthetic agents in patients with RSE and SRSE (Woodward et al., 2023). Better understanding of the impact of ECT for patients who develop SRSE on seizure burden and outcomes is still needed.

Stage 1: Identifying the Research Question

Study Rationale

Although electroconvulsive therapy (ECT) has been used off-label to treat super refractory status epilepticus (SRSE) for many years, the efficacy and safety of this treatment for this indication in both the adult and pediatric populations are currently poorly understood. Given the significant morbidity and mortality associated with SRSE and lack of guidelines or evidence-based treatments, better understanding of the impact of this therapy on seizure burden and outcomes is needed. This is particularly important given logistical and legal barriers that limit the use of ECT in some settings (Livingston et al., 2018).

Understanding the role of ECT in treating SRSE requires an overview of relevant, existing literature. This is best accomplished by a scoping review, which can both map existing knowledge and identify gaps to be addressed by future research (Arskey and O'Malley, 2005). This review protocol is based on guidelines from the Joanna Briggs Institute (JBI) and follows guidelines from the Preferred Reporting Items Checklist for Systematic Reviews and Meta-analyses (PRISMA) extension for Scoping Reviews checklist (Tricco et al., 2018, Peters et al., 2020).

To prevent unnecessary duplication, a preliminary search using the terms "electroconvulsive therapy" and "status epilepticus" of PROSPERO, JBI Evidence Synthesis, and the Cochrane database of systematic reviews was done on December 21st, 2023. No relevant systematic or scoping reviews were identified.

Study Aim and Objectives

The aim of this review is to understand the current knowledge regarding the efficacy of ECT in aborting SRSE, and in doing so, inform future research priorities. This aim will be achieved by addressing the following objectives:

1. To characterize the efficacy of ECT in treating seizures in patients who develop SRSE
2. To determine the safety profile of ECT when used in the setting of SRSE

Stage 2: Identifying Relevant Studies

Inclusion Criteria

<u>Population</u>

Super refractory status epilepticus (SRSE) is a rare condition that affects individuals of all ages and is associated with significant morbidity and mortality. Therefore, this review will include papers that focus on both adult and pediatric patients who develop SRSE and are treated with electroconvulsive therapy (ECT) in intensive care unit (ICU) settings. The focus of this review will include patients who develop SRSE regardless of demographic information, etiology of seizures, medical co-morbidities, and neurologic co-morbidities. This is justified by the fact that relevant literature is anticipated to be limited and inclusion of a heterogeneous patient population may provide further information that addresses the study aim and objectives. Studies published over the past twenty years (2004-2024) will be included.

Concept

Studies that include the usage of ECT to treat seizures that are refractory to traditional, evidence-based treatment with first- and second-line agents will be included. Studies that describe the usage of ECT to wean off anesthetic agents initiated to control seizures will also be included. Studies describing seizures and/or non-convulsive status epilepticus (NCSE) following ECT for other indications (i.e. psychiatric indications such as depression and catatonia) will be excluded.

Context

Since this study aims to delineate all available knowledge about the efficacy of ECT in aborting seizures in patients who develop SRSE and are treated in ICU settings, no exclusion criteria will be applied based on study context. Authors plan to include studies regardless of context-specific factors such as country of origin, medical system, or practice setting.

Types of Studies

Studies will not be excluded based on type of research, research design, or quality. Studies will not be excluded based on study design if studies meet criteria for patient population and concept. Relevant studies will only include those that are peer-reviewed and published in academic journals. Conference presentations, policy documents, abstracts, and personal communications will be excluded. Only studies that cannot be translated into English will be excluded.

Search Strategy

Information sources

Medline (Ovid)

The Cochrane Library (Wiley)

Embase (Elsevier)

Web of Science

CINAHL (EBSCO)

Search Strategy

Search terms and strategies will be developed closely with an experienced librarian (DN). The search strategy will combine keywords and controlled vocabulary terms for electroconvulsive therapy and super refractory epileptic state. We will develop the search in Embase and adapt it to the pre-specified databases. We will not impose any date or language limitations. We will review the reference list of included studies for relevant citations.

No	Query	Results	Date
1	'epileptic state'/exp OR 'super refractory status epilepticus'/exp OR 'super refractory epileptic state' OR 'superrefractory status epilepticus' OR 'super refractory status epilepticus'	29953	26-Jan-24
2	'electroconvulsive therapy'/exp OR 'ect' OR 'electric convulsive therapy' OR 'electroconvulsant therapy' OR 'electroconvulsive shock therapy' OR 'electroconvulsive treatment' OR 'electroshock therapy' OR 'electroshock treatment' OR 'electroconvulsive therapy'	35923	26-Jan-24
3	1 AND 2	314	26-Jan-24

Stage 3: Study Selection

Selection Process

The study authors will manage the search results using a reference manager software program (Covidence, Melbourne, Australia). Two investigators will independently screen the references' titles and abstracts against the inclusion criteria for relevance. Ties will be broken by a third investigator. Final eligibility will be determined using a PRISMA-ScR flowchart, and a narrative description of the literature search and study selection process will be included in the review.

Critical Appraisal

Critical appraisal of the articles will be done in accordance with the JBI guidance to evaluate evidence depending on study type and documented in the study proforma in a summative statement.

Stage 4: Charting the Data

Data will be collated in a prespecified proforma and will include author, date of publication, location of study, type of study, aims/purpose, sample size, age of individuals included in study, and gender of individuals included in study. Additional data relevant to clinical course, efficacy, and safety profile of electroconvulsive therapy (ECT) will also be extrapolated. This data will include the following: adjunct therapies including anti-seizure medications (ASMs), anesthetic agents, immunomodulatory therapies, non-pharmacological therapies used prior to and/or concurrently with ECT; adverse events related to ECT; modified Rankin Scale at time of hospital discharge (mRS); and mortality if available.

To minimize bias, both reviewing investigators will independently review the studies. Disagreements will be resolved by a third reviewing investigator.

Ethics and Dissemination

The authors will disseminate the findings of this review by submitting it for publication in a peer-reviewed academic journal. Since the review forms the foundation for additional research, additional dissemination may occur through the review being referenced in future academic papers. The review itself will deal exclusively with secondary data and thus will not require ethical approval.

Abbreviations

SE – status epilepticus

ILAE – International League Against Epilepsy

RSE – refractory status epilepticus

SRSE – super refractory status epilepticus

ASM – anti-seizure medication

EEG – electroencephalogram

ECT – electroconvulsive therapy

NORSE – new onset super refractory status epilepticus

FIRES – febrile infection related epilepsy syndrome

JBI – Joanna Briggs Institute

PRISMA – Preferred Reporting Item Checklist for Systematic Reviews and Meta-analyses

ICU – intensive care unit

NCSE – non-convulsive status epilepticus

mRS – modified Rankin Scale

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