A Presedation Fluid Bolus Does Not Decrease the Incidence of Propofol-Induced Hypotension in Pediatric Patients

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ABSTRACT

BACKGROUND AND OBJECTIVE: Propofol is commonly used in pediatric sedation, which may cause hypotension during induction. Our goal was to determine the effect of a preinduction 20-mL/kg isotonic fluid bolus on propofol-induced hypotension, assess clinical signs of hypoperfusion during hypotension, and evaluate for age-related propofol dosing differences.

METHODS: This prospective, randomized, controlled, nonblinded study was conducted at Children's Hospital of Illinois. Patients were children 6 to 60 months of age who needed sedation for MRI or auditory brainstem-evoked response testing. The treatment group received a preinduction 20-mL/kg isotonic saline bolus before procedure initiation. Patients were continuously monitored via cardiorespiratory monitor with pulse oximetry and end-tidal carbon dioxide measurements. Cardiovascular indices and clinical signs of hypoperfusion were compared between groups, and propofol dosing differences were compared between age groups.

RESULTS: One hundred twenty-six patients were randomly assigned to treatment (n = 52) or control (n = 74) conditions. Twelve patients in the treatment group and 14 patients in the control group experienced postinduction hypotension, as defined by the Pediatric Advanced Life Support guidelines. One patient in each group was given volume resuscitation when blood pressure did not improve after a reduction in the propofol infusion rate. No hypotensive patients had physical signs of hypoperfusion, and patients ≤1 year of age needed significantly more propofol.

CONCLUSIONS: A 20-mL/kg preinduction isotonic saline bolus does not prevent propofol-induced hypotension. No clinical signs of hypoperfusion were noted with induced hypotension, and infants ≤12 months old need significantly more propofol per kilogram for procedures.
age, height, and weight percentiles as in the Pediatric Advanced Life Support (PALS) guidelines.13

In the pediatric patient, the potential reduction in blood pressure with propofol induction may be significant enough to result in clinical signs of hypoperfusion, thus raising concern about a possible temporary decrease in end organ perfusion. The effect of hypotension in the neonate and in children with trauma or sepsis has been extensively studied, but very few studies address hypotension in healthy children undergoing sedation or general anesthesia. Because there are no good data supporting a safe low blood pressure cutoff in children, the present literature supports preventing and treating hypotension secondary to anesthetic agents.14

Outcomes of hypotension secondary to anesthesia have been studied in adults, and a greater postoperative length of stay and greater mortality at 1 year were found.15,16 The adult patients with secondary events had a higher American Society of Anesthesiologists (ASA) classification and a lower baseline blood pressure, however. Other studies in the adult population have investigated preinduction treatments to prevent hypotension during propofol induction, including the use of isotonic fluids,12,18 hetastarch,19 ephedrine,12,20,21 phenylephrine,22 dopamine, dobutamine,20 ketamine,23–25 and calcium chloride.26 However, little research has been conducted specifically to determine whether there is a significant risk to the pediatric patient during propofol-induced hypotension or whether there is an effective method to prevent the reduction in blood pressure associated with propofol induction in this patient population.

We hypothesized that a preinduction 20–mL/kg isotonic saline bolus would decrease the incidence of propofol-induced hypotension. The purpose of our randomized controlled trial was to evaluate our hypothesis during procedural sedation in pediatric patients. Other objectives were to assess for clinical signs of hypoperfusion in the hypotensive patients and to measure differences in propofol dosing in relation to age, because earlier studies suggested that a larger milligram per kilogram amount might be needed in infants than in children.22,28

METHODS

A prospective, randomized, controlled, nonblinded study was conducted with approval from the Peoria Institutional Review Board. Written informed consent was obtained from the parent or legal guardian before entrance into the study. Pediatric patients between the ages of 6 and 60 months with an ASA classification of I, II, or III who were scheduled for MRI or ABR testing were considered eligible for the study. All patients during the designated study period were approached consecutively for enrollment. A 1-sided t test, prestudy power calculation (α = .05, power = 0.8), with reasonable assumptions about population SDs, suggested 115 patients per group to be sufficient to detect a clinically significant change. Children with a history of allergies to eggs, craniofacial anomalies (eg, Pierre Robin syndrome), acute respiratory infections, or ASA category IV or V were considered ineligible for the study.

After registration and evaluation by the sedation nurse and consent for study participation, a sedation nurse attained the randomization information to allocate each patient into the appropriate study. A randomization table was used to determine which patients would be enrolled in the treatment or control groups. Both the physician and sedation nurse performed a preprocedure physical examination that included examination of peripheral pulses, skin color and temperature. A peripheral intravenous (IV) catheter was placed in all patients before the procedure, and patients assigned to the treatment group received a 20–mL/kg bolus of isotonic saline over 30 minutes before undergoing sedation with propofol. All patients were placed on nil per os (NPO) orders as follows: solid food for 8 hours, milk or infant formula for 6 hours, breast milk for 4 hours, and clear liquids for 2 hours before the procedure.

The procedural sedation for MRI or ABR with propofol was performed under the direct supervision of a pediatric intensivist or hospitalist. Multiple syringes containing 1 mg/kg of propofol were prepared by the sedation nurse before the start of the procedure, which allowed easy dose administration and calibration. Patients were then placed on the cardiorespiratory monitor with pulse oximetry before administration of the loading dose of propofol. All patients received 1 mL of 1% lidocaine intravenously before propofol induction to reduce the pain associated with propofol administration. Propofol manufacturers suggest 2.5 to 3.5 mg/kg to be given over 30 seconds for induction in pediatric patients; therefore, propofol was administered in incremental doses of 1 mg/kg for induction, with a maximum dose of 6 mg/kg. Induction was considered complete when the patient was asleep, unresponsive to verbal or
gentle tactile stimulation, and with intact cardiorespiratory drive. Propofol infusion was continued with the hourly infusion rate equal to the dose needed for induction. Thus, if a patient required three 1-mg/kg boluses of propofol to achieve adequate sedation, then the infusion rate would be started at 3 mg/kg per hour. This dosing protocol was routinely used at our institution before the commencement of our study because it was effective at keeping the patients adequately sedated for the duration of the required procedure.

Once the patient was sedated, a nasal cannula was placed in the nostrils to deliver supplemental oxygen in the event a desaturation occurred and to allow monitoring of end-tidal carbon dioxide. All patients were monitored continuously for heart rate, respiratory rate, oxygen saturations with pulse oximetry, and end-tidal carbon dioxide levels. Blood pressure was measured via an automated blood pressure monitor (MEDRAD Veris MR; MEDRAD, Inc, Warrendale, PA), with an appropriately sized cuff, once before induction, once immediately after induction, and at 5-minute intervals thereafter until the patient was awake and alert after the procedure, when the final recovery blood pressure was obtained.

**Hypotension Protocol**

A priori, hypotension was defined as a systolic blood pressure of ≤70 mm Hg for ages 6 months to 1 year and, in patients >1 year old, a systolic blood pressure of ≤70 + (age × 2) mm Hg, as defined in PALS guidelines. Patients with documented hypotension were examined physically for signs of hypoperfusion in the lower extremities, including capillary refill >3 seconds, presence of cool extremities, and decreased dorsalis pedis or posterior tibial arterial pulses. For patients with systolic hypotension without signs of peripheral hypoperfusion, the propofol infusion rate was reduced by 0.5 mg to 1 mg/kg per hour at the discretion of the physician every 5 minutes until the hypotension resolved. If a patient had continued hypotension despite 2 reductions in the propofol infusion rate, a 20-ml/kg isotonic saline bolus was administered and blood pressure was reassessed; the procedure was resumed with the resolution of the hypotension. For patients with signs of hypoperfusion, the patient was given a 20-ml/kg normal saline IV bolus and the propofol infusion rate was decreased by 0.5 mg to 1 mg/kg per hour at the discretion of the physician every 5 minutes until the signs of hypoperfusion resolved. If hypotension or hypoperfusion persisted despite the isotonic saline bolus and the reduction in propofol infusion rate, the MRI or ABR was aborted, and the procedure was rescheduled with the department of anesthesia.

**Statistical Methods**

The data was entered into a Microsoft Excel (Microsoft, Redmond, WA) spreadsheet, verified by the authors, and analyzed using SPSS 17.0 (IBM SPSS Statistics, IBM Corporation) based on the intent to treat. In each group, the systolic and diastolic blood pressure values were averaged during 3 time intervals: preinduction, lowest during the procedure (low-procedural), and recovery. Although serial BP measurements were obtained every 5 minutes after induction, for the purpose of statistical analysis the single lowest BP reading was used as the low procedural value. Nominal variable differences for 2 groups were determined by χ² and by t tests for scalar variables. Repeated-measures differences between 2 groups for interval variables were tested with mixed effect regressions. Two-sided P values <.05 were considered significant.

**RESULTS**

Between December 2006 and January 2008, 157 patients between the ages of 6 and 60 months who were scheduled for MRI or ABR testing with procedural sedation were approached for enrollment. The study was stopped after 14 months due to slow enrollment and because of the delays in the MRI schedule that was created when a treatment patient received the pre-procedure IV bolus.

Thirty-one parents or legal guardians declined their child’s participation in the study, leaving 126 subjects randomly assigned to the experimental and control conditions. The use of a randomization table resulted in an unequal distribution of patients between groups: 52 treatment and 74 control. Patient demographics are provided in Table 1. Two oncology patients without active disease, 1 in each arm, were the only ASA category III study participants. There was no significant difference in race, gender, age, weight, ASA class, BMI, or NPO time between groups.

Systolic and diastolic blood pressures decreased significantly (P < .001) after propofol induction in both groups. Systolic blood pressure decreased by 25.5 and 21.9 mmHg and diastolic blood pressures decreased by 22.4 and 20 mmHg in the treatment and control groups, respectively, as shown in Figs 1 and 2. However, the preinduction, low-procedural, and recovery systolic
and diastolic blood pressures were not significantly different between treatment and control groups (systolic $P = .46$, diastolic $P = .76$), demonstrating no effect from the preinduction isotonic fluid bolus.

Twenty-six patients, 12 (23.1%) in the treatment group and 14 (18.9%) in the control group, had $\geq 1$ documented reading of hypotension, which were not statistically different (Fisher’s exact $P = .66$). The average total dose of propofol was slightly higher in the treatment group, but the difference was also not significant ($10.4 \pm 5.5$ mg/kg vs $8.2 \pm 4$ mg/kg; $P = .26$). Four patients experienced hypotension during induction, and the other patients had hypotension at various times after induction through the end of the procedure. Hypotension resolved in 24 of the 26 patients with a reduction in their propofol infusion rate, and 1 patient from each arm received a 20-mL/kg isotonic saline bolus for persistent hypotension despite a reduction in their propofol infusion rate. None of the 26 patients who developed propofol-induced hypotension had clinical signs of hypoperfusion, and all patients successfully completed the procedure and recovered without complications.

Table 2 compares the demographic information between the hypotensive and nonhypotensive patients. Overall, the hypotensive patients received a significantly larger total amount of propofol per kilogram than the nonhypotensive patients and had a significantly longer procedure time. The average procedure time for MRI compared with ABR was significantly different (56.22 $\pm$ 15.45 minutes vs 43.98 $\pm$ 14.52 minutes, respectively; $P < .001$), and 24 of the 26 hypotensive patients underwent MRI. No significant differences were found between the hypotensive patients and nonhypotensive patients for age, weight, BMI, NPO time, race, or ASA classification.

Last, when we controlled for procedure time, patients $\leq 12$ months old ($n = 9$) needed a significantly larger average total amount of propofol than patients $>12$ months of age ($n = 117$) (11.29 $\pm$ 5.59 mg/kg vs 6.83 $\pm$ 3.37 mg/kg, respectively; $P = .04$).

**DISCUSSION**

The positive attributes of propofol have generated a significant increase in its use for pediatric sedation, and its hypotensive effects have been well documented. However, there has been little research to determine whether there is a significant risk to the pediatric patient from propofol-induced hypotension or whether there is an effective method to prevent the induced hypotension, thus prompting this study.

This was the first prospective, randomized, controlled trial in the pediatric population to test a nondrug intervention to attenuate the hypotensive effects of propofol during induction.$^*$ Although the presedation bolus did not demonstrate an effect in this study, our study did demonstrate

$^*$ A presubmission PubMed search using the words propofol and hypotension in the title search filter did not reveal any studies of this type in the pediatric population.
the ease of reversing propofol-induced hypotension by decreasing the infusion rate by 0.5 to 1 mg/kg per hour, which resulted in immediate blood pressure improvement without the use of additional measures. The low blood pressures in the hypotensive patients were an average of 4.3 mm Hg below the PALS threshold for hypotension. Our study was not designed to assess for possible long-term effects from the propofol-induced hypotension, but it does add to the current literature indicating that using the PALS guidelines as a threshold to assess and treat transient hypotension secondary to propofol is safe in the short term.

The decrease in blood pressure secondary to propofol induction is caused by direct and indirect vasodilation and myocardial depression.8,9,27–32 The 20-mL/kg isotonic fluid bolus was used because it is the standard IV fluid bolus amount provided during resuscitative efforts in pediatric patients,13 but it was not sufficient to counter the vasodilatory and myocardial depressive effects of propofol. As suggested by Hertzog et al,5 a calculated preprocedure fluid deficit could be provided before or during the procedure, which may decrease the incidence of propofol-induced hypotension. This raises the question of what effect NPO status had on the development of hypotension. An adult study by Morley et al33 did not find a relationship to fluid abstinence and hypotension during propofol induction. However, Nafiu et al14 noted that older children who were able to maintain a longer NPO status before surgery were more likely to become hypotensive after anesthetic induction. In our study, the hypotensive and normotensive patients had a similar NPO time, but the NPO status was not stratified into liquids, formula, or solids that would have allowed additional breakdown of the data.

Clinical impression of diminished distal pulses, prolonged capillary refill time, skin color, and decreased extremity temperature were evaluated when concern for hypoperfusion was present. There was no evidence of hypoperfusion in the subjects who experienced propofol-induced hypotension by the aforementioned criteria, a finding that is consistent with previous studies.5,34 The aforementioned physical signs are subjective measures, however, with significant interrater variability, which reduces their reliability.

The average procedure time for MRI was 12 minutes longer than for ABR, and thus the continuous infusion of propofol was longer in the patients undergoing MRI. Twenty-four of the 26 hypotensive patients underwent MRI, which could account for the increased total amount of propofol in the hypotensive patients.

TABLE 2 Comparison of Hypotensive and Normotensive Patients

<table>
<thead>
<tr>
<th>Variable</th>
<th>Hypotensive (n = 26)</th>
<th>Nonhypotensive (n = 100)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean propofol</td>
<td>2.97 ± 1.34</td>
<td>2.77 ± 1.49</td>
<td>.54</td>
</tr>
<tr>
<td>induction dose, mg/kg</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean total propofol, mg/kg</td>
<td>9.07 ± 4.96</td>
<td>6.65 ± 3.18</td>
<td>.03</td>
</tr>
<tr>
<td>Procedure time, min</td>
<td>59.73 ± 18.95</td>
<td>48.89 ± 14.64</td>
<td>.01</td>
</tr>
<tr>
<td>Age, mo</td>
<td>32.96 ± 17.11</td>
<td>30.18 ± 13.79</td>
<td>.45</td>
</tr>
<tr>
<td>Wt, kg</td>
<td>13.93 ± 4.39</td>
<td>13.78 ± 3.76</td>
<td>.86</td>
</tr>
<tr>
<td>BMI</td>
<td>17.18 ± 5.49</td>
<td>16.64 ± 4.05</td>
<td>.65</td>
</tr>
<tr>
<td>NPO time, h</td>
<td>8.6 ± 4.05</td>
<td>9.13 ± 3.16</td>
<td>.48</td>
</tr>
<tr>
<td>Caucasian, %</td>
<td>76.9</td>
<td>78</td>
<td>.77</td>
</tr>
<tr>
<td>ASA classification</td>
<td>1.31 ± 0.47</td>
<td>1.29 ± 0.50</td>
<td>.87</td>
</tr>
</tbody>
</table>

Data are means, means ± SDs, or percentages.
* Total = induction dose + infusion dose.
Propofol has multicompartmental pharmacokinetics, such that during induction a very large peripheral volume of distribution results in rapid distribution with slower redistribution.\textsuperscript{21} Neonates and young infants have a high total body water to body fat ratio, which results in a larger peripheral volume of distribution for lipophilic medications such as propofol.\textsuperscript{3-7} The large peripheral volume of distribution may be the reason that patients in our study, \( \leq 1 \) year of age, needed significantly more propofol per kilogram than patients \( >1 \) year of age.

There are multiple limitations to our study, the most significant being the early termination of the study before we achieved the desired sample size because of slow enrollment and the effect the study was having on the MRI schedule. Because of this limitation, a post hoc sample size calculation was performed to establish the sample size that would have been needed to detect a clinically significant change in the incidence of propofol-induced hypotension. Using our low systolic blood pressure population mean of 81.5 mm Hg and SD of 9, with a power of 80\% and \( \alpha \) of .05, we calculated a substantially smaller sample size of 7 per group to be adequate to detect a meaningful change. We believe the much larger, originally projected sample size probably reflected an overestimation of the SD of the sample. Although this new information was performed post hoc, we think it provides additional evidence that our interpretation of no significant difference between groups is valid.

Comprehensive data on patients who did not participate in the study were not collected for comparison. The unequal random assignment of subjects into the control and treatment groups was also unfortunate and probably a consequence of discontinuing the study earlier than planned. Blocked randomization may have eliminated this problem, or had the duration of the study continued as originally planned, the inequality in group number probably would have been much less or eliminated.

NPO status could have been further stratified, which may have uncovered a relationship to the duration of abstinence from fluid intake and propofol-induced hypotension. The traditional assessment of blood pressure by using a cuff can be less accurate, and therefore using this device as a trigger to assess for hypoperfusion is suboptimal. Invasive hemodynamic monitoring would be ideal to determine hypotension and trigger an assessment for hypoperfusion, but such monitoring was not practical in a research study involving an outpatient procedure. Finally, this was a single-center study, which can influence bias.

CONCLUSIONS

The administration of a presedation 20-mL/kg isotonic saline bolus did not decrease the incidence of propofol-induced hypotension in our study, contrary to our hypothesis. Additional studies are needed to determine the utility of a presedation bolus before propofol induction. By using the PALS threshold for hypotension, we did not find evidence of short-term adverse effects from the propofol-induced hypotension, nor did we find evidence of hypoperfusion in our hypotensive patients by using the defined subjective assessments. Propofol-induced hypotension can readily be reversed with a small reduction in the propofol infusion rate. Children <1 year of age need a significantly larger amount of propofol per kilogram than older children.

ACKNOWLEDGMENTS

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REFERENCES


37. Westrin P. The induction dose of propofol by guest on December 21, 2017http://hosppeds.aappublications.org/Downloaded from
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