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Review

Can anesthetic treatment worsen outcome in status epilepticus?

Raoul Sutter [a,b,*], Peter W. Kaplan [c]

[a] Clinic for Intensive Care Medicine, University Hospital Basel, Switzerland
[b] Division of Clinical Neurophysiology, Department of Neurology, University Hospital Basel, Basel, Switzerland
[c] Department of Neurology, Johns Hopkins Bayview Medical Center, Baltimore, MD, USA

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ABSTRACT

Status epilepticus refractory to first-line and second-line antiepileptic treatments challenges neurologists and intensivists as mortality increases with treatment refractoriness and seizure duration. International guidelines advocate anesthetic drugs, such as continuously administered high-dose midazolam, propofol, and barbiturates, for the induction of therapeutic coma in patients with treatment-refractory status epilepticus. The seizure-suppressing effect of anesthetic drugs is believed to be so strong that some experts recommend using them after benzodiazepines have failed. Although the rationale for the use of anesthetic drugs in patients with treatment-refractory status epilepticus seems clear, the recommendation of their use in treating status epilepticus is based on expert opinions rather than on strong evidence. Randomized trials in this context are lacking, and recent studies provide disturbing results, as the administration of anesthetics was associated with poor outcome independent of possible confounders. This calls for caution in the straightforward use of anesthetics in treating status epilepticus. However, there are still more questions than answers, and current evidence for the adverse effects of anesthetic drugs in patients with status epilepticus remains too limited to advocate a change of treatment algorithms.
In this overview, the rationale and the conflicting clinical implications of anesthetic drugs in patients with treatment-refractory status epilepticus are discussed, and remaining questions are elaborated.

This article is part of a Special Issue entitled "Status Epilepticus".

1. Introduction

In 10 to 40% of patients with status epilepticus, seizures cannot be controlled with first-line (e.g., benzodiazepines) and second-line antiepileptic drugs (e.g., phenytoin, valproate, or levetiracetam), resulting in a mortality of up to 40% [1].

Most opinion leaders recommend intravenous anesthetic drugs (IVADs) such as thiopental, midazolam, propofol, and high-dose phenobarbital for treatment-refractory status epilepticus to induce total seizure suppression, or therapeutic coma with an electroencephalography (EEG) burst-suppression pattern [2], or an isoelectric EEG [3]. However, there is no consensus regarding the best agent or level of sedation by which to accomplish seizure control, and the risk–benefit ratio of therapeutic coma induced by continuously administering IVADs in this setting is unclear [4]. The Neurocritical Care Society outlines the role of IVADs but notes the lack of strong evidence [5], and the European Federation of Neurological Societies points to the need for further studies [6]. Recent observational studies from different cohorts of patients with status epilepticus provide disturbing results, as the administration of anesthetics was associated with poor outcome independent of possible clinical confounders [7–9]. These results call for caution in the straightforward use of anesthetic drugs in this context and raise several questions.

In this review, we compile the rationale and the conflicting clinical implications of anesthetic drugs in patients with treatment-refractory status epilepticus and elaborate remaining questions.

2. The rationale for the use of anesthetics in treating status epilepticus

The main reason for the use of anesthetic therapy in treating status epilepticus is that this is the only treatment which sufficiently blocks electrographic activity and, thereby, terminates seizures. Rapid seizure control is a main goal in the management of status epilepticus, as several animal models demonstrate ictal brain damage (i.e., excitotoxic neuronal damage) [10–14]. In humans, seizure duration is linked with outcome in patients with status epilepticus [15]. Some studies describe a brain-damaging effect of prolonged seizures [16], and case series report that patients develop marked volume reduction in the hippocampus, the amygdala, or the entorhinal and perirhinal cortices at 1 year after prolonged status epilepticus [17]. Studies of patients with treatment-refractory

* Corresponding author at: Department of Intensive Care Medicine & Neurology, University Hospital Basel, Petersgraben 4, CH-4031 Basel, Switzerland.
E-mail address: Raoul.sutter@usb.ch (R. Sutter).

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status epilepticus add further credence to this limited body of evidence, as they reveal that seizure duration is significantly longer in nonsurvivors [18,19] and independently associated with death for every hour of persistent seizure activity [20]. Seizure duration of more than 1 h is a major determinant for mortality in two identified studies on status epilepticus outcome [21,22], and status epilepticus exceeding 24 h is associated with a 2.3-fold relative risk for death, as compared to patients with status epilepticus duration of less than 2 h [23]. Based on these findings, rapid treatment escalation including administration of IVADs to rapidly terminate intractable status epilepticus is believed to be key for better outcome.

3. Is there enough evidence for the use of anesthetics in treating status epilepticus?

3.1. Important caveats

Although the rationale for the use of IVADs in patients with treatment-refractory status epilepticus seems clear at first glance, there are several caveats calling for caution. Randomized trials regarding risks and benefits of IVADs are lacking and not registered according to the U.S. National Institute of Health (www.clinicaltrials.org), mirroring ethical restrictions of assigning or excluding patients with treatment-refractory status epilepticus from treatment with IVADs, with the inherent risk of sustained status epilepticus. These limitations add to the drawback of already small sample sizes, resulting in insufficient statistical power. In addition, animal models demonstrating ictal damage are flawed because most models imperfectly represent human brain function, and the lesions inducing seizures and status epilepticus may themselves produce deficits. The main challenge in this context is distinguishing effects of initial brain insult from possible consequences of subsequent ictal activity. In addition, human studies on the role of seizure duration and outcome are hampered by the inevitable approximation of seizure duration. Although early small studies provide some evidence of brain injury in association with prolonged seizures, it remains unclear if seizures are casually linked to cerebral damage, and population-based studies and systematic reviews fail to confirm a true association between status epilepticus duration and brain injury [23–26]. Furthermore, an observational study of patients with status epilepticus treated in intensive care units (ICUs) reveals that patients dying from status epilepticus had significantly longer seizure periods than did survivors — a finding not seen in the subgroup of patients with acute or fatal etiologies, such as brain tumors or hypoxic encephalopathy [20]. These findings indicate that the role of seizure duration on outcome diminishes with the increasing severity of status epilepticus etiology and that the cause of status epilepticus determines outcome more than does its duration (Fig. 1) [20].

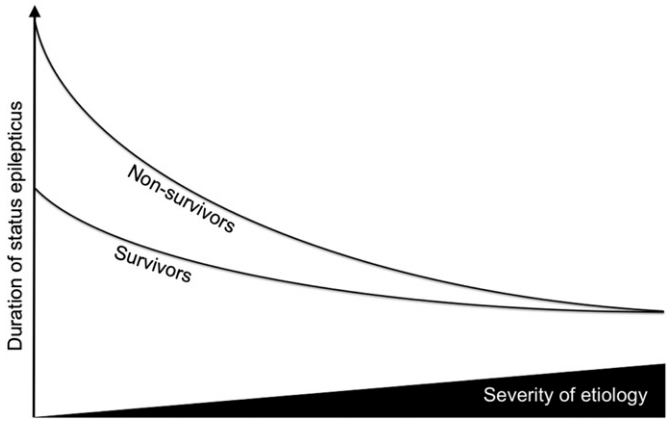

Fig. 1. The duration of status epilepticus in survivors and nonsurvivors dependent of the severity of etiology (based on the results from the original study [20]). Seizure duration is longer in non-survivors as compared to survivors. This relation is less distinct in patients with more severe underlying etiology of status epilepticus (e.g., patients with brain tumors, or patients with hypoxic-ischemic brain injury).

3.2. Perturbing latest results

In the last three years, three observational studies of different cohorts of adult patients with status epilepticus treated in three academic tertiary medical care centers raise great concern regarding the safety of administering IVADs during the management of treatment-refractory status epilepticus [7–9].

A first analysis of 126 consecutive patients with mainly convulsive status epilepticus treated on intensive care units (ICUs) revealed that the administration of IVADs was associated with poor neurofunctional outcome and death [7]. Of the 47 status epilepticus episodes treated with IVADs, 94% required mechanical ventilation, with median ventilation duration of 10 days (range: 1–56), and 45% were treated with vasopressors. Vasopressors were administered concurrently with IVADs in 18 cases (86% of the patients receiving vasopressors). However, interpretation of this study is impeded by the lack of adjustment for important possible confounders (Fig. 2), such as patients' comorbidities, severity, and duration of status epilepticus.

This study was followed by another investigation of 171 consecutive patients with status epilepticus treated in ICUs designed to evaluate the risk of IVADs and to adjust for important possible confounders [8]. Of the 171 patients, 37% were treated with IVADs. Patients treated with IVADs had more infections during status epilepticus (43% versus 11%; $p < 0.0001$) and a 2.9-fold relative risk for death after adjustment for possible confounders, such as status epilepticus duration and severity (graded by the Status Epilepticus Severity Score [STESS] [27]), critical medical conditions, and the use of nonsedating third-line antiepileptic drugs. Analyses regarding possible effect modification did not detect any significant modification by different grades of status epilepticus severity and etiologies. Despite controlling for several important possible confounders, concerns regarding residual confounding were raised [28].

In the latest study of 467 ICU and non-ICU patients with status epilepticus treated with or without IVADs for the induction of therapeutic coma, analyses revealed that patients treated with therapeutic coma had a prolonged hospital stay, higher infection rates, and increased mortality, as compared to patients without therapeutic coma [9] — even after taking possible confounders into account, such as age, seizure history, etiology, status epilepticus severity (graded by the STESS [27]), and the Charlson Comorbidity Index, variables all known to be strongly associated with mortality [15,20,29]. In subgroup analyses, the association between therapeutic coma and unfavorable outcome appeared to be even stronger in patients with more benign status epilepticus types, such as simple partial, absence, myoclonic, or complex partial status epilepticus, as compared to those with generalized convulsive or nonconvulsive status epilepticus in coma.

However, there are some important limitations of these studies, such as the restriction to single tertiary medical care centers and the retrospective assessment of data. Although, in all three studies, patients were treated according to the international treatment guidelines [5], the nonrandomized allocation of therapeutic coma induced by IVADs remains a further limitation. In particular, the study design in all three studies cannot exclude the possibility that patients treated with IVADs were probably "more ill", a possible confounding factor (Fig. 2) that may not have been sufficiently accounted for by the applied multivariable analyses.

4. Should we be concerned?

The results from the current studies mentioned above add further credence to the limited body of evidence that the use of IVADs can have an adverse impact on the course and outcome of patients with status epilepticus. Although the studies mentioned above are limited to