



Only a Fine Line Separates Genius, Insanity, and Anesthetic Medication for Coma Induction in Status Epilepticus

Epilepsy Currents
2021, Vol. 21(6) 424–426
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DOI: 10.1177/15357597211041829
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“Safety and Efficacy of Coma Induction Following First-Line Treatment in Status Epilepticus: A Two-Center Study”

De Stefano P, Baumann SM, Semmlack S, et al. *Neurology*. 2021;97:e564-e576. doi:10.1212/WNL.0000000000012292

Objective: This study aims to explore safety and efficacy of artificial coma induction to treat status epilepticus (SE) immediately after first-line antiseizure treatment instead of following the recommended approach of first using second-line drugs. **Methods:** Clinical and electrophysiologic data of all adult patients treated for SE from 2017 to 2018 in the Swiss academic medical care centers from Basel and Geneva were retrospectively assessed. Primary outcomes were return to premorbid neurologic function and in-hospital death. Secondary outcomes were the emergence of complications during SE, duration of SE, and ICU and hospital stay. **Results:** Of 230 patients, 205 received treatment escalation after first-line medication. Of those, 27.3% were directly treated with artificial coma and 72.7% with second-line non-anesthetic antiseizure drugs. Of the latter, 16.6% were subsequently put on artificial coma after failure of second-line treatment. Multivariable analyses revealed increasing odds for coma induction after first-line treatment with younger age, the presence of convulsions, and with an increased SE severity as quantified by the Status Epilepticus Severity Score. While outcomes and complications did not differ compared to patients with treatment escalation according to the guidelines, coma induction after first-line treatment was associated with shorter SE duration, ICU, and hospital stay. **Conclusions:** Early induction of artificial coma is performed in more than every fourth patient and especially in younger patients presenting with convulsions and more severe SE. Our data demonstrate that this aggressive treatment escalation was not associated with an increase in complications but with shorter duration of SE, ICU, and hospital stays. **Classification of Evidence:** This study provides Class III evidence that early induction of artificial coma after unsuccessful first-line treatment for SE is associated with shorter duration of SE, ICU, and hospital stays than the use of a second-line non-anesthetic antiseizure drug instead or prior to anesthetics, without an associated increase in complications.

Commentary

“Contradiction is not a sign of falsity, nor the lack of contradiction a sign of truth.”—Blaise Pascal

Coma induction with anesthetic medications has been a mainstay for the treatment of status epilepticus (SE) unresponsive to the first- or second-line antiseizure medications (ASMs), despite there being relatively little data as to when, how long, or to what depth of sedation they should be deployed.¹ Though the iatrogenic complications of these medications have long been appreciated, it was brought to the forefront of our community’s consciousness with the publication of the Swiss experience from the University Hospital of Basel in 2014, demonstrating rather convincingly that at face value, the use of anesthetic medications was associated with poor outcome by a variety of measures.² In that study, 171 consecutive adult SE patients, of whom 37% received IV anesthetic drugs (IVAD), were collected over a 6-year period at a single institution. Those who received IVAD had greater risk of infections, severe hypotension, longer ICU/hospital stays, and

most significantly, greater mortality (30% vs 10%). The relative effect of IVAD was greater in patients with simple partial, complex partial, or absence seizures and to a small degree, in patients who were awake. The results of this study have been replicated to a large degree by multiple groups.³⁻⁵ Given the plausible biological mechanisms for detrimental effects of IVAD, this would suggest that at the very least, there is a delicate, dangerous balance between risk and benefit in the use of these IVADs in the management of refractory SE.

It is that context that makes the currently reviewed study by the same investigators particularly interesting.⁶ This is a retrospective evaluation of a prospectively collected cohort of 230 adult patients presenting with SE at 2 experienced Swiss epilepsy centers, Geneva and Basel. As expected, the vast majority (205 patients) received medications besides the first-line benzodiazepines. Approximately a quarter of patients (27.3%) were treated directly with coma induction with an anesthetic, almost always with propofol. Of the rest of patients who were treated with a traditional second-line ASM, about a quarter eventually required coma induction due to treatment failure. Patients who were placed into immediate coma were younger, had fewer





comorbidities, were more likely to present with convulsions, and had more severe SE.

Treatment in the early coma-induction group clearly breaks all of the currently published guidelines.^{1,7} Several interesting patterns emerge. Overall, early coma induction occurred in a high number of patients, though it may be difficult to tell who merely underwent intubation for airway protection vs coma induction, even if the authors tried to account for this. Patients with early coma induction were mechanically ventilated more often, but the duration was shorter than patients from the traditional treatment group who were eventually intubated. The early coma group also had shorter SE duration and ICU/hospital length of stay and was more likely to have a return to premonitory neurological functioning. Importantly, there were no differences in complications and outcomes, including mortality.

There was a significant difference between the 2 study sites; the proportion of patients placed into early coma at the Geneva site was 3 times higher than that at Basel. In fact, the SE protocol at the Geneva site does allow for early coma induction after benzodiazepine failure, whereas the Basel site does not (verified directly with the authors). The Geneva site therefore did not adhere to the existing guidelines by design, and as such, the recent study is not an observation of organic deviation from existing guidelines. Readers should not expect to find similar rates of early coma induction at their sites. In the 2014 study where guidelines existing at that time were followed, IVADs were administered for generalized convulsive seizures in about a quarter of patients (10 of 38), whereas in the recent study, nearly half (45 of 89) were placed under early coma, and overall mortality appears to have decreased by about 50% in the recent study.

There are a couple of important caveats. The Established Status Epilepticus Treatment Trial study, which randomized traditional second-line ASMs (fosphenytoin, valproate, and levetiracetam), demonstrated extremely early response, often within several minutes, in most patients with established SE who achieved control after one conventional second-line ASM.⁸ Furthermore, none of the three tested ASMs provided either incremental benefit or fewer side effects than the other two—despite concern from retrospective studies that levetiracetam may be less effective⁹ but potentially safer. Extrapolating these results, it may not matter, either in terms of efficacy or safety, what second-line “treatment” is administered, whether it is coma-inducing anesthetic or conventional ASM. Patients whose SE will be brought under control will tend to do so rapidly with any treatment.

Thus, without a randomized trial, I am not sure whether the effectiveness of early coma induction can be more firmly established, though a propensity score analysis may be helpful in future observational studies, once the factors leading to early coma induction are established. Furthermore, there may be 2 contributions to the observed results: the actual early effectiveness of treatment with early coma induction and the selection of patients who may respond to early administration of any treatment; the relative weights of these contributions remain to be determined. My suspicion is that a randomized clinical

trial may not show a difference between early coma induction and conventional second-line ASMs. However, this may not matter as much as one might think. Conceptually, early aggressive treatment is critical, and perhaps the most important intervention in any SE treatment cascade is the early and proper dosing of first-line benzodiazepines. Furthermore, one needs to keep in mind that identifying and quickly reversing the underlying etiology provides the best hope for good outcomes. In an optimized milieu where both are addressed, and if rapid coma induction results in early and proper dosing of second-line treatments, then this may inevitably result in better outcomes, regardless of relative effectiveness of the second-line treatment administered.

One message to avoid taking away from this study is that guidelines do not need to be followed. There are multiple studies demonstrating that failure to follow guidelines leads to poorer outcomes.¹⁰ In this particular situation, in expert hands (with an emphasis on expert), patient care did not suffer from guideline deviation—at least I do not think it did. Nonetheless, in this situation, once a patient is intubated, the additional step of quickly increasing sedation to coma and seizure control seems like a reasonable step. In that respect, it is extremely reassuring that the mere act of placing patients into an anesthetic coma does not appear to cause additional complications.

Taken at face value, the recent study seems to contradict the authors’ previous work. I would prefer to take the view that the 2 articles come full circle: IVAD for SE is potentially harmful if used improperly (especially patients with simple/complex partial seizures), but in properly selected patients, use of IVADs is potentially beneficial. More definitive studies are needed regarding the efficacy of early coma induction, but early results are promising.

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Declaration of Conflicting Interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Funding

The author(s) received no financial support for the research, authorship, and/or publication of this article.

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