Intermittent Bolus versus Continuous Infusion of Propofol for Deep Sedation during ABR/Nuclear Medicine Studies

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Abstract

Objective A comparison of intermittent bolus (IB) versus continuous infusion of propofol for deep sedation.

Material and Methods A retrospective review of patients sedated for Auditory Brainstem Response (ABR)/nuclear medicine studies between September 2008 and February 2015. A ketamine bolus (0.5 mg/kg $<$ 20 kg, 0.25 mg/kg $>$ 20 kg) followed by propofol bolus of 1 mg/kg over 2 minutes. In the IB group, maintenance of deep sedation was with incremental bolus of 10 to 20 mg of propofol. In continuous infusion group (CG), maintenance was with a continuous infusion of 83 mcg/kg/min of propofol.

Results Of the 326 cases completed, 181 were in CG group and 145 were in IB group. There were no statistical differences in patient's age, weight, and American Society of Anesthesiologist (ASA) classification. The cardiovascular and respiratory parameters in the two groups were not different statistically. Mean total propofol dose was higher in CG group versus IB group (CG 7.6 mg $\pm$ 3.6 mg, IB 6.5 mg $\pm$ 3.6 mg; $p = 0.008$). Procedure time in CG group was longer by 8 minutes compared with IB group (CG 49.8 min $\pm$ 25.4 min versus 42.3 min $\pm$ 19.2 min; $p = .003$). CG group has both shorter recovery time (CG 8.1 min $\pm$ 4.7 min versus IB 10.0 min $\pm$ 8.5 min; $p = 0.01$) and discharge time.

Conclusion Satisfactory sedation and completion of the procedure was accomplished with both sedation protocols.

Keywords
- deep sedation
- incremental bolus
- continuous infusion

Introduction

Young children and children with various developmental delays frequently require sedation to complete nonpainful procedures like ABR, bone scan, and MRI. Keeping them motionless during the procedure is important to attain accurate results. Chloral Hydrate, the standard sedative agent prescribed for many years for such studies is not available anymore in the United States. This has resulted in significant increase in interest of using propofol for these diagnostic procedures. Propofol possesses many of the qualities of an ideal sedative drug. These properties are rapid onset, short duration of action, high clearance rate, minimum drug accumulation, and no active metabolite.[1]

To maintain a deep sedation, propofol can be given using an intermittent bolus (IB) technique or a continuous infusion technique with supplemental boluses as needed.[2–4] The infusion pump allows the sedating physician to titrate and maintain a constant therapeutic plasma drug level that minimizes the fluctuations of drug concentration in the blood and results in smooth deep sedation. In either technique, a

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bolus dose is required to fill the volume of distribution of the drug. The review of anesthesia literature, although unsettled, reveals that there is a possibility to gain desired sedation levels with lesser drug and a more rapid recovery when a continuous technique is used.[5] The purpose of this retrospective study was to compare administration of propofol using an incremental bolus technique versus continuous infusion in patients undergoing ABR/nuclear medicine studies. In this study, dosage, hemodynamics, procedure, recovery, and discharge times were reviewed.

Methods

This is an institutional board approved retrospective electronic chart review of all the patients sedated with propofol for ABR/nuclear medicine studies between September 2008 and February 2015 at Riley Hospital for Children at Indiana University. Initially, we sedated patients using IB method. The change in group practice occurred after the infusion pump was available to sedate these patients using continuous propofol infusion. A total of 326 patient charts were reviewed in both groups and no patient sedated for this procedure was excluded. Data included patient demographics, underlying and acute diagnosis, and occurrence of adverse events, physiologic variables, drug dosages, procedures, sedation, and recovery times. Our facility has an intensivist-based sedation program that adheres to policies and guidelines based on the recommendations by the Joint Commissions on Accreditation of Health Care Organization (JCAHO) and American Academy of Pediatrics (AAP).[6,7] Patients are prescreened via phone interview by a sedation nurse with a parent/guardian or via a review of the primary care physician's chart. The sedation nurses and physicians also assessed patients at the time of sedation.

A peri-procedure process is standard for all the children being sedated, including the telephone conversation with the family prior to the procedure date, a quiet room near the sedation suite, minimal separation from the attachment figure (such as the mother), use of distraction techniques such as iPad games and music for IV and monitoring leads placement, and the option of oral or intranasal medication for IV placement.

Patients were given a ketamine bolus (0.5 mg/kg $<$ 20 kg, 0.25 mg/kg $>$ 20 kg) followed by induction of deep sedation by propofol bolus of 1 mg/kg over 1 to 2 minutes. In the IB group, maintenance of deep sedation was achieved with IB of 10 to 20 mg of propofol. The amount and timing of the bolus was at the judgment of sedating physician. The IB was given in anticipation to the response to a stimulus or if there were signs of inadequate sedation like low Ramsay scale, increasing heart rate, respiratory rate, blood pressure, making sounds, and movements.

In the continuous infusion group (CG), sedation was maintained with a propofol infusion of 83 mcg/kg/min. The infusion rate of 83 mcg/kg/min was selected based on the existing literature.[8] A minimum Ramsay (RSS) score of 4 was targeted. RSS is clinically derived sedation score generally accepted as a tool for assessing depth of sedation along with monitoring of vital signs.[9] The continuous rate could be increased or decreased as necessary. The increase in rate occurs only if the patient has signs suggestive of insufficient sedation (such as low Ramsay score, increased heart rate, blood pressure, respiratory rate, or excessive movement). The infusion rate was decreased when there were signs suggestive of development of anesthetic state like Ramsay score of 6, decreasing blood pressure, respiratory rate, hypotension, or both. The sedation team agreed upon protocol and was instructed to make minimal changes to infusion rate; however, the sedating physician had complete discretion of procedural sedation management. Throughout the procedure, patients were monitored continuously by a dedicated sedation nurse via continuous pulse oximetry, heart rate, and noninvasive blood pressure monitoring, and nasal capnography. The sedating physician was present in the room throughout the entire procedure and was the one administering propofol in intermittent group. Patients were monitored until they were awake, drinking fluids and had a minimal alderete score of nine points.[10]

Peak onset of sedation is the time from start of loading dose to achievement of a Ramsay score of 4. Procedure time is defined as the time from achieving the acquired Ramsay score to the end of procedure (stoppage of drug administration). Recovery time was defined as the time from the end of the procedure to actual time the patient was back to his baseline status. Discharge time was defined as the time of leaving the recovery room after patient recovery to his baseline status.

The two patient groups were compared with respect to demographic, clinical, and time variables. Data was analyzed using dedicated statistical software, SAS v.9.3 (SAS Institute, Cary, NC). Propofol induced vital sign changes from baseline in each group were compared using standard Student's *t*-test or the Mann–Whitney rank sum test, depending on whether the data was normally distributed or skewed, for continuous data, and Fisher's Exact Test for categorical data. Data was presented as mean ±standard deviation, unless otherwise specified. A *p*-value of 0.05 was considered significant. Complications (apnea, desaturation, hypotension) and nuclear medicine tests were also analyzed to see if there were differences between treatment groups, as the participants may be different between test/complication groups, or these complications may attenuate the outcomes.

Results

Three hundred twenty-six patients were sedated, of which 181 were in CG group and 145 were in IB group. In CG group, the most common procedure was ABR $n = 111$ (61%) followed by MIBG $n = 58$ (32%) and bone scan $n = 11$ (6.1%). While in IB group, the most common procedure was also ABR $n = 68$ (47%) followed by bone scan $n = 57$ (39%) and MIBG $n = 20$ (14%). In both groups, age (CG 2.7 yr ± 2.6 yr versus IB 2.8 yr ± 1.8 yr; $p = 0.90$) and weight (CG 13.5 kg ± 5.0 kg versus IB 14.0 kg ± 5.3 kg; $p = 0.31$) of the patients were comparable. The CG group has 25 more female patients than IB group, but the difference was not statistically significant (►**Table 1**). Most of the patients in both groups were in ASA II and only one patient sedated in IB group was in ASA IV (►**Table 2**). All the patients in both groups were maintained in

Table 1 Demographics

	Continuous sedation ($n = 181$)	Intermittent sedation ($n = 145$)	*p*-Value
Age (years)	2.78 (2.66)	2.81 (1.81)	0.903
Sex (female)	91 (50.3)	66 (45.5)	0.435
Weight (kg)	13.45 (5.09)	14.03 (5.37)	0.317

Note: Values are mean (standard deviation) for continuous variables and frequency (percent) for categorical variables. *p*-Values are from Student's *t*-test for continuous variables and Fisher's Exact Test for categorical variables.

Table 2 ASA classification

	Continuous sedation ($n = 181$)	Intermittent sedation ($n = 145$)	*p*-Value
ASA			
I	4 (2.2)	1 (0.7)	0.372
II	163 (90.1)	135 (93.1)	
III	14 (7.7)	8 (5.5)	
IV	0 (0)	1 (0.7)	
Complications (yes)	16 (8.8)	24 (16.6)	0.042*

Abbreviation: ASA, American Society of Anesthesiologist.
Note: Values are frequency (percent) with *p*-values coming from Fisher's Exact Test.

deep state of sedation and completed procedures with 100% success.

Respiratory depression was defined as decrease in respiratory rate >20% from the baseline and incidence of hypoventilation was 27 (14.9%) and 26 (17.9%) in CG group and IB group, respectively, and didn't reach any significant statistical difference among the group. One patient in each group has an apneic episode and mild hypoxemia ($SaO_2 < 90\%$) occurred in 17% ($n = 24$) of the patients in IB group versus 8%($n = 15$) in CG group. All these patients responded to supplemental oxygen via nasal cannula and required no bag and mask ventilation.

Hypotension was defined as a decrease in systolic blood pressure >20% from the baseline.[11] The incidence of hypotension between the groups was not statistically different ($p = 0.4$). Although a drop in blood pressure was commonly observed, medical intervention was not needed.

During the entire procedure, none of the patients had heart rates below previously published age-specific reported normal values,[10] nor did the lowest recorded heart rate fall ≥20% below the given baseline average range.[11] Bradycardia (HR < 60/min), as defined according to Pediatric Advance Life Support (PALS) guidelines, was not observed in any child. Mean total dose of propofol was higher in CG group versus IB group (CG 7.6 mg ± 3.6 mg, IB 6.5 mg ± 3.6 mg; $p = 0.008$) consistent with longer procedure time of CG group. Procedure time in CG group was longer by ~8 minutes compared with IB group (CG 49.8 min ± 25.4 min versus IB 42.3 min ± 19.2 min; $p = .003$) (►**Fig. 1**). Despite longer procedure time, CG group has shorter recovery times (CG 8.18 min ± 4.7 min versus IB 10.0 min ± 8.5 min; $p = 0.018$). Discharge time was also shorter in CG group but didn't reach to a statistically significant difference between the groups ($p = 0.15$) (►**Table 3**, ►**Fig. 2**).

As procedure time may influence the medication dose, we have analyzed the dose outcomes to determine if there are differences between the treatment groups after adjusting for the length of procedure time. This does attenuate the associations: total dose (CG 7.2 mg versus IB 7.0 mg, $p = .46$); propofol (CG 6.7 mg versus IB 6.5 mg, $p = .49$); ketamine (CG 0.4 mg versus IB 0.4 mg, $p = .22$).

For complications and nuclear medicine tests (►**Table 4**), although there was a significant difference in the complication desaturation between treatment groups (8% infusion pump group versus 17% no-pump group; $p = 0.025$), the addition of this variable did not attenuate the main outcomes. There were also significant differences in the proportion of

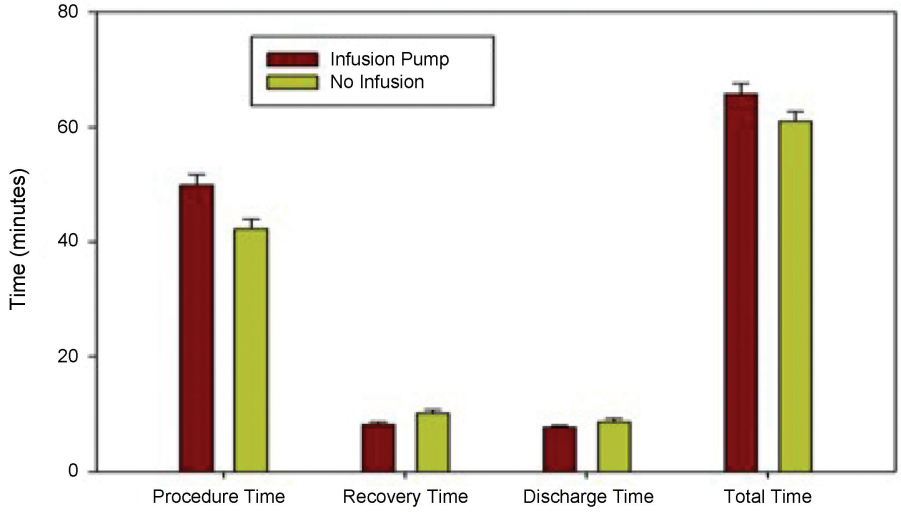

Fig. 1 Total sedation time.

Table 3 Total propofol dose and sedation time

	Continuous sedation ($n = 181$)	Intermittent sedation ($n = 145$)	*p*-Value
Total dose (mg/kg)	7.61 (3.63);	6.54 (3.61);	0.008*
	6.67 (2.47–21.56)	5.20 (1.62–23.70)	
Propofol dose (mg/kg)	7.16 (3.63);	6.10 (3.60);	0.009*
	6.25 (2.00–21.10)	4.78 (1.15–23.20)	
Propofol dosage adjusted to time length(mcg/kg/min)	6.78	6.58	0.49
Ketamine dose (mg/kg)	0.45 (0.07);	0.44 (0.10);	0.231
	0.47 (0.22–0.93)	0.47 (0.22–1.00)	
Total time (min)	65.67 (26.18);	60.94 (21.64);	0.075
	59 (26–150)	56 (24–130)	
Procedure time (min)	49.86 (25.45)	42.30 (19.29);	0.003*
	44 (12–129)	36 (12–102)	
Recovery time (min)	8.18 (4.75);	10.06 (8.52);	0.018*
	7 (1–26)	9 (0–75)	
Discharge time (min)	7.64 (4.30);	8.58 (6.94);	0.153
	5 (0–25)	5 (0–55)	

Note: Propofol dose, total infusion dose only; Total dose, propofol bolus for induction + maintenance infusion.
Values are mean (standard deviation); median (range) with *p*-values coming from Student's *t*-test.

those with a bone scan and MIBG, as well, but these, too, did not attenuate the main outcomes (data not shown), indicating that complications did not adjust the associations found between groups for our main variables of interest. Adjusted models were performed using ANCOVA models, to adjust for the covariates listed.

Discussion

An IB of sedative medication is a standard method to provide procedural sedation for short-term painful procedures and also has been used successfully to provide sedation in noninvasive prolonged procedures like ABR and bone scan. The potential disadvantages associated with this technique include hypoventilation, apnea, and fluctuation in blood pressure and heart rate. Another alternative method for sedative medication delivery is that of a continuous infusion. Proponents of continuous infusion technique suggest a decrease in potential adverse effects due to minimal plasma drug concentration variability. Importantly, the infusion can easily be titrated up or down in response to clinical signs.[12]

Table 4 Sedation related complications

	Continuous sedation	Intermittent sedation	*p*-Value
During sedation (any)	16 (8.8)	24 (16.6)	0.0416
Desat (yes)	15 (8.3)	24 (16.6)	0.0258
Apnea (yes)	1 (0.6)	1 (0.7)	1.0000
Hypotension (yes)	0 (0)	1 (0.7)	0.4448
Vomiting (yes)	0 (0)	0 (0)	n/a
Bradycardia (yes)	0 (0)	0 (0)	n/a
Transfer to higher care	0 (0)	0 (0)	n/a
Other (yes)	1 (0.6)	0 (0)	1.0000

Note: Values are frequency (percent) and *p*-value is from Fisher's Exact Test.

For noninvasive procedures like ABR or nuclear medicines studies, the study quality depends on the elimination of patient movement during the study. Younger patients or those with developmental delay are usually unable to cooperate and sedation is required. The ideal agent used for sedation in those procedures should have a rapid onset of action, short half-life and a safety profile with low risk of potential complication (hemodynamic instability and respiratory depression). Several medications have been used including narcotics, benzodiazepines, ketamine, pentobarbital, and chloral hydrate, but propofol use has recently achieved immense favorability.[13] Propofol is a rapidly acting sedative–hypnotic with a shorter duration of action (because of rapid equilibration between plasma and the brain) and a subsequent short recovery.[14] Because of these properties, propofol can be used for outpatient sedation for noninvasive procedures effectively. As reported in previous studies, inadequate sedation during noninvasive procedures (MRI) occurred in 5 to 15% of cases resulting in failure to complete the study in 3.7% of the cases.[15,16] In our study, both sedative techniques using propofol provided satisfactory conditions to complete the procedure successfully. Respiratory events constitute a large proportion (5.5–31.7%) of sedation complication in children.[17,18] We observed the similar level of

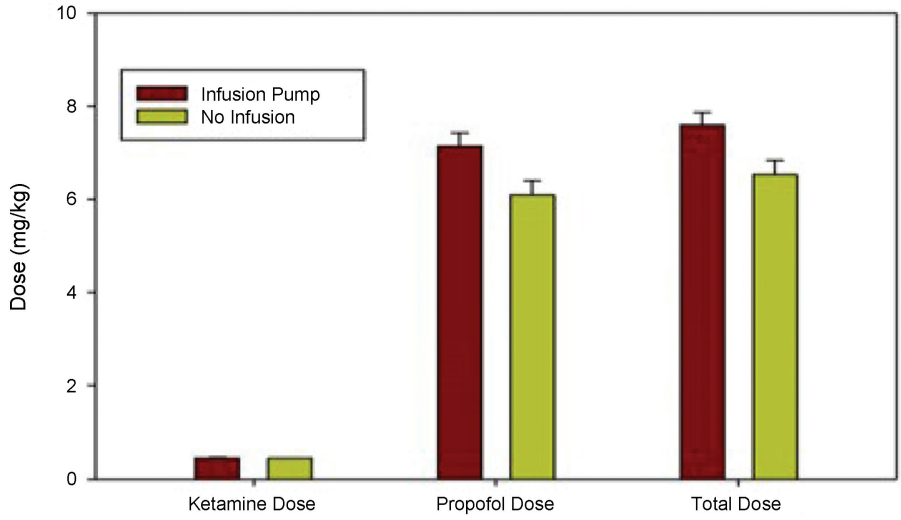

Fig. 2 Total Propofol.

hypoxemia, but the occurrence was higher in IB group (17%) versus CG group (8%). This frequency of hypoxemia appears to depend on the dose and rate of administration with a higher incidence reported with larger doses.[19,20] This could be a possible explanation of higher occurrence of hypoxemia in IB group. We observed one apneic episode in each group resolved spontaneously using jaw-thrust maneuver. All of the patients who developed hypoxemia responded to simple airway positioning and use of supplemental oxygen and did not require bag mask ventilation.

Bradycardia has been described as a possible adverse effect of propofol when administered in IBs or as infusion. In our study, the incidence of bradycardia (defined as a decrease in heart rate >20% from baseline) was only 1% in both groups and didn't require any intervention.[21,22] Propofol has also been shown to cause transient decrease in blood pressure (defined as >20% decrease in blood pressure from baseline) when administered as a bolus or prolonged infusion.[21,22] The incidence was low in CG group (2.3% vs 3.5%), which could be due to a well-known sympathetic inhibitory effect of propofol and consistent with observation reported in other studies. None of the hypotensive episodes were considered clinically significant and required any intervention.

It has been suggested that less propofol is required to maintain sedation with continuous infusion.[23] This was not the case in our study, which showed an increased maintenance dose of propofol for the patient receiving a continuous infusion (►**Table 3**). As mentioned in the results, the procedure time in CG group was 20% longer than the IB group .This prolonged procedure time in CG group could be due to 40% more ABR cases in this group, which is one of the lengthiest noninvasive procedures performed. This could be a possible explanation of increased maintenance dose of propofol in CG group as the longer the procedure, the more of the drug you need to keep the patient sedated. Despite more propofol being used in patients sedated with using continuous infusion techniques, the recovery time was shorter; however, there was no difference between groups in time to meet discharge criteria after early recovery.

The limitations of our study include its retrospective nature and single center experience. The current study presents a 100% success with propofol for noninvasive procedure using either intermittent or continuous infusion of administration. It could be asserted that the reported efficacy is due to the use of intensivist-based specialized sedation team rather than to delivery of propofol itself. This is reasonably true to some extent as specialization and experience should increase both success and efficiency. In spite of that, this can be stated with confidence; much of the reported success is specifically a function of propofol. This is a descriptive study and few, if any conclusion can be drawn about safety, is also underpowered to comment on safety, because the occurrence of serious sedation-related side effects are, fortunately, rare.[24] Additional prospective studies of the sedation for noninvasive procedures in children using a greater number of patients are warranted to provide a true idea of safety.

Conclusion

This study, although finds an advantage of ease of administration of drug and shorter recovery time in the CG, indicates there are no significant differences in satisfactory sedation and quality of diagnostic studies with both techniques.

Conflict of Interest
None.

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