Balancing the risks and benefits of anesthetics in status epilepticus

Sutter, Raoul; Jünger, Anja L.; Baumann, Sira M.; Grzonka, Pascale; De Stefano, Pia; Fisch, Urs

How to cite

SUTTER, Raoul et al. Balancing the risks and benefits of anesthetics in status epilepticus. In: Epilepsy & behavior, 2023, vol. 138, p. 109027. doi: 10.1016/j.yebeh.2022.109027

This publication URL: https://archive-ouverte.unige.ch/unige:175435
Publication DOI: 10.1016/j.yebeh.2022.109027

Epilepsy & Behavior 138 (2023) 109027

Contents lists available at ScienceDirect

Epilepsy & Behavior

journal homepage: www.elsevier.com/locate/yebeh

Balancing the risks and benefits of anesthetics in status epilepticus

Raoul Sutter [a,b,c,*], Anja L. Jünger [a,d], Sira M. Baumann [a], Pascale Grzonka [a], Pia De Stefano [e,f], Urs Fisch [b]

[a] Intensive Care Medicine, Department of Acute Medical Care, University Hospital Basel, Basel, Switzerland
[b] Department of Neurology, University Hospital Basel, Basel, Switzerland
[c] Medical Faculty of the University of Basel, Basel, Switzerland
[d] Center for Interdisciplinary Brain Sciences Research, Department of Psychiatry and Behavioral Sciences, Stanford University School of Medicine, Stanford, CA, United States
[e] Neuro-Intensive Care Unit, Department of Intensive Care, University Hospital of Geneva, Geneva, Switzerland
[f] EEG and Epilepsy Unit, Department of Clinical Neurosciences and Faculty of Medicine of Geneva, University Hospital of Geneva, Geneva, Switzerland

ARTICLE INFO

Article history:
Revised 23 November 2022
Accepted 23 November 2022
Available online 7 December 2022

Keywords:
Intravenous anesthetic drugs
Status epilepticus
Treatment refractory status epilepticus
Adverse effects
Neurocritical care

ABSTRACT

Purpose: According to international guidelines, status epilepticus refractory to first- and second-line antiseizure medication should be treated with anesthetics. Therefore, continuously delivered intravenous midazolam, propofol, or barbiturates are recommended as third-line therapy. While electroencephalographically (EEG)-controlled titration of anesthetics to seizure termination or to the emergence of an EEG burst-suppression pattern makes sense, evidence of the efficacy and tolerability of such third-line treatment is limited and concerns regarding the risks of anesthesia remain. The lack of treatment alternatives and persistent international discord reflecting contradictory results from some studies leave clinicians on their own when deciding to escalate treatment.

In this conference-accompanying narrative review, we highlight the challenges of EEG-monitored third-line treatment and discuss recent studies that examined earlier administration of anesthetics.

Results: Based on the literature, maintaining continuous burst suppression is difficult despite the constant administration of anesthetics, and the evidence for burst suppression as an adequate surrogate target is limited by methodological shortcomings as acknowledged by international guidelines. In our Swiss cohort including 102 patients with refractory status epilepticus, burst suppression as defined by the American Clinical Neurophysiology Society's Critical Care EEG Terminology 2021 was established in only 21%. Besides case reports suggesting that rapid but short-termed anesthesia can be sufficient to permanently stop seizures, a study including 205 patients revealed that anesthesia as second-line treatment was associated with a shorter median duration of status epilepticus (0.5 versus 12.5 days, $p < 0.001$), median ICU (2 versus 5.5 days, $p < 0.001$) and hospital stay (8 versus 17 days, $p < 0.001$) with equal rates of complications when compared to anesthesia as third-line treatment.

Conclusions: Recent investigations have led to important findings and new insights regarding the use of anesthetics in refractory status epilepticus. However, numerous methodological limitations and remaining questions need to be considered when it comes to the translation into clinical practice, and, in consequence, call for prospective randomized studies.

This paper was presented at the 8th London-Innsbruck Colloquium on Status Epilepticus and Acute Seizures held in September 2022.

1. Introduction

Status epilepticus (SE) is a life-threatening neurologic emergency with ongoing epileptic seizures [1] that comes along with high morbidity and mortality [2–4]. When emergency medical treatment with the administration of first- and second-line antiseizure drugs fails to terminate seizures, SE is defined as treatment-refractory (RSE). A patient with RSE faces a greatly increased risk of death which is mirrored by an in-hospital case fatality rate of up to 40% [4]. This calls for an urgent transfer of the patient to an intensive care unit (ICU) to closely monitor and stop seizures by the induction of deep coma and to prevent and treat disease-related complications.

International guidelines recommend the continuous intravenous administration of anesthetic drugs, including midazolam, propofol, or barbiturates for 24 to 48 hours as a third-line treat-

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

https://doi.org/10.1016/j.yebeh.2022.109027
1525-5050/

ment to end seizures in patients with RSE [5,6]. To achieve such deep coma, the dosage of anesthetics must be steadily increased during electroencephalographic (EEG) monitoring, until surrogates for seizure termination are noted, such as either persistent cessation of electrographic seizures, or the emergence of a burst-suppression pattern or an isoelectric EEG. However, the continuous and high-dose administration of anesthetics may be accompanied by potentially severe and harmful side effects. Several studies have reported unfavorable outcomes of patients with RSE independently associated with continuously administered anesthetics [7–11]. These reports call for heightened awareness of appropriate patient selection due to potential adverse events that may be linked to high doses and prolonged duration of anesthetic treatment [12,13]. The limitations of such studies, including the retrospective design, along with the limited body of evidence for the use of anesthetics to treat refractory SE, and the fact that recommendations for anesthetics are primarily based on expert opinion, fuel an ongoing debate when it comes to the optimal usage of third-line treatment. Therefore, these decisions are often left to the physician's judgment when the question of further therapy escalation arises after the failure of first- and second-line treatment.

In this conference-accompanying narrative review, we highlight the challenges of EEG-monitored third-line treatment of RSE and discuss recent findings regarding the effect of earlier administration of anesthetic treatment. We further examine whether certain subgroups of SE patients might benefit more or less from the administration of anesthetics as second-line treatment.

2. Challenges of third-line treatment of refractory SE

Reports and studies have uncovered and discussed many potential adverse events of anesthetics, including respiratory tract infections that are associated with prolonged mechanical ventilation [8,14], propofol infusion syndrome [15–17], a rare syndrome leading to cardiac failure, rhabdomyolysis, metabolic acidosis, and kidney failure, as well as severe arterial hypotension, cardiotoxicity, and gastrointestinal paralysis with barbiturates [18,19]. These complications come along with the clinical challenges when it comes to the adequate and rapid titration of anesthetics to establish a sufficient treatment response in RSE. At first, glance, following and strictly adhering to the treatment guidelines [5,6] seems to be straightforward and not very challenging. A multi-national survey identified EEG burst suppression as the preferred titration target for anesthetic treatment for RSE [20] with the experts' opinion that an interburst interval of 10 seconds should be established [21]. Further, burst suppression seems to be easily recognizable even for the untrained EEG reader after a short training session [22]. However, at second glance, the presumed effortlessness of these treatment procedures turns out to be rather deceptive. Maintaining a continuous sufficient burst-suppression pattern on EEG is difficult despite constant intravenous administration of anesthetics [23], and the evidence for burst-suppression as an adequate surrogate target is limited by methodological shortcomings as acknowledged by international guidelines themselves [5,6]. Furthermore, the current American Clinical Neurophysiology Society's (ACNS) Standardized Critical Care EEG Terminology definition of 2021 of a burst suppression requires a suppression or attenuation proportion of $\geq$50% of the EEG recording which seems to be a rather arbitrary cut-off [24]. Preliminary results of our upcoming observational study including a semiquantitative EEG analysis of 102 adult patients treated with anesthetics in RSE, showed that such "complete" burst-suppression with the recommended $\geq$50% suppression or attenuation proportion was established in 21% of patients within a median of 51 hours (IQR 16.1–103.7). In another 14% of the 102 patients, burst suppression was achieved earlier (within a median of 23 hours [IQR 1.0–28.9]) but with an attenuation or suppression proportion of <50% (i.e., "incomplete" burst suppression). Hence, in 65% of the 102 patients, no burst-suppression ("complete" or "incomplete") could be achieved and in 79% of the 102 patients "complete" burst-suppression could not be established. These results are in line with previous results that underscored the difficulties to induce and maintain a burst-suppression pattern: a retrospective study meticulously quantitatively analyzed the proportion of achieved burst-suppression pattern and demonstrated a remarkable inter-patient and intra-patient variability of suppression proportions despite a constant and continuous administration rate of anesthetic with most patients not meeting the titration goal of a predefined burst-suppression suppression rate of 80% despite continuous EEG monitoring [23]. Even in a prospective randomized study, burst suppression as the main intervention could not be established in several patients [25]. If such inconsistencies of burst suppression are clinically relevant in our cohort and whether they are associated with specific patient characteristics and outcomes is currently under investigation. Prior studies, however, revealed contradictory results regarding the associations with different titration goals, such as with EEG-detected seizure termination, burst-suppression, or isoelectric EEG, and outcomes [18,26–31]. Unfortunately, despite the results of these previous studies, many questions remain and should be addressed in future studies:

- Should a burst-suppression pattern be preferred instead of an isoelectric EEG?
- Can the titration phase of anesthetics and the stability of burst suppression be optimized by quantitative EEG analysis and an increased number of EEG-trained nurses or physicians in the ICU?
- Is the quality of burst suppression dependent on the type of anesthetic drug?
- Should we keep the titration phase as short as possible when administering anesthetics and does this influence treatment success?

3. Early administration of anesthetics in RSE and outcomes

Although treatment guidelines for SE recommend starting continuously administered anesthetics as a third-line treatment, little is known regarding the importance and effect of the exact time of the initiation of anesthesia in SE patients. Previous case reports suggested that in selected patients with RSE and a reversible cause, a rapid but short-termed anesthetic induction is sufficient to permanently stop seizures [32]. A recent study including 205 adult SE patients from two Swiss academic medical care centers, aimed to explore the safety and efficacy of anesthetics when administered immediately after first-line antiseizure treatment [33]. Seventy-three percent were treated according to the guidelines and 27% were treated with artificial coma immediately after the failure of first-line treatment. While the primary outcome (i.e., in-hospital death) did not differ between the two groups, coma induction after first-line treatment was associated with a shorter median SE duration (0.5 days with anesthetics as second-line versus 12.5 days with anesthetics as third-line, $p < 0.001$) and a shorter median ICU and hospital stay (ICU stay: 2 days with anesthetics as second-line versus 5.5 days with anesthetics as third-line, $p < 0.001$; hospital stay: 8 days with anesthetics as second-line versus 17 days with anesthetics as third-line, $p < 0.001$), without increasing the rate of complications. The result that non-adherence to treatment guidelines when it comes to the administration of antiseizure drugs did not have a negative impact on outcomes in terms of increased death and complications or reduced rate of return to premorbid neurologic function after SE is in line

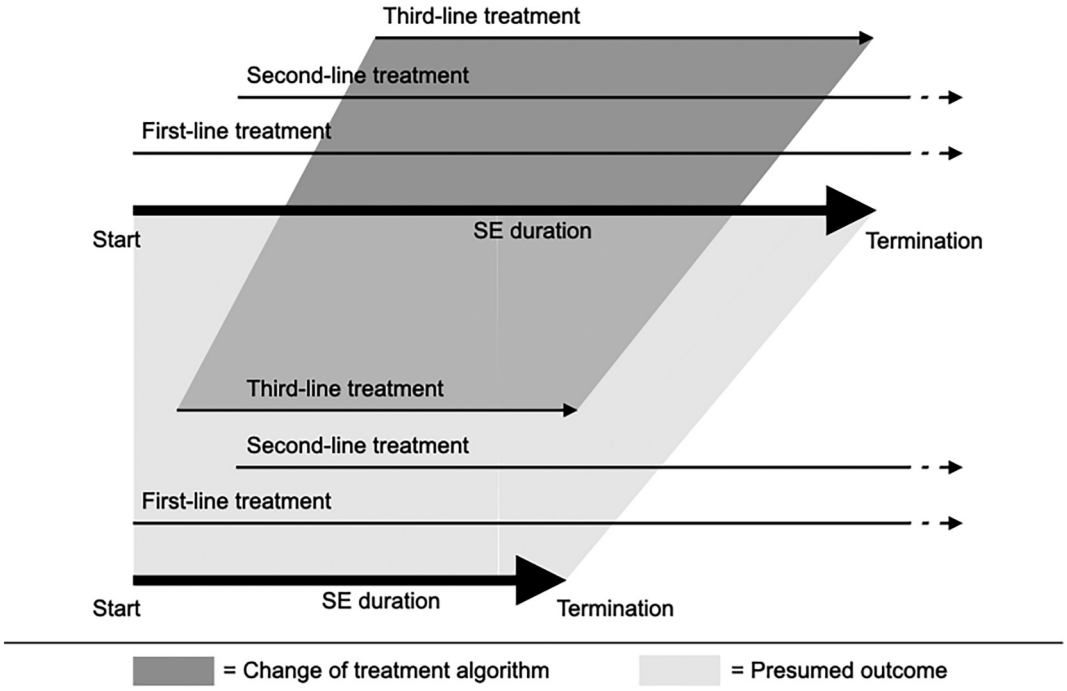

Fig. 1. A proposed hypothesis, based on recent studies, to improve outcomes and shorten the duration of status epilepticus by bringing forward third-line anesthetic treatment (lower half of graphic). SE = status epilepticus.

with prior studies [34]. Importantly, the duration of ICU stay and especially mechanical ventilation and extubation delay are strongly associated with medical in-hospital complications, including delirium and the duration of administered anesthetics has been correlated with the emergence of progressive brain atrophy [35–39]. Hence, it seems more than plausible that shorter ICU and hospital stays by direct and early coma induction may reduce complication rates and costs related to critical care as well as improve the availability of ICU beds. However, subgroup analyses revealed that improvement of outcome with such early coma induction after first-line treatment was restricted to patients without presumed fatal etiologies of SE. This more aggressive approach is in accordance with the idea that patients who continue to have clinical or EEG evidence of seizures after first-line treatment with benzodiazepines should already be considered to have RSE and should in consequence be treated with anesthetics [40]. Although the results with such an unconventional approach are promising, the limitations (mainly resulting from the semiquantitative EEG analyses and the retrospective nature of the study) call for further studies to confirm or disprove these findings and the mechanistic hypothesis that earlier treatment escalation with third-line medication may shorten RSE duration, ICU and hospital stay, as well as reduced complication rates in SE patients without any underlying fatal etiology (Fig. 1). However, as the current studies cannot exclude that some patients treated with early anesthesia (i.e., as second-line treatment) would have responded to non-anesthetic second-line antiseizure drugs and not have required anesthesia, randomized controlled trials are needed in this context.

4. Conclusions

While the first studies raised serious concerns about the continuous administration of anesthetics as third-line treatment in RSE, recent investigations have led to important findings and indications related to the management and use of anesthetics in refractory SE. However, numerous methodological limitations and remaining questions need to be considered when it comes to translation into clinical practice, and, in consequence, urgently call for prospective randomized studies. Meanwhile, clinicians treating patients in RSE must continue to carefully balance the risks and benefits that treatment escalation may bring to the individual patient.

Submission declaration and verification

The authors confirm that the work has not been published previously, that it is not under consideration for publication elsewhere, that its publication is approved by all authors, and tacitly or explicitly by the responsible authorities where the work was carried out, and that, if accepted, it will not be published elsewhere in the same form, in English or any other language, including electronically without the written consent of the copyright- holder.

Declaration of Competing Interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: Raoul Sutter received research grants from the Swiss National Foundation (No 320030_169379), the Research Fund of the University Basel, the Scientific Society Basel, and the Gottfried Julia Bangerter-Rhyner Foundation. He received personal grants from UCB-pharma and holds stocks from Novartis, Roche, Alcon, and Johnson & Johnson. Anja Jünger reports no disclosures. Sira M. Baumann reports no disclosures. Pascale Grzonka reports no disclosures. Pia De Stefano reports no disclosures. Urs Fisch reports no disclosures.

Acknowledgements

None.

Funding

The authors confirm that there was no funding received for this work.

References

[1] Trinka E, Cock H, Hesdorffer D, Rossetti AO, Scheffer IE, Shinnar S, et al. A definition and classification of status epilepticus–Report of the ILAE Task Force on Classification of Status Epilepticus. Epilepsia 2015;56(10):1515–23.
[2] Sutter R, Kaplan PW, Rüegg S. Outcome predictors for status epilepticus—what really counts. Nat Rev Neurol 2013;9(9):525–34.
[3] Sutter R, Semmlack S, Kaplan PW. Nonconvulsive status epilepticus in adults - insights into the invisible. Nat Rev Neurol 2016;12(5):281–93.
[4] Sutter R, Marsch S, Fuhr P, Rüegg S. Mortality and recovery from refractory status epilepticus in the ICU: a 7-year observational study. Epilepsia 2013;54:502–11.
[5] Meierkord H, Boon P, Engelsen B, Gocke K, Shorvon S, Tinuper P, et al. European Federation of Neurological S. EFNS guideline on the management of status epilepticus in adults. Eur J Neurol 2010;17:348–55.
[6] Brophy GM, Bell R, Claassen J, Alldredge B, Bleck TP, Glauser T, et al. Guidelines for the evaluation and management of status epilepticus. Neurocrit Care 2012;17(1):3–23.
[7] Marchi NA, Novy J, Faouzi M, Stähli C, Burnand B, Rossetti AO. Status epilepticus: impact of therapeutic coma on outcome. Crit Care Med 2015;43 (5):1003–9.
[8] Sutter R, De Marchis GM, Semmlack S, Fuhr P, Rüegg S, Marsch S, et al. Anesthetics and Outcome in Status Epilepticus: A Matched Two-Center Cohort Study. CNS Drugs 2017;31(1):65–74.
[9] Sutter R, Marsch S, Fuhr P, Kaplan PW, Ruegg S. Anesthetic drugs in status epilepticus: risk or rescue? A 6-year cohort study. Neurology 2014;82 (8):656–64.
[10] Kowalski RG, Ziai WC, Rees RN, Werner JK, Kim G, Goodwin H, et al. Third-line antiepileptic therapy and outcome in status epilepticus: The impact of vasopressor use and prolonged mechanical ventilation. Crit Care Med 2012;40(9):2677–84.
[11] Sutter R, Tschudin-Sutter S, Grize L, Fuhr P, Bonten MJ, Widmer AF, et al. Associations between infections and clinical outcome parameters in status epilepticus: a retrospective 5-year cohort study. Epilepsia 2012;53:1489–97.
[12] Sutter R, Kaplan PW. Can anesthetic treatment worsen outcome in status epilepticus? Epilepsy Behav 2015;49:294–7.
[13] Opic P, Sutter R. The Unease When Using Anesthetics for Treatment-Refractory Status Epilepticus: Still Far Too Many Questions. J Clin Neurophysiol 2020;37:399–405.
[14] Sutter R, Marsch S, Fuhr P, Kaplan PW, Rüegg S. Anesthetic drugs in status epilepticus – risk or rescue? A six-year cohort study. Neurology 2014;82:656–64.
[15] Iyer VN, Hoel R, Rabinstein AA. Propofol infusion syndrome in patients with refractory status epilepticus: an 11-year clinical experience. Crit Care Med 2009;37(12):3024–30.
[16] Roberts RJ, Barletta JF, Fong JJ, Schumaker G, Kuper PJ, Papadopoulos S, et al. Incidence of propofol-related infusion syndrome in critically ill adults: a prospective, multicenter study. Crit Care 2009;13(5):R169.
[17] Walli A, Poulsen TD, Dam M, Børglum J. Propofol Infusion Syndrome in Refractory Status Epilepticus: A Case Report and Topical Review. Case Rep Emerg Med 2016;2016:1–4.
[18] Claassen J, Hirsch L, Emerson R, Mayer S. Treatment of refractory status epilepticus with pentobarbital, propofol, or midazolam: a systematic review. Epilepsia 2002;43(2):146–53.
[19] Newey CR, Wisco D, Nattanmai P, Sarwal A. Observed medical and surgical complications of prolonged barbiturate coma for refractory status epilepticus. Ther Adv Drug Saf 2016;7(5):195–203.
[20] Holtkamp M, Masuhr F, Harms L, Einhäupl KM, Meierkord H, Buchheim K. The management of refractory generalised convulsive and complex partial status epilepticus in three European countries: a survey among epileptologists and critical care neurologists. J Neurol Neurosurg Psychiatry 2003;74:1095–9.
[21] Rossetti AO, Lowenstein DH. Management of refractory status epilepticus in adults: still more questions than answers. Lancet Neurol 2011;10(10):922–30.
[22] Bombardieri AM, Wildes TS, Stevens T, Wolfson M, Steinhorn R, Ben Abdallah A, et al. Practical Training of Anesthesia Clinicians in Electroencephalogram-Based Determination of Hypnotic Depth of General Anesthesia. Anesth Analg 2020;130(3):777–86.
[23] An J, Jonnalagadda D, Moura V, Purdon PL, Brown EN, Westover MB, et al. Variability in pharmacologically-induced coma for treatment of refractory status epilepticus. PLoS One 2018;13(10):e0205789.
[24] Hirsch LJ, Fong MWK, Leitinger M, LaRoche SM, Beniczky S, Abend NS, et al. American Clinical Neurophysiology Society's Standardized Critical Care EEG Terminology: 2021 Version. J Clin Neurophysiol 2021;38:1–29.
[25] Rossetti AO, Milligan TA, Vulliémoz S, Michaelides C, Bertschi M, Lee JW. A randomized trial for the treatment of refractory status epilepticus. Neurocrit Care 2011;14(1):4–10.
[26] Krishnamurthy KB, Drislane FW. Depth of EEG Suppression and Outcome in Barbiturate Anesthetic Treatment for Refractory Status Epilepticus. Epilepsia 1999;40(6):759–62.
[27] Hocker SE, Britton JW, Mandrekar JN, Wijdicks EFM, Rabinstein AA. Predictors of Outcome in Refractory Status Epilepticus. JAMA Neurol 2013;70(1):72.
[28] Rossetti AO, Logroscino G, Bromfield EB. Refractory Status Epilepticus: Effect of Treatment Aggressiveness on Prognosis. Arch Neurol 2005;62(11):1698.
[29] Peedicail J, Mehdiratta N, Zhu S, Nedjadrasul P, Ng MC. Quantitative burst suppression on serial intermittent EEG in refractory status epilepticus. Clin Neurophysiol Pract 2021;6:275–80.
[30] Kang BS, Jung K-H, Shin J-W, Moon JS, Byun J-I, Lim J-A, et al. Induction of burst suppression or coma using intravenous anesthetics in refractory status epilepticus. J Clin Neurosci 2015;22(5):854–8.
[31] Phabphal K, Chisurajinda S, Somboon T, Unwongse K, Geater A. Does burst-suppression achieve seizure control in refractory status epilepticus? BMC Neurol 2018;18:46.
[32] Das AS, Lee JW, Izzy S, Vaitkevicius H. Ultra-short burst suppression as a "reset switch" for refractory status epilepticus. Seizure 2019;64:41–4.
[33] De Stefano P, Baumann SM, Semmlack S, Rüegg S, Marsch S, Seeck M, et al. Safety and Efficacy of Coma Induction Following First-Line Treatment in Status Epilepticus: A 2-Center Study. Neurology 2021;97(6). e564–e576.
[34] Rossetti AO, Alvarez V, Januel J-M, Burnand B. Treatment deviating from guidelines does not influence status epilepticus prognosis. J Neurol 2013;260 (2):421–8.
[35] Hayashi Y, Morisawa K, Klompas M, Jones M, Bandeshe H, Boots R, et al. Toward improved surveillance: the impact of ventilator-associated complications on length of stay and antibiotic use in patients in intensive care units. Clin Infect Dis 2013;56:471–7.
[36] Coplin WM, Pierson DJ, Cooley KD, Newell DW, Rubenfeld GD. Implications of extubation delay in brain-injured patients meeting standard weaning criteria. Am J Respir Crit Care Med 2000;161(5):1530–6.
[37] Baumann SM, Semmlack S, Rybitschka A, Kliem PSC, De Marchis GM, Rüegg S, et al. Prolonged mechanical ventilation in patients with terminated status epilepticus and outcome: An observational cohort study. Epilepsia 2021;62 (12):3042–57.
[38] Baumann SM, Semmlack S, Hunziker S, Kaplan PW, De Marchis GM, Ruegg S, et al. Prediction of Postictal Delirium Following Status Epilepticus in the ICU: First Insights of an Observational Cohort Study. Crit Care Med 2021;49. e1241–e1251.
[39] Hocker S, Nagarajan E, Rabinstein AA, Hanson D, Britton JW. Progressive Brain Atrophy in Super-refractory Status Epilepticus. JAMA Neurol 2016;73:1201–7.
[40] Marik PE, Varon J. The management of status epilepticus. Chest 2004;126 (2):582–91.