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Research Article

How Much Propofol is needed when Treating Status Epilepticus? A Case Series

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Abstract

Objective:

The objective was to retrospectively review the management of status epilepticus at Tufts Medical Center in patients who failed the initial standard of care benzodiazepine triage of status epilepticus. This article sought to determine the minimal average dose/infusion rate of propofol that was associated with conversion of the EEG long term monitoring (LTM) from status epilepticus to an EEG that was devoid of organized seizure activity.

Background:

Literature has not clearly delineated an actual minimal dose or infusion rate of propofol in studies of patients with status epilepticus. Timely and adequate treatment of status epilepticus has treatment implications especially if patients are to be transported from various locations to another center as EEG may not always be readily available. Identifying the minimal dose of propofol required in this setting that allows effective intubation, induction which would also allow treating providers to have confidence that a minimal dose requirement that is associated with converting EEG patterns to patterns devoid of electrographic seizure activity may have clinical utility.

Design/Methods:

With IRB approval, a retrospective database was created from 2015-2020 reviewing patients with the clinical diagnosis of status epilepticus at Tufts Medical Center, Boston, MA who failed maximal initial standard of care triage and treatment with benzodiazepines were identified. Multiple clinicopathologic variables were tabulated in a database along with minimal and maximal doses of infused medications and when EEG LTM converted to a pattern devoid of organized seizure activity during treatment. Maximal dose of Propofol was identified daily and dose data was averaged among the patients to report the estimated mean dose.

Results:

21 such patients were identified who had real time direct management with both an epileptologist and a neurointensivist during real time assessment as propofol was infused. Treating status epilepticus involved complex decision making with multiple comorbidities and diagnostic variables and considerations as outlined in Table 1. The minimal propofol dose identified that terminated status epilepticus or was associated with EEG conversion to a pattern devoid of such was 42 mcg/kg/min.

Conclusions

Our single center retrospective review of treating status epilepticus identified that propofol at a dose of 42 mcg/kg/min was the minimal effective average dose for converting EEG LTM from status epilepticus to a pattern devoid of organized seizure activity in a small heterogeneous clinical population of patients that failed initial treatment with benzodiazepines.

Keywords: status epilepticus; EEG monitoring; intensive care unit; refractory status epilepticus; propofol

Background

Status Epilepticus represents a neurologic emergency and literature is evolving regarding optimal management [1-10]. This work retrospectively seeks to identify the minimal dose of propofol that may be helpful when prescribed in an FDA on label fashion as an anesthetic inducing agent prior to intubation during the management of status epilepticus in patients that fail initial triage or treatment with benzodiazepines. The identification of the minimal dose of propofol required that allows effective intubation and induction that is associated with converting EEG patterns to patterns devoid of electrographic seizure activity may have clinical utility. This article seeks to determine the minimal average infusion rate of propofol that was associated with conversion of the EEG during long term monitoring (LTM) from status epilepticus to an EEG that was devoid of organized seizure activity. The minimal propofol dose identified that terminated status epilepticus or was associated with EEG conversion to a pattern devoid of such was 42 mcg/kg/min in a small heterogenous clinical population of patients that failed initial treatment with benzodiazepines.

Methods

With IRB approval, a retrospective database was created from 2015-2020 reviewing patient charts with the clinical diagnosis of status epilepticus. Various clinicopathologic variables were tabulated (such as age, suspected etiology of status epilepticus, comorbid conditions, whether death occurred, days propofol was infused, and total number of anti-seizure medications) in a database along with minimal and maximal dose of infused medications and other information (Table 1). Propofol was used to provide anesthesia upon intubation while other anti-seizure medications were titrated to ultimately treat the status epilepticus.

Propofol was titrated upwards to achieve both anesthesia and sedation for intubation. Table 1 lists those 21 cases that were identified showing initially status epilepticus by EEG long term monitoring reviewed in real time either with a physically present epileptologist or one reviewing and communicating in real time remotely over an active internet connection.

TABLE 1:

Age at Status	Sex	Cause	Un	Avg Dose	Max Dose	Min Dose	Starting Dose	Days Used	Outcome	Line of therapy	# of therapies
72	F	Stroke	No	20	20	20	20	17	Passed	1	7
41	F	Unknown	No	58	70	40	40	5	Resolved	3	13
41	M	critical condition after elective VP shunt placement	No	43	50	10	10	10	Resolved	3	9
59	F	Overdose	No	65	65	40	40	4	Passed	2	5
58	F	Seizures in setting of sepsis, pneumonia	No	65	100	30	30	1	Resolved	2	4
67	F	left sided SDH	No	42.5	45	30	45	6	Resolved	3	7
70	F	seizures/status epilepticus associated with prior stroke	No	41	50	30	30	4	Resolved	5	6
53	F	Cardiac arrest	No	35	40	30	40	4	Passed	2	5
28	M	Overdose	No	50	50	50	50	7	Passed	3	7
28	M	Overdose	No	25	25	25	25	2	Resolved	1	3
58	F	Stroke	No	35	35	35	35	2	Resolved	4	4
52	M	Cardiac arrest	No	40	50	10	40	10	Passed	1	6
74	F	Unsure- hyponatremia	No	43	45	40	45	6	Resolved	2	2
63	M	seizures in setting of alc abuse	No	40	40	40	40	5	Resolved	2	5
57	M	Overdose	No	30	50	10	50	2	Passed	6	7
34	M	Super refractory status, acute respiratory failure	No	50	50	50	50	5	Resolved	4	9
68	F	Cardiac arrest	No	25	25	25	25	3	Resolved	1	4
70	F	Cognitive impairment s/p left SDH	No	65	65	65	65	2	Passed	5	5
28	M	Status Asthmaticus	No	30	30	30	30	1	Passed	2	2
21	F	Drug Overdose	No	30	40	20	20	7	Resolved	2	8
65	F	Cardiogenic shock	No	50	50	50	50	1	Passed	2	2

Age at Status	Sex	Avg Dose	Max Dose	Min Dose	Starting Dose	Days Used	Line of therapy	# of therapies
52.7 years	M:8 F:13	42.02	47.38	32.38	37.14	4.95	2.67	5.71

Table 1: Patient characteristics of the study population are noted. Age, Sex, Underlying diagnosis thought to be the cause of status epilepticus along with outcome, starting dose of propofol, minimal, maximal and average dose of propofol used along with days used, and line of therapy among the total number of anti-seizure medication therapies tried on each patient are tabulated.

Propofol was administered at the discretion of the Neurointensivists after deemed benzodiazepine failure. Hemodynamic responses and side effects were closely monitored and treated with either intravenous fluids or vasopressors (e.g., norepinephrine) as needed during the treatment course in a neurologic ICU. Epileptologist and Neurointensivist communications were essential in the effective management of each case and discussion and documentation regarding whether or not seizure activity was or was not present occurred at minimum once daily and more

frequently in the acute setting. Exactly when the EEG converted to a pattern devoid of organized seizure activity during treatment was determined through clinical and electrographic evaluation in real time for clinical management and verified retrospectively for analysis of this dataset. Patients whose EEG patterns either did not identify seizures or at any point identified ictal continuum at any time were excluded from this analysis. Dose of effective seizure eradication was determined by the highest propofol dose or infusion rate associated with electrographic and or clinical timepoints when no further seizures on EEG were identified. This data set did not include patients who had readmissions. This dataset did not have multiple EEG readers or a committee in real time delineating protocolled review of the EEGs or protocolled determination of any particular treatment strategy. American Clinical Neurophysiology Society (ACNS) criteria for identifying electrographic seizure activity and other activities were used by the epileptologists in determining the presence or absence of electrographic seizure activity for this study both prospectively during the treatment phases and in retrospective review for determining the presence or absence of electrographic seizure activity in the data analysis. [11] Patients with psychogenic non epileptic seizures were excluded. Patients were deemed to have had benzodiazepine failure when either 8 mg lorazepam was administered, 10 mg of diazepam was administered, or further administration of benzodiazepines at any dose regimen would require further critical care.

Results

Of 73 patients that were identified to exhibit Status Epilepticus at Tufts Medical Center from 2015-2020, 21 of these patients had induction of anesthesia and intubation with propofol while under VEEG/as described. The average propofol dose that was identified that terminated status epilepticus was approximately 42 mcg/kg/min. Propofol was administered for an average of 3.7 days, excluding a notable outlier that required sedation for 17 days.

Discussion

Status epilepticus (SE) is a neurological emergency defined by the occurrence of five minutes of consecutive seizure activity or with seizure activity occurring to such an extent that the recurrence precludes return to baseline. [1-7] The condition is associated with significant mortality and morbidity and is estimated to occur between 1.29-73.1/100,000. [1] Timely and adequate treatment of status epilepticus can have lasting implications. [1-10] Early seizure termination decreases the risk of cardiac and respiratory complications and effective and efficient treatment of status epilepticus is associated with reduced risks in such patients [1-7].

Current published guidelines and treatment protocols recommend the initial use of benzodiazepines, followed by intravenous antiepileptic drugs, and if necessary, anesthetics to provide effective anesthesia upon intubation for further management as anti -seizure medications are administered [3-8] Although this treatment paradigm is widely used, authoritative dosing for the anesthetics and sedatives are based on limited evidence [3-8]. If seizures fail to response to first and second-line treatments using common anti-seizure medications and benzodiazepines, it is considered Refractory Status Epilepticus (RSE) and ICU care may be required with subsequent intubation and administration of an anesthetic agent for such patients [3-8]. Seizures that continue 24 hours or more after onset of anesthetics are administered are considered Super Refractory Status Epilepticus (SRSE). [5-7] Approximately 12–43% of those presenting to the hospital with SE progress to having RSE and 10–15% of patients develop super-refractory status epilepticus [5-7].

In the context of benzodiazepine-refractory status epilepticus, the anticonvulsant drugs levetiracetam, fosphenytoin, and valproate in a recent literature review each led to seizure cessation and improved alertness by 60 minutes in approximately half of patients in the literature, and the three drugs were associated with similar incidences of adverse events[8] However, many cases require ICU level of care with intubating such patients and a number of intravenous anesthetic drugs are often used in this setting of treating RSE, such as barbiturates, midazolam, ketamine, and propofol concomitantly [5-7].

Propofol has been proposed as a first line treatment as an anesthetic agent for RSE and literature is evolving supporting its use as a first-line anesthetic given its pharmacokinetic characteristics of rapid onset and short half-life [5-7]. Approximately 20 years ago caution was advised in scattered case reports identifying risks of increased mortality with use of anesthetic agents in treating status epilepticus, although some articles as cited indicate that propofol may be associated with faster onsets of anesthetic effect and less hypotension compared to other agents [5,9,10]. Propofol carries risks of adverse reactions, such as hypotension, severe metabolic acidosis, and rhabdomyolysis. [5,9,10] The risks of developing propofol-related infusion syndrome especially at higher doses and in regimens that involve prolonged administration has been noted and therefore determining minimally effective dosing would prove helpful [5-8]. Studies have yet to determine what other anti-seizure medication regimens should be administered concomitantly and how durable a treatment regimen might be, i.e., to what extent seizures might re-emerge clinically or electrographically upon down titration of propofol. Of note Propofol's FDA approved indication and use as an anesthetic has been studied in various settings including continuation of sedation and anesthesia for neurologic indications in pivotal trials involving intensive care unit settings, and may be dosed up to 100-200 mcg/kg/minute over multiple days, and therefore no off-label use or other off label dosing regimens outside of these parameters occurred within the context of this study. [12]

The dose of propofol that constitutes a therapeutic window between induction of effective anesthesia for intubation and adequate treatment in suppressing the EEG or changing the EEG to a pattern devoid of seizures while potentially minimizing side effects from starting with low doses and escalating to a minimally effective clinical dose regimen is not currently known authoritatively in the literature- and retrospectively determining this dose was the rationale for proceeding with this study. A minimum dose for propofol titration is therefore a potentially useful metric that would allow clinicians to reach therapeutic anesthesia and suppressing seizures on EEG in a timely manner and additionally potentially avoiding risks of negative outcomes associated with untreated seizures as patients are intubated. Moreover, this minimal propofol dose would also serve as a baseline that may offset the side effect risks associated with an over aggressive up-titration of anesthetic which may be associated with the previously noted risks of such agents as other anti-seizure medications are administered and titrated. The findings from this retrospective case series may inform future prospective status epilepticus trials and allow treating providers to have confidence in identifying a minimal dose requirement for propofol for providing effective anesthesia for intubation while to effectively terminating clinical and electrographic seizure activity.

Limitations of the current study include that this study represents a small number of cases with potentially significant heterogeneity and confounding in clinical variables and real-time decision making was done without a specific protocolled treatment plan as would occur in a prospective randomized clinical trial. The current case series includes various cases with either unknown durations of status epilepticus or had a heterogeneous timing or timeline of therapy which may be impacting clinical outcome. It may be stated that there may have been arbitrary implementation of propofol as a first line anesthetic agent as opposed to other anesthetics without further rationale or indication specified. The lack of standardization for continuing such therapy for a certain duration

among dosing regimens and infusion rates remain without guidelines and is overall not studied, and follow up was limited to status epilepticus being treated in a solitary admission on a case-by-case basis so timelines and comorbid clinical courses, concomitant medications and comorbidities varied from case to case. Additionally, lack of analyses of the cases in a comparison which either had resolution with another anesthetic or did not have successful treatment of status epilepticus compared to the current dataset that were treated as noted remain additional limitations or undefined elements in the current study. Although there was agreement retrospectively among the EEGs between the two involved interpreters retrospectively in this analysis (JO and KP), verification with multiple readers was not performed in real time during a protocoled approach to treatment strategy as noted which may also confound the data analysis and discussion. No study of long-term clinical outcome beyond termination of seizure activity or death as indicated was made with this dataset. No claim is being made that propofol actually represents a short term or a long-term option or has long term potential to be used as an anti-seizure medication to treat seizure disorders.

Although successful management of the small number of patients in this current study is noted, determining what multiple complex medication regimens are recommended in diverse clinical scenarios remains largely unknown. Additionally, to what extent propofol infusions must be maintained or what degree of burst suppression is required remain unknown. Cases involving titration of the EEG monitoring to a state devoid of seizure activity and or burst suppression were included in this heterogenous population and such dataset was not further analyzed for this study other than as noted above.

Conclusion

Despite the confounding issues discussed, the data derived from this study indicate that Propofol used as its FDA approved indication as an anesthetic during intubation and for maintenance of mechanical ventilation or induction during treatment of status epilepticus eradicated status epilepticus on EEG long term monitoring at approximately 42 mcg/kg/min in this series of patients who failed initial treatment with benzodiazepines. Further analysis of such a study population may be useful in guiding future research.

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