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Research Article

Propofol's EEG Fast Activity is Dose-Dependent

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Abstract

Introduction: For patients with a first-time suspected seizure, electroencephalograms (EEG) are part of the initial evaluation. Most sedatives result in EEG artifact "fast activity" (FA), making the EEG difficult to read. During propofol-sedated EEGs, we noticed that FA would diminish when the propofol infusion rate was low. The purpose of this study is to investigate propofol dosing and its relationship to EEG FA artifact.

Methods: This study involved retrospective chart reviews of a pediatric database for sedated EEG encounters in patients under 7 years of age. Data was collected from a total of 55 charts. Total doses of propofol (mg/kg/hr) were calculated for the first half and second half. The actual EEGs were reviewed by a pediatric neurologist study investigator, to classify the degree of FA as: none, mild, moderate, severe. We then examined whether total doses of propofol given during the EEG (mg/kg/hr) halves affected the severity of FA using ordinal logistic regression.

Results: The results are summarized in Table 1, which shows that propofol doses (paired T-test, $p<0.001$) and EEG FA (Bowker's test of symmetry, $p=0.002$) were higher in the first half compared to the second half. Figure 1 graphs each data point independently, which shows via linear and ordinal logistic regression a positive relationship between propofol dosing and FA severity ($p=0.0014$, OR=1.20, 95% CI=1.08-1.34, respectively).

Conclusion: Fast activity due to propofol appears to be dose-dependent. Lower doses of propofol resulted in less FA on EEG, suggesting that reducing the dose can reduce the FA artifact.

***Keywords:** Propofol, Electroencephalogram (EEG), EEG fast activity, EEG drug artifact, Procedural sedation.*

Introduction

In pediatric patients with a first-time suspected unprovoked seizure, an electroencephalogram (EEG) is a valuable diagnostic tool. In some instances, sedation is necessary to minimize movement artifact or anxiety during the EEG. Propofol is a commonly used procedural sedation agent, but it is known to induce EEG changes. Moderate sedation can elicit increased oscillations in the spindle (12-15 Hz) and beta (13-25 Hz) ranges globally, while deep sedation can have additionally more pronounced spindle and beta activity in the frontal area.[1] These EEG changes are drug artifacts, also known as "increased fast activity." Fast activity presents as generalized periodic discharges (GPD), characterized by biphasic EEG changes, and occurs with nearly all sedative agents, with the notable exceptions being chloral hydrate and ketamine. Chloral hydrate is no longer available in the U.S. Ketamine requires longer post-procedure recovery time and has a higher risk of emesis and emergence reactions.

Propofol is a sedative-hypnotic that modulates the gamma-aminobutyric acid (GABA) type A receptor and predominantly inhibits postsynaptic currents.[2] Propofol increases slow-delta, delta, and alpha power, particularly in the frontal regions.[3] Its short induction and recovery time provides great utility for outpatient procedures. For most procedures, propofol sedation requires an initial bolus in the range of 1 to 3 mg/kg, followed by an infusion rate of 3 to 4 mg/kg/hr along with periodic bolus doses as needed.[4]

Borgeat et al. assessed EEG activity during the induction of anesthesia in pediatric patients without epilepsy, comparing 3 groups: 1) Propofol 3 mg/kg with 0.1 mg/kg/min infusion; 2) Propofol 5 mg/kg with 0.1 mg/kg/min infusion; 3) Thiopental 5-7 mg/kg with halothane (0.5-1%).[5] This study demonstrated a similar EEG pattern between all three groups, showing biphasic EEG changes immediately after the sedative loading dose. (EEG changes were described as a transition from alpha to beta waves (increase in frequency), then slowly replaced by delta waves, and finally an incomplete replacement of delta waves with reappearing beta waves. Spike wave patterns, rhythmic theta waves, or burst suppressions were not observed.[5] Primarily focusing on the comparison between the two propofol groups (as thiopental is no longer available in the U.S.), Borgeat et al. demonstrates that EEG activity is seen with a propofol bolus dose as low as 3 mg/kg which is important to note since this is a commonly used dose for pediatric sedation.[5]

Propofol-induced EEG changes are known; however, there is a possibility such artifacts may be dose-dependent. The EEG team anecdotally noticed this during sedated EEGs at our facility.[4] The fast activity would be present, but it would resolve when the propofol dosing was reduced to 1 mg/kg/hour.[4] In a study of 30 neurosurgical adult patients with or without seizure history (control), subjects were either administered a lower propofol bolus dose (0.5-1 mg/kg) or a higher dose (2-2.5 mg/kg). Overall results showed a greater occurrence of spike or sharp waves in the epileptic and non-epileptic patients who received the high dose of propofol compared to those who received the lower dosage.[6] This finding supports the anecdote of a dose-dependent effect on propofol and EEG fast activity.

The critical dose of propofol to induce fast activity is not clear. More specifically, there is limited data on propofol-induced EEG changes in pediatric cases. Given the usefulness of sedation in obtaining an EEG for some patients, we conducted this retrospective study designed to investigate propofol dosing and its relationship to EEG drug artifact. The purpose of this study is to investigate our hypothesis that a low dose of propofol administration will result in less EEG fast activity drug artifact while still providing sufficient sedation to obtain the EEG study.

Methods

This study is a retrospective chart review of pediatric sedated EEG cases. Physician CPT (current procedural terminology) EEG interpretation billing codes generated by the employed pediatric neurologist group were used to identify children under 7 years of age who had an EEG performed during the period January 1, 2006 to June 30, 2021. These records were then manually reviewed by study investigators. Non-sedated EEGs and patients already on anti-convulsants were excluded. Sedated EEGs were reviewed further as described below. We initially planned to stop after 50 encounters were reviewed to see if statistical significance was achieved and if not, we planned to review an additional 50 encounters to increase our sample size. Since statistical significance was achieved after the first set of encounters, no additional encounters were reviewed.

55 charts in total were reviewed, with 9 of these cases removed due to incomplete data and an additional 7 cases removed due to anticonvulsant use. Our total sample population was 39. The following items were collected: patient weight, EEG start/stop times, drug infusion start/stop times, drug infusion dosing rate times, dosing adjustment times, and drug bolus dosing (dose and time), were recorded. Propofol bolus, infusion, and dosing adjustments were recorded on the anesthesia record. Since sedation generally requires a larger dose of propofol initially, the level of propofol in the patient's system is almost always higher during the initial sedation period compared to the later sedation period just before the end of the procedure. To account for this, we divided the procedure into an initial first half and a later second. Total doses of propofol (mg/kg/hr) were calculated for the first half (start time of sedation to the time at the midpoint of EEG) and second half (midpoint of EEG to end of EEG). In most instances, propofol is administered to patients by a credentialed physician and nurse pair, in an area designated for sedation. Once sedation is achieved, the patient is then moved to the EEG room where the EEG wire leads are applied, and then the EEG recording begins (start time of the EEG). Note that the "first half" period includes the initial sedation time, transport to EEG time, and the application of the EEG wire leads, thus the "first half" is always longer than the "second half" period.

EEGs were then reviewed by a pediatric neurologist study investigator to classify the degree of fast activity as: none, mild, moderate, and severe for each half of the EEG. This neurologist reviewer was given the patient's medical record number to access the EEG tracing in the EMR. Although the patient's name and entire medical record were potentially visible to this neurologist reviewer, we asked him not to review the chart so that its informational content (propofol dosing, concurrent anticonvulsants, EEG interpretation report, MRI scans, etc.) would not affect his interpretation of the EEG fast activity.

A paired T-Test and Bowker's test of symmetry were run to determine if the propofol doses in the first and second-half of the EEG and the EEG fast activity classifications were significantly different. We considered the first half of the EEG encounters separate from the second half and each EEG encounter contributed two data points. We then examined whether total doses of propofol given during the EEG (mg/kg/hr) halves affected the severity of fast activity using ordinal logistic regression and linear regression analysis. All analyses were run using SAS OnDemand [SAS Institute Inc., Cary, North Carolina].

Results

The mean propofol dose in the first half of the EEG was 8.9 mg/kg/hr (SD 2.0), which was significantly greater than the mean propofol dose in the second half of the EEG 2.4 mg/kg/hr (SD 0.9) using the paired T-test. The mean of the paired differences was 6.6 mg/kg/hr (SD 1.9, $p<0.001$).

The Bowker's test of symmetry compared the EEG fast activity classifications between the first and second halves of the EEG encounters as summarized in Table 1. This showed that fast activity was significantly different ($p=0.002$) in the two halves. Table 1 describes the mean propofol doses stratified by the amount of EEG fast activity noted in the first half of the EEG and the second half of the EEG. Note that a given study subject could be classified into different fast activity groups for the first half and the second half. Thus, each study subject contributed two data points to the totals. While this lacks true sample independence, there is an inherent systematic bias in that most of the lower propofol doses are in the second half of the EEG since the bolus dose (typically 3mg/kg) is administered during the first half of the EEG. Thus, to obtain a sufficient spread range of propofol dosing, we had to include both the first-half and second-half values together.

Table 1 – Mean doses of propofol (mg/kg/hr) by fast activity categories.

	First Half of EEG		Second Half of EEG	
Fast Activity	n (%)	Dose ± SD	n (%)	Dose ± SD
None	1 (3%)	8.2	2 (5%)	3.5 ± 2.1
Mild	10 (26%)	9.4 ± 2.8	22 (56%)	2.2 ± 0.5
Moderate	13 (33%)	8.8 ± 1.7	8 (20%)	2.1 ± 3.5
Severe	15 (38%)	9.0 ± 2.0	7 (18%)	2.7 ± 1.5

Simple linear regression and ordinal logistic regression were used to determine if the propofol dose was significantly associated with fast activity severity. Applying linear regression with the fast activity categories (0, 1 ,2, 3, representing none, mild, moderate, severe, respectively) as the dependent variable and propofol dosing as the independent variable (using the first half and second half data points in a combined group) showed significant correlation ($r^2=0.11$, $r=0.33$, $p=0.0014$). Figure 1 graphs these data points. Applying ordinal logistic regression using the same dependent and independent variables (since the fast activity categories are ordinal variables rather than continuous variables) showed a significant correlation (OR=1.20, 95% CI=1.08 to 1.34, $p=0.0012$). Both methods demonstrate a positive dose-response relationship.

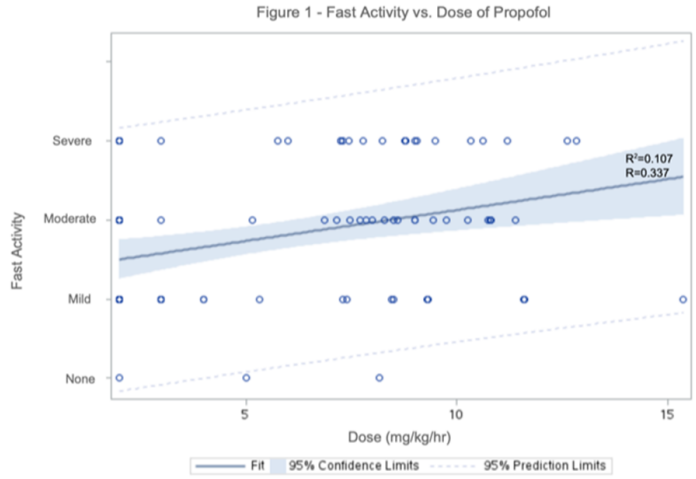

Figure 1 – *Graph of propofol dosing during the first or second half of the EEG on the x-axis and the degree of EEG fast activity on the y-axis. Each patient contributes two data points on this graph (from the first half and second half of the EEG) and shows the best-fit linear relationship. The shaded areas represent the 95% confidence intervals of the best-fit line, confirming a dose-response relationship between propofol dosing and fast activity.*

Discussion and Conclusion

Fast activity due to propofol appears to be dose-dependent. Lower doses of propofol resulted in less fast activity on EEG, suggesting that reducing the propofol dose can reduce the fast activity artifact, improving the evaluation of EEGs. More fast activity can be expected at the beginning of sedation time due to larger bolus doses needed to sedate patients. Since propofol's half-life is short, a large initial dose to sedate the patient can result in lower propofol levels relatively soon if the infusion rate is very slow allowing the total propofol level in the body to decline. While a high dose is initially required to sedate an uncooperative child, a sedated state can be maintained with a lower infusion dose rate by utilizing a quiet and darkened environment to facilitate sleep and minimize arousal.

Despite the awareness of EEG fast activity caused by propofol being dose-dependent, current literature lacks an established dosage threshold. It has been proposed by some that the generalized paroxysmal fast activity seen on EEG with propofol sedation is a result of subcortical glycine inhibition, while others propose that the proconvulsive component of propofol was largely influenced by the rapid changes in drug concentration during the start or end of anesthesia.[7,8] Yet propofol is felt to have net anticonvulsant properties.[9] Previous studies have evaluated dose-dependent EEG changes during the use of propofol sedation including generalized spikes, generalized slowing, focal spikes, and suppression of spike-wave patterns but have not reported on fast activity.[8] Similarly, little is known about the influence of the rate of propofol infusion on EEG fast activity. In a previous study, frontal lobe EEG activity and brainstem reflexes during induction with IV propofol were compared in 2 groups: typical fast bolus infusion and slower infusion. They found that the underlying mechanism by which sedation is achieved is rate dependent, but did not comment on fast activity in relation to speed of infusion.[10]

Our study measured EEG activity based on the entire dose given throughout the procedure, which showed that an increase in overall dose was associated with more fast activity. However, looking at the results of the EEG divided into halves, we saw fewer cases with moderate and severe fast activity in the second half compared to the first which is likely because, at the halfway point of the procedure, sedation was maintained with infusions rather than additional boluses. This supports the anecdote from the sedation physicians and EEG technicians who have commented that fast activity appears to be eliminated as the propofol infusion rate declines to less than 1 mg/kg/hour (on a real-time minute-by-minute observation). This finding is potentially related to the nature of propofol which has short induction and recovery times, likely due to its biphasic nature with an initial half-life of 40 minutes, then a terminal half-life of 4-7 hours.[11]

Since the second half of the procedure was providing patients with lower but continued amounts of propofol, and with its short half-life, there is less saturation of the drug amount which means that lessening the propofol can decrease the severity of fast activity. Propofol's mechanism of action includes GABA(a) inhibition in the following areas: 1) inhibitory interneurons to the excitatory pyramidal neurons 2) thalamus to cortex, 3) preoptic area to arousal centers (midbrain, pons, and hypothalamus).[1] Through bispectral index monitoring, the mentioned study demonstrated that increased sedation with propofol was associated with increased waveforms which was proposed to be the effect of where propofol acts in the brain

The limitations and strengths of this study should be taken into consideration when interpreting the findings. This was a retrospective study with a sample size of 39 encounters which is relatively small; however, the researchers of this study decided to stop at this point given that statistical significance had been reached in the results.

To achieve greater sample independence it would have been ideal to separate the initial propofol bolus to yield the true infusion rate during the first half of sedation; however, this was felt to unfairly reduce the estimated propofol level in the body during the initial half of the EEG.

Our study demonstrates a dose-dependent effect of propofol on EEG fast activity, where lower propofol doses result in less fast activity. We recommend lower propofol doses for pediatric patients that require sedation during an EEG to achieve successful sedation without EEG artifact. One of the main purposes for administering propofol in pediatric patients is to avoid movement that could generate misleading epileptiform activity; however, this problem can be either remedied or exacerbated based on the dose of propofol given. It may be possible that the fast activity is dependent on the initial bolus since anecdotal evidence showed elimination of fast activity when infusion rates were less than 1 mg/kg/hour. Our findings are based on the overall propofol dose given throughout the entirety of an EEG study; however, this may be a point for further investigation by compartmentalizing the effects of the bolus vs infusion.

In conclusion, our study demonstrates a dose-response relationship of propofol on EEG fast activity, such that lower doses of propofol can reduce the degree of EEG fast activity.

Conflict of Interest

The authors declare no conflict of interest.

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