Neurocrit Care (2021) 35:611–612
https://doi.org/10.1007/s12028-021-01249-6

NEUROCRITICAL CARE SOCIETY

INVITED COMMENTARY

Commentary on Isoflurane in Refractory and Super-Refractory Status Epilepticus

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The neurointensivist faces few conditions more challenging than refractory status epilepticus (RSE) and super-refractory status epilepticus (SRSE). RSE is defined as an acute seizure that does not respond to at least two standard antiepileptic drugs, whereas SRSE is status epilepticus that lasts over 24 h despite anesthetic treatment, or that recurs on the cessation of anesthesia [1]. Both conditions are advanced stages of usually generalized (by the time they are received in the intensive care unit, at least) convulsive or nonconvulsive seizures. Many, if not most, cases are related to new insults to the brain, which can damage the brain, in addition to harmful contributions from the seizures themselves. Not surprisingly, mortality and morbidity are high [2, 3].

RSE and SRSE and their therapies are difficult to study in humans, as they do not lend themselves to prospective, double-blinded randomized controlled trials. They are infrequent, desperate emergency situations with much heterogeneity. In this issue Stetefeld and colleagues [4] present a carefully analyzed retrospective multicenter study of patients with RSE and SRSE who received isoflurane, a volatile anesthetic agent.

The ideal treatment for RSE and SRSE should (1) be effective in stopping the seizures, (2) act promptly, (3) be easy to titrate and administer, (4) have low incidence of toxicity and side effects, and (5) have a short half-life so that sedation is not prolonged. Isoflurane certainly is effective in promptly stopping clinical and electrographic seizures, as the authors have shown. With modern anesthetic technology, it can be administered safely outside of the operating room, and the dose can be titrated by monitoring concentrations in the alveolar or expired air. The effects on the brain can be monitored with continuous electroencephalography. The anesthetic effects of isoflurane are brief; however, with longer use, e.g., with days of continuous administration, sedation can be prolonged, possibly due to isoflurane going into fat stores and then redistributing [5]. Ideally, an anesthetist who is familiar with isoflurane should be involved. Isoflurane, like other anesthetic agents, causes hypotension in most patients. Infections, especially pulmonary, are also common, possibly facilitated by the inhibitory effects of isoflurane on respiratory cilia [6]. We and others have expressed concern about possible neurotoxic effects of isoflurane, especially in the hippocampi, thalamus, and cerebellum [7–9]. It has been difficult, however, to reliably attribute these insults strictly to the isoflurane, as they can be complications of status epilepticus itself and sometimes of the underlying etiologies of the seizures. It is somewhat reassuring that Stetefeld et al. [4] found only two patients (9% of their series) for whom isoflurane could have played a contributory role in magnetic resonance imaging-evaluated brain changes.

The authors are to be congratulated for accomplishing this study on RSE and SRSE, doing as well as possible with human cases. Further study in animal models might provide answers regarding volatile anesthetics' effectiveness in specific seizure models with the status of various durations, allowing head-to-head comparisons with other agents, and further addressing the issues of neurotoxicity and side effects that are not sufficiently resolved.

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This article is related to the original article available at https://link.springer.com/article/10.1007/s12028-021-01250-z

Funding
No funding was received for this work.

Declarations

Springer

Conflict of interest
The author declares no conflict of interest.

Publisher's Note

Received: 2 April 2021 Accepted: 7 April 2021
Published online: 20 July 2021

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