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Clinical Study

Induction of burst suppression or coma using intravenous anesthetics in refractory status epilepticus

Bong Su Kang [a,1], Keun-Hwa Jung [b,1], Jeong-Won Shin [c], Jang Sup Moon [b], Jung-Ick Byun [b], Jung-Ah Lim [b], Hye Jin Moon [d], Young-Soo Kim [e], Soon-Tae Lee [b], Kon Chu [b], Sang Kun Lee [b,*]

[a] Department of Neurology, Korea University Anam Hospital, Seoul, South Korea
[b] Department of Neurology, Laboratory for Neurotherapeutics, Comprehensive Epilepsy Center, Biomedical Research Institute, Seoul National University Hospital, College of Medicine, Seoul National University, 101, Daehangno, Chongro-Gu, Seoul 110-744, South Korea
[c] Department of Neurology, CHA Bundang Medical Center, CHA University, Seongnam, South Korea
[d] Department of Neurology, Dongsan Medical Center, Keimyung University, Daegu, South Korea
[e] Department of Neurology, Samsung Changwon Hospital, Sungkyunkwan University School of Medicine, Changwon, South Korea

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ABSTRACT

General anesthetic-induced coma therapy has been recommended for the treatment of refractory status epilepticus (RSE). However, the influence of electroencephalographic (EEG) burst suppression (BS) on outcomes still remains unclear. This study investigated the impact of intravenous anesthetic-induced BS on the prognosis of RSE using a retrospective analysis of all consecutive adult patients who received intravenous anesthetic treatment for RSE at the Seoul National University Hospital between January 2006 and June 2011. Twenty-two of the 111 episodes of RSE were enrolled in this study. Of the 22 RSE patients, 12 (54.5%) were women and 18 (81.4%) exhibited generalized convulsive status epilepticus. Sixteen patients (72.7%) were classified as having acute symptomatic etiology, including three patients with anoxic encephalopathy, and others with remote symptomatic etiology. Only two patients (9.1%) had a favorable Status Epilepticus Severity Score (0–2) at admission. All patients received midazolam (MDZ) as a primary intravenous anesthetic drug for RSE treatment; three (13.6%) received MDZ and propofol, and one (4.5%) received MDZ and pentobarbital. The rates of mortality and poor outcome at discharge were 13.6% (n = 3) and 54.5% (n = 12), respectively. While BS was achieved in six (27.5%) patients, it was not associated with mortality or poor outcome. Induced BS was associated with prolonged hospital stay in subgroup analysis when excluding anoxic encephalopathy. Our results suggest that induction of BS for treating RSE did not affect mortality or outcome at discharge and may lead to an increased length of hospital stay.

1. Introduction

Refractory status epilepticus (RSE) is recognized as one of the most critical neurologic emergencies with high mortality and morbidity. RSE develops in approximately 30–40% of patients with status epilepticus (SE) and the reported mortality ranges between 19–67% depending on the type of SE [1,2]. However, there is no universally accepted definition of RSE. Most studies have defined RSE as SE which is resistant to treatment with two or more intravenous anti-epileptic drugs (AED) [3–5], whereas others have defined it as a duration of seizure activity over 60 minutes [6,7].

Despite its clinical and socioeconomic impacts, to our knowledge the management of RSE has only been studied in small retrospective reviews [4,8] and a prospective study without controls [9]. These reports suggest that early pharmacologic coma induction using a general anesthetic, such as MDZ, propofol, or pentobarbital, can treat RSE [3,10,11]. Although recent guidelines have recommended that the general goal of anesthetic treatment is not only to suppress seizure activity but also to achieve burst suppression (BS) on electroencephalography (EEG), typically for 12–24 hours [10,11], the evidence of any correlation between BS on EEG and clinical outcomes is limited. Only limited clinical data have been reported indicating that more intensive suppression on EEG may result in fewer seizure relapses and better outcomes [12]. In contrast, a recent retrospective study suggested that seizure control without BS or isoelectric EEG may be associated with better

* Corresponding author. Tel.: +82 2 2072 2923; fax: +82 2 2072 7553.
E-mail address: sangkun2923@gmail.com (S.K. Lee).
[1] These authors have contributed equally to the manuscript.

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functional outcome [4]. Thus, our study was designed to investigate the impact of intravenous anesthetic-induced BS on the prognosis of RSE in a tertiary referral, national epilepsy center.

2. Materials and methods

We analyzed all consecutive patients who received intravenous anesthetic treatment for RSE at the Seoul National University Hospital from January 2006 to June 2011. The inclusion criteria were the following: (1) patients aged 18 years or older; (2) RSE defined as convulsive status epilepticus or non-convulsive status epilepticus (NCSE) unresponsiveness to treatment with at least two or more AED; (3) patients received intravenous anesthetic treatment for seizure control; and (4) patients received continuous EEG monitoring. Exclusion criteria were: (1) epilepsia partialis continua; (2) psychogenic SE; and (3) absence SE. We screened our computerized database to identify patients and reviewed the electronic medical record and the computerized EEG report system for variables including age, sex, history of epilepsy, history of SE, type of SE, etiology of SE, severity of SE, seizure duration (minutes) before initial treatment, AED regimen before anesthetic treatment, type of anesthetic, anesthetic treatment duration (days), results of continuous EEG monitoring during anesthetic treatment, use of additional AED for seizure control, complications, and functional status before onset and at discharge.

The type of SE was classified according to the initial manifestation as generalized convulsive status epilepticus (GCSE) or NCSE. If SE began with a generalized tonic–clonic seizure with continuous convulsion or evolution to non-convulsive status, it was defined as GCSE. NSCE was defined as prolonged electrographic seizure activity resulting from non-convulsive behavioral and/or cognitive changes from the baseline [4]. The etiology of SE was classified into: (1) acute symptomatic, defined as seizures occurring concurrently with an acute neurologic insult or systemic disturbance; (2) remote symptomatic (RS) with acute precipitant; and (3) RS without acute precipitant. RS was defined as seizures occurring with a time gap following a neurologic insult associated with an increased risk of seizure [13]. The severity of SE was graded using the Status Epilepticus Severity Score (STESS) according to previous guidelines, and 0–2 was regarded as a favorable score [14].

The results of continuous EEG monitoring were interpreted using the maximum level of suppression during intravenous anesthetic treatment and categorized into those that achieved BS or were isoelectric.

Systemic complications were categorized into: (1) respiratory distress, defined as presence of hypoxia which required intubation and mechanical ventilation or the development of pulmonary edema; (2) cardiac distress, including hypotension, cardiac arrhythmia, hypotension (systolic blood pressure <90 mmHg or mean arterial pressure <50 mmHg), bradycardia (<60 beats per minute) and tachycardia (>100 beats per minute); (3) infections requiring antibiotics; and (4) other. The functional status of patients was determined before onset and at discharge using the modified Rankin Scale (mRS).

The primary outcome variable was defined as in-hospital mortality. Secondary outcome variables were defined as poor functional outcome (mRS score $\geqslant$4) and hospital stay longer than 30 days.

Statistical analyses were performed using the Statistical Package for the Social Sciences version 12.0 (SPSS, Chicago, IL, USA). Categorized variables were summarized as counts and proportions, and continuous variables were summarized as the mean and standard deviation. For mortality, poor functional outcome, and BS, categorical variables were compared using Fisher's exact test or the chi-squared test and continuous categorical variables were compared using Student's *t*-test or the Mann–Whitney *U* test. *p* values of $\leqslant$0.05 were considered statistically significant.

3. Results

Of all 111 episodes of SE, 22 received intravenous anesthetic treatment for controlling seizures (Fig. 1). The median age of the patients was 60.0 years (interquartile range [IQR] 30.8–68.5 years) and 12 patients (54.5%) were women. Six patients (27.3%) had a history of epilepsy, including three patients with generalized

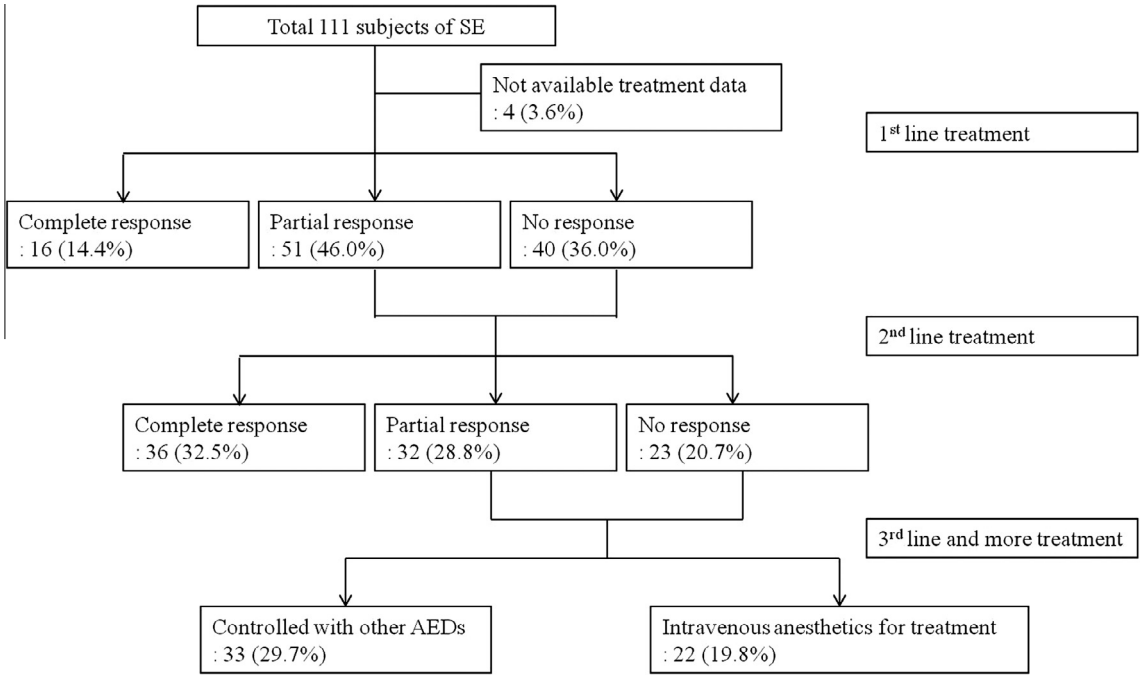

Fig. 1. Flowchart of Treatment response in patients with status epilepticus and selection of the 22 patients included in this study. AEDs = anti-epileptic drugs, SE = status epilepticus.