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Comparison of Propofol With Pentobarbital/Midazolam/Fentanyl Sedation for Magnetic Resonance Imaging of the Brain in Children

Jay Pershad, MD, FAAP, Jim Wan, PhD, Doralina L. Anghelescu, MD

*Department of Pediatrics, Division of Emergency Services, University of Tennessee Health Science Center and LeBonheur Children’s Medical Center, Memphis, Tennessee; †Department of Preventive Medicine, University of Tennessee Health Science Center, Memphis, Tennessee; ‡Division of Anesthesiology, St Jude Children’s Research Hospital, Memphis, Tennessee

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ABSTRACT

OBJECTIVE. Propofol and pentobarbital, alone or combined with other agents, are frequently used to induce deep sedation in children for MRI. However, we are unaware of a previous comparison of these 2 agents as part of a randomized, controlled trial. We compared the recovery time of children after deep sedation with single-agent propofol with a pentobarbital-based regimen for MRI and considered additional variables of safety and efficacy.

METHODS. This prospective, randomized trial at a tertiary children’s hospital enrolled 60 patients 1 to 17 years old who required intravenous sedation for elective cranial MRI. Patients were assigned randomly to receive a loading dose of propofol followed by continuous intravenous infusion of propofol or to receive sequential doses of midazolam, pentobarbital, and fentanyl until a modified Ramsay score of >4 was attained. A nurse who was blind to group assignment assessed discharge readiness (Aldrete score > 8) and administered a follow-up questionnaire. We compared recovery time, time to induction of sedation, total sedation time, quality of imaging, number of repeat-image sequences, adverse events, caregiver satisfaction, and time to return to presedation functional status.

RESULTS. The groups were similar in age, gender, race, American Society of Anesthesiology physical status class, and frequency of cognitive impairment. No sedation failure or significant adverse events were observed. Propofol offered significantly shorter sedation induction time, recovery time, total sedation time, and time to return to baseline functional status. Caregiver satisfaction scores were also significantly higher in the patients in the propofol group.

CONCLUSIONS. Propofol permits faster onset and recovery than, and comparable efficacy to, a pentobarbital/midazolam/fentanyl regimen for sedation of children for MRI.
Over the past decade, propofol-based sedation has been used increasingly for procedures outside of the traditional operating room setting. However, there are few data from prospective, randomized, controlled trials evaluating the use of single-agent propofol to provide deep sedation of pediatric patients for MRI. The use of propofol with inhalational induction agents or as the sole agent (total intravenous anesthesia) in spontaneously breathing patients undergoing MRI has been retrospectively studied. Pentobarbital, a short-acting barbiturate, has a proven record of safety and efficacy when used with midazolam or fentanyl for sedation during pediatric diagnostic imaging. The overall incidence of inadequate or failed sedation during imaging procedures in children varies widely from 1% to 16%. We are not aware of any prospective, randomized clinical trial comparing deep sedation with propofol versus pentobarbital for pediatric MRI.

Propofol is an ultra–short-acting, nonbarbiturate, nonbenzodiazepine sedative-hypnotic agent with an arm-brain circulation time of 90 to 100 seconds. Sedation is quickly induced by rapid distribution of the highly lipophilic drug into the vessel-rich organs, including the brain. Its rapid redistribution and clearance account for its brief sedation effect and the need for repeated boluses or continuous infusion to maintain the level of anesthesia and sedation. Propofol induces dose-dependent central nervous system depression. At the recommended dose for induction in children 3 to 12 years old (2.5–3 mg/kg), a 21% incidence of transient apnea has been reported. However, sedation regimens during imaging procedures require lower doses and are associated with a lower overall incidence of hypoxia or respiratory depression, ranging from 0% to 10%. At subhypnotic doses, propofol induces sedation, amnesia, and antiemetic activity. The rapid titrability, brief pharmacologic effect, and maintenance of spontaneous ventilation make intravenous propofol an ideal agent for deep sedation during pediatric MRI.

At our institution, pediatric patients are sedated for diagnostic imaging with intravenous propofol or pentobarbital/midazolam/fentanyl regimens. Pentobarbital-based regimens are usually used for MRI, whereas propofol is preferred for the shorter-duration computed tomography studies. All sedation in the radiology suite at our institution is performed by a radiology sedation service that is staffed and supervised exclusively by board-certified pediatric emergency physicians.

The primary objective of this study was to compare the recovery time (RT) after sedation with propofol versus a pentobarbital-based regimen for cranial MRI studies in children. Secondary outcome measures were induction time (IT), total sedation time (TST), time to return to baseline (TTB; presedation) functional status, number of repeat imaging sequences, quality of images obtained, caregiver satisfaction with sedation, and frequency of immediate and delayed adverse events.

Materials and Methods

Patients

Our study was a randomized, prospective, partially blinded comparative trial of patients 1 to 17 years of age who were scheduled for elective cranial MRI and who required sedation. The study was conducted in the department of radiology at an urban, tertiary-level pediatric facility.

We excluded patients whose American Society of Anesthesiology (ASA) physical status class was >3, those requiring diagnostic imaging for trauma, and those for whom any of the agents investigated were contraindicated. A convenience sample of eligible patients was given the opportunity to participate in this study, based on the availability of the principal investigator. Our institutional review board approved the study. Informed consent was obtained from patients, parents, or guardians, as appropriate, and Health Insurance Portability and Accountability Act regulations were followed.

Sedation Protocol

Patients were assigned randomly to 1 of 2 groups by using the method of randomly permuted blocks of size 10. The random allocation sequence was generated by a biostatistician (Dr Wan) and provided in sealed numbered envelopes. The sequence was concealed from the sedating physician, until intervention was assigned. The principal investigator enrolled participants and assigned participants to 1 of 2 groups. Parents were present during induction and recovery. Patients in the pentobarbital group received midazolam, pentobarbital, and fentanyl in sequential doses until the desired level of sedation was achieved. Midazolam (0.1 mg/kg) was administered intravenously up to a maximum dose of 5 mg, and pentobarbital (2 mg/kg) was then given intravenously. Additional doses of 1 mg/kg pentobarbital were then administered until the desired level of sedation was achieved, up to a maximum of 6 mg/kg. The cumulative dose of pentobarbital was limited to 200 mg. If adequate sedation was not achieved, fentanyl (1 µg/kg) was administered intravenously, up to a maximum dose of 100 µg.

Patients in the propofol group received an initial dose of 0.5 mg/kg lidocaine mixed in the same syringe, to decrease the pain associated with injection of intravenous propofol. A loading dose of intravenous propofol was administered in 1 mg/kg aliquots, each administered over a period of 60 seconds, until loss of eyelid reflex was observed. Supplemental doses of 0.5 mg/kg were administered until the desired level of sedation was attained. A maintenance infusion was initiated at 6 mg/kg per hour. If the patient moved before or during the scan, addi-
tional 0.5 mg/kg propofol boluses were administered and the infusion rate was incrementally increased by 10%, up to a maximum of 15 mg/kg per hour.

In accordance with our institution’s sedation policy, all patients received continuous heart rate, pulse oximetry, and nasal capnography monitoring, and respiratory rate and blood pressure were assessed every 5 minutes. Patients received preoxygenation with blow-by oxygen via facemask to maintain oxygen saturation of >95%. A registered nurse with specialized training in sedation monitored the patient before, during, and after the procedure, until the patient was ready for discharge. Because MRI necessitated remote monitoring, close vigilance was provided throughout the scanning procedure. An attending pediatric emergency medicine physician credentialed by our institution to provide procedural sedation was present at all times to monitor the patient and provide immediate intervention as needed.

While sedated, patients were closely observed for signs of upper-airway obstruction, such as snoring, stridor, decreasing hemoglobin oxygen saturation, loss of exhaled carbon dioxide, or progressive hypercapnia, as detected by the end-tidal capnographic waveform. Airway rescue measures, including airway manipulation, suction, and insertion of a nasal airway, were used sequentially as needed. If the patient’s ventilatory status or oxygenation did not improve, assisted ventilation was initiated, and the procedure was aborted according to the decision of the principal investigator.

After completion of the scans, a registered nurse not associated with the study who was blind to the type of medication received evaluated discharge readiness. Standard discharge criteria (Aldrete score) were used. Recovery was graded at 5-minute intervals. Patients met discharge criteria when they reached an Aldrete score of ≥8 or reached a score within 2 points of their presedation score.

### Assessment of Sedation Efficacy and Adverse Events

Sedation was considered efficacious if the patient lost consciousness, underwent the procedure without movement, and maintained spontaneous, adequate respiratory effort. We used the Ramsay scale to measure the level of sedation. Our goal was to achieve a level of >4 on the Ramsay scale.

Failure to achieve adequate sedation (ie, patient awakened or moved, interfering with completion of the MRI) despite maximal doses was considered a failure of the sedation regimen, and the procedure was rescheduled. Sedation was also considered to have failed if the procedure was aborted because of a significant adverse event.

Possible “major” adverse events during sedation include hypotension, hypoxemia, emesis, agitation, apnea, respiratory depression, laryngospasm, and bradycardia. Hypotension was defined as systolic blood pressure <70 plus twice the patient’s age in years, associated with altered peripheral perfusion (delayed capillary refill time). Hypotension was treated with a 20 mL/kg intravenous bolus of crystalloids and a 10% reduction in the propofol infusion rate. Hypoxemia was defined as a pulse oximetry value <90% and prompted immediate intervention. Emesis was defined as presence of stomach contents in the pharynx, at any time after administration of the sedation drugs. Agitation was defined as uncontrollable distress or inconsolability despite parental presence. Apnea was defined as cessation of respiration for >20 seconds. Bradycardia was defined as a heart rate below 50 beats per minute. Laryngospasm was identified by the occurrence of airway obstruction or stridor with a decline in pulse oximetry readings that was not relieved by airway manipulation, suction and insertion of oral or nasal airway, and required assisted ventilation or neuromuscular blockade to achieve adequate ventilation. “Immediate” adverse events were those that occurred during sedation or before discharge. Delayed adverse events were adverse effects that occurred after discharge, as noted during the follow-up satisfaction survey. We did not record “minor” adverse events that were self-limited and typically associated with administration of parenteral sedatives. These include pain or discomfort during injection (usually observed with propofol), transient myoclonus (usually noted with propofol), and facial pruritis with fentanyl administration.

### Assessment of Other Variables

The following data were collected for each patient: age, gender, indication for diagnostic study, presence or absence of cognitive impairment, sedation IT, scan time, RT, TST, sedation efficacy or failure, frequency and timing of adverse effects, imaging efficacy (quality of MRI scan), and satisfaction of the caregiver with procedural sedation. IT was defined as the time from initial administration of the drug to achievement of sedation adequate to perform the MRI. Scan time was defined as the length of time between the patient’s placement on the MRI table and completion of the imaging sequences. RT was defined as the time that elapsed between scan completion and meeting of discharge criteria. TST was defined as the time between administration of the first dose of drug and patient readiness for discharge. Quality of images was rated on a 5-point Likert scale based on the presence or absence of motion artifact, by an independent radiologist, blind to the identity of the patient and the sedation regimen. Scans were assigned quality ratings of 1 (poor) through 5 (excellent). An independent nurse blind to the sedation regimen made a follow-up telephone call 24 to 48 hours after discharge to determine the time at which the child returned to the baseline level of function and whether delayed adverse events were observed. During this telephone call, parents or caregivers were asked to assign a score on a 5-point
Likert scale (5 being extremely satisfied and 1 being not at all satisfied) assessing their satisfaction with the overall sedation process.

Data Analysis

The primary outcome measure was RT. Secondary outcome measures were IT, TST, quality of imaging, number of repeat image sequences, frequency of immediate and delayed adverse events, sedation success or failure, caregiver satisfaction, and caregiver report of TTB. According to Kienstra et al and Mason et al, the standard deviation for the RT in the pentobarbital group was 32 minutes. From Hasan et al, the standard deviation for the RT in the propofol group was 21 minutes. Assuming a probability (P) of type I error of .05 and a power of 80%, the required sample size to detect a 20 minute difference in RT was 30 subjects for each group. The 2-sample t test was used to test the difference in RT between the 2 groups. For secondary outcomes, categorical variables with small sample size, such as the frequency of adverse events and sedation failures, were compared between the 2 groups using Fisher’s exact test. The Mantel 1-degree-of-freedom χ² test was used to compare the Likert-scale variables. All analyses were performed by using by SAS 9.1.3 statistical software (SAS Institute Inc Cary, NC).
RESULTS
Sixty patients were assigned randomly to 1 of 2 groups (Fig 1). The groups were similar in age, gender, race, American Society of Anesthesiology physical status class, and proportion of patients with cognitive impairment (Table 1). The mean total dose of each drug is listed in Table 2. No sedation failures or significant adverse events were recorded. RT, sedation IT, TST, TTB functional status, and caregiver satisfaction scores significantly favored propofol over pentobarbital. No significant differences were observed between the groups in imaging quality or in the number of repeat images (Tables 3 and 4).

The adverse events that occurred were relatively minor. We observed 11 immediate adverse events, 8 in the propofol group, and 3 in the pentobarbital group. The propofol-related immediate adverse events were transient decreased blood pressure without signs of compromised peripheral perfusion in 4 cases and respiratory depression in 4 cases. The 4 cases of respiratory depression occurred during induction. Two children developed partial airway obstruction without desaturation, which corrected with airway manipulation including chin lift maneuver. Two patients experienced a decrease of oxygen saturation into the 80s and 70s, respectively, that lasted for <1 minute. One subject responded to airway manipulation, readjustment of oxygen mask, and suction. The other patient required brief (<60 seconds) assisted ventilation with a bag mask and insertion of nasal airway, after which adequate spontaneous ventilation was observed. The nasal airway was maintained for the duration of the scan. None of these cases received tracheal intubation or escalation of care to warrant aborting the procedure. The remainder of the scanning procedures in these patients was uneventful. Pentobarbital sedation was associated with 3 immediate adverse events: 1 episode of transient decreased blood pressure and 2 cases of emergence agitation. Seven delayed adverse events were noted, all in the pentobarbital group. These comprised 6 cases of prolonged sedation and 1 case of delayed agitation.

DISCUSSION
Our results demonstrate that propofol provided significantly shorter recovery, sedation induction, TSTs, TTB functional status, and better caregiver satisfaction scores compared with a pentobarbital/midazolam/fentanyl regimen. The differences in mean induction, recovery and TSTs were 8, 17, and 20 minutes, respectively, in favor of propofol. When extrapolated to multiple sedations, we believe that these differences have clinical significance and pharmacoeconomic impact by optimizing the use of the MRI scanner. In a previous prospective trial, Bloomfield et al noted propofol to be associated with a shorter time to arousal and time to discharge then pentobarbital. Our trial differed from theirs in that all participants were assigned randomly to the treatment groups. In addition, the nurse responsible for monitoring recovery and discharge and for conducting the telephone follow-up in our study was blind to the type of agent received. Although subjects in both studies were preoxygenated, end-tidal carbon dioxide monitoring was not part of the protocol used by Bloomfield et al. In addition, pentobarbital was used as a single agent in doses higher than those used in our study (maximum total dose: 7.5 vs 6 mg/kg), and the details of pentobarbital dosing and the incidence of adverse events were not described.

Our study has several limitations. This was a convenience sample of eligible patients based on the availability of the principal investigator. The physician investigator responsible for administration of propofol and supervision of procedural sedation in both groups was not blind to the agent received. Although this factor may have introduced some bias, the presence of the investigator ensured strict adherence to the sedation protocol. The fact that we restricted enrollment to patients scheduled exclusively for cranial MRI may limit extrapolation of our results to MRI studies of other body parts. However, this restriction was designed to reduce variation in scan time among the study subjects.

It could be argued that the use of midazolam as an

| TABLE 1 | Demographic Characteristics of the Study Groups |  |  |  |  |
| --- | --- | --- | --- | --- |
| Characteristic | Propofol Group | Pentobarbital Group |  |
|  | (N = 30) | (N = 30) |  |
| Age, mean ± SD, y | 5.2 ± 3.1 | 6.0 ± 3.6 | .366 |
| Gender, female | 17 (57) | 15 (50) | .605 |
| Race, black | 14 (48) | 16 (53) | .698 |
| ASA class 2 | 15 (50) | 19 (66) | .228 |
| ASA class 3 | 15 (50) | 11 (37) |  |
| No. of subjects with cognitive impairment | 11 (37) | 15 (50) | .297 |

| TABLE 2 | Sedation Medication Regimens |  |  |  |  |
| --- | --- | --- | --- | --- |
| Medication | Mean Total Dose, mg/kg | Range, mg/kg |  |
| Propofol regimen | 7.6 | 4–15 |  |
| Pentobarbital regimen |  |  |  |
| Pentobarbital | 4.1 | 0–7 |  |
| Midazolam | 0.089 | 0.03–0.11 |  |
| Fentanyl | 0.3 | 0–2 |  |
adjunct to pentobarbital may have prolonged the RT.20 Our institution currently leaves the choice of sedative agent for MRI to the discretion of the practicing physician. For more than a decade, the practice in our radiology department has been to premedicate with midazolam. Because of the success of this experience, midazolam sedation was included in our trial in an attempt to reduce the total dose of pentobarbital, an intermediate-acting barbiturate.

The maximum allowed infusion rate of 15 mg/kg per hour of propofol in our protocol was higher than the 9 to 10 mg/kg per hour cited in the literature, although our starting rate of 6 mg/kg per hour is a standard approach.14,15 Also, subsequent boluses for patient movement during the scanning procedure were administered in 0.5 mg/kg aliquots, with a 10% incremental adjustment in drip rate. This was lower than the 1 to 2 mg/kg doses of propofol for subsequent boluses used in previous studies; therefore, our increments were more conservative.14,15

The cumulative maximum dose of pentobarbital in our study was 6 mg/kg (200 mg). This was consistent with the dose used in 2 previous studies22,24 and higher than the 5 mg/kg used in 2 other trials.21,36 In contrast, 1 previous study used a maximum dose of 6.5 mg/kg of pentobarbital.37 Furthermore, the method of administration of pentobarbital in our study was an initial bolus of 2 mg/kg followed by additional aliquots of 1 mg/kg until adequate sedation was achieved. Previous studies used 2 mg/kg boluses for additional dosing.22,24 Others used a smaller dose for subsequent boluses ranging from 1 to 2 mg/kg aliquots of pentobarbital.20,21 It is possible that the relatively smaller incremental doses of pentobarbital used in our study may have led to a bias in favor of the propofol group.

Overall, the difference in frequency of adverse events between the 2 groups in our study was not statistically significant. However, given the small numbers, we were unable to exclude the possibility of a type II error. Adverse events of respiratory depression during induction and hypotension, observed with propofol administration in our study were similar to those previously reported.14,15,29 We noted transient respiratory depression in 4 (13.3%) of 30 patients in the propofol group versus 0 (0%) of 30 in the pentobarbital group. This difference was not statistically significant (P = .11). The relatively higher incidence of respiratory adverse events in the propofol group highlights the importance of having a physician trained in advanced airway management immediately available. The pentobarbital regimen was associated with prolonged sedation in 6 patients (20%) and emergence agitation in 2 patients (6.7%). One subject experienced delayed agitation after discharge from the hospital. The incidence of emergence agitation noted in our study is consistent with the incidence reported in the literature. The incidence of paradoxical hyperactivity for all drug regimens, including pentobarbital, as reported by Rubin et al38 was 1.8%. Emergence agitation noted with the use of pentobarbital alone varies greatly between studies: 0% in Mason et al19 in 2004, 1.2% in Karian et al,23 1.5% in Mason et al,20 7% in Greenberg et al,24 12% in Kienstra et al,21 and 14% by Malviya et al.36 Furthermore, the incidence of paradoxical hyperactivity with pentobarbital was comparable when considered

<table>
<thead>
<tr>
<th>Variable</th>
<th>Propofol Group</th>
<th>Pentobarbital Group</th>
<th>95% Confidence Interval</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of repeat sequences, mean ± SD</td>
<td>0.4 ± 0.8</td>
<td>0.3 ± 0.8</td>
<td></td>
<td>622</td>
</tr>
<tr>
<td>Quality of images, Likert scale, 1–5, mean ± SD</td>
<td>4.6 ± 0.7</td>
<td>4.5 ± 0.6</td>
<td></td>
<td>538</td>
</tr>
<tr>
<td>Caregiver satisfaction with sedation, Likert scale, 1–5, mean ± SD</td>
<td>4.8 ± 0.4</td>
<td>3.9 ± 1.5</td>
<td></td>
<td>.006 (–1.4 to –0.3)</td>
</tr>
<tr>
<td>Parental desire to repeat same sedation technique (&quot;no&quot; or &quot;yes&quot;), n (%)</td>
<td>28 (93)</td>
<td>22 (76)</td>
<td></td>
<td>.080</td>
</tr>
<tr>
<td>Adverse events, n (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Immediate</td>
<td>8 (26.6)</td>
<td>3 (10)</td>
<td></td>
<td>.095</td>
</tr>
<tr>
<td>Delayed</td>
<td>0 (0.0)</td>
<td>7 (23)</td>
<td></td>
<td>.011</td>
</tr>
</tbody>
</table>

* 95% confidence intervals of the effect size (ie, difference between the groups).*
with and without adjunctive midazolam (1.6% vs 1.5%). The report of prolonged sedation in our study, was based on subjective responses obtained from the parents or caregivers, on the 24- to 48-hour postdischarge follow-up survey. This may have led to some bias against the subjects assigned to the pentobarbital medication regimen.

CONCLUSIONS
Our results highlight the favorable induction and recovery profile of propofol sedation, while showing comparable efficacy to a pentobarbital-based regimen in pediatric patients undergoing cranial MRI. Although absolute reduction in induction and RT were relatively small, when extrapolated to multiple encounters for a busy sedation service, the time savings and potential economic impact may be significant.

ACKNOWLEDGMENTS
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