Original Contribution

Prevention of propofol-induced pain in children: pretreatment with small doses of ketamine

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Abstract

Study Objective: To evaluate the efficacy of ketamine in preventing propofol injection pain in children.

Design: Prospective, randomized, double-blinded, placebo-controlled study.

Setting: University-affiliated hospital.

Patients: 192 ASA physical status 1 and 2 pediatric patients.

Interventions: Patients were randomly assigned to 4 groups. Group S (control) received normal saline as a placebo; Group K1, Group K3, and Group K5 received 0.1 mg/kg, 0.3 mg/kg, and 0.5 mg/kg of ketamine, respectively. Fifteen seconds after the ketamine injection, patients were injected with propofol at a rate of 12 mL/min until loss-of-eyelash reflex.

Measurement: Pain was evaluated blindly at the time of induction using a 4-point scale: 0 = no pain, 1 = mild pain, 2 = moderate pain, and 3 = severe pain. Adverse effects were recorded. Characteristics of induction of anesthesia, such as dose of propofol and time from propofol injection to loss of consciousness (induction duration), were noted.

Main Results: 39 (84.8%) Group S (control) patients had pain. Pretreatment with ketamine reduced the frequency of pain significantly to 56.5%, 17.0%, and 14.9% in Groups K1, K3, and K5, respectively. Furthermore, the frequency of moderate and severe pain in Group K1 (21.8%), Group K3 (6.4%), and Group K5 (4.3%) was significantly (P < 0.001, respectively) reduced compared with Group S (76.1%). Moreover, the dose of propofol for induction in Group K5 was smaller than in Group S, Group K1, and Group K3 (P < 0.05). One patient in Group K5 had emergence agitation.

Conclusion: Pretreatment with a small dose of ketamine (0.3 mg/kg) reduced the frequency and intensity of propofol injection pain without severe adverse effects.

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1. Introduction

Propofol is a popular general anesthetic due to its rapid onset and recovery. However, propofol injection induces
local pain and discomfort. The incidence of propofol injection pain may be as high as 85% in children [1].

Many strategies have been introduced to reduce propofol injection pain, including pretreatment with ketamine [2,3]. Ketamine provides potent analgesic and anesthetic effects. Pretreatment with ketamine at a dose of 0.5 mg/kg is effective in preventing propofol injection pain in children [4]; however, the high dose of ketamine is likely to increase the risk of laryngospasm, emergence agitation, or other side effects.

A small dose of ketamine, 0.1 mg/kg, is effective in preventing propofol injection pain in adults [2,5,6]. However, this dose has not been studied in children. Therefore, we designed this prospective, randomized, double-blinded, placebo-controlled study to determine the optimal dose of ketamine required for reducing the frequency of injection pain in children.

2. Materials and methods

2.1. Patients

The study was approved by the Ethics Committee of China Medical University. Written, informed consent was obtained from the parents of the children. One hundred ninety-two ASA physical status 1 and 2 children, aged 3-10 years, who were scheduled for elective orthopedic and urologic procedures with general anesthesia, were recruited. Patients with cardiac, pulmonary, or liver disease, or neurological deficits were excluded. Crying children and patients who had received anesthetics or sedatives within 24 hours of surgery also were excluded. The individual body weight of patients was ≤ 40 kg.

No sedative premedication was given before induction. Patients were fasted for 6 to 8 hours. Only clear liquids were allowed up to two hours before induction of anesthesia. A 22-gauge cannula was inserted into the vein on the dorsum of the hand without any local anesthetic.

2.2. Randomization and interventions

Electrocardiogram, pulse oximeter, and noninvasive blood pressure (BP) monitors were attached. Atropine at a dose of 0.01 mg/kg was administered intravenously (IV) 5 minutes before anesthetic induction. Patients were randomized to 4 groups (n = 48 in each group). Children in Group S (control) received 2.0 mL of 0.9% normal saline; children in Groups K1, K3, and K5 received 0.1 mg/kg, 0.3 mg/kg, and 0.5 mg/kg, respectively, of a racemic mixture of ketamine (ketamine hydrochloride; Heng Rui Co, Lianyungang, China). The total volume in each group was 2.0 mL, diluted with normal saline. One percent solution of propofol (Diprivan 1%; Zeneca, Ltd., Macclesfield, Cheshire, UK) was injected 15 seconds later through a three-way stopcock directly connected to the IV catheter at a rate of 200 μL/sec by syringe pump, until loss-of-eyelash reflex.

All drugs were prepared and stored at ambient temperatures (20°C - 22°C), and used within 10 minutes of preparation. Patients and the doctor who assessed pain severity were blinded to the nature of the drugs being administered.

Injection pain was recorded every 5 seconds during propofol injection in all children. Injection pain was assessed using a 4-point behavioral pain scale proposed by Cameron et al [7], where 0 = no pain, 1 = mild pain (grimace), 2 = moderate pain (grimace + cry), and 3 = severe pain (cry + withdrawal). The highest pain score was recorded for each patient. Pain assessment was made from the beginning of the propofol injection to the point at which the patient lost consciousness. The investigators who assessed each patient’s pain scores and adverse events were unaware of treatment assignment. Crystalloids were administered at a maintenance rate according to each patient’s body weight.

All adverse effects such as laryngospasm and post-anesthesia emergence agitation were recorded. The primary outcome criterion was the frequency and severity of pain during injection of propofol. Secondary outcomes were cardiac and respiratory parameters, and adverse events during anesthesia induction and recovery. Baseline parameters were recorded. Heart rate and oxygen saturation (SpO2) were recorded every minute, while noninvasive BP was recorded every three minutes.

Before induction of anesthesia, the number of patients with a 20% change in heart rate (HR) and/or mean arterial pressure (MAP) was recorded, and desaturation was defined as SpO2 below 92%. Characteristics of induction of anesthesia, such as dose of propofol and time from propofol injection to loss of consciousness (duration of induction) were recorded.

Fentanyl (2.0 μg/kg) was administered for intraoperative analgesia. Vecuronium was given for muscle relaxation as required. Isoflurane (1.0% ~ 2.0%) together with nitrous oxide (N2O) 50% in oxygen (O2) was given for maintenance. At the end of anesthesia, an experienced nurse who was blinded to the study treatments checked for abnormal behavioral responses, including hallucinations, illusions, and delirium. Duration of surgery and anesthetic recovery were recorded.

2.3. Statistical analysis

The frequency of pain after IV propofol was assumed at 80% in children, based on previous studies [3,4]. To achieve a discriminating power of 80% with a two-sided alpha-level of 5%, a sample size of 48 patients in each group was sufficient.

All data are expressed as means ± SD, medians, or absolute numbers (%). Continuous data were compared by one-way analysis of variance and least significant difference multi-comparison or Kruskal-Wallis test, which was
normally distributed, as determined by the Kolmogorov-Smirnov test. Categorical data were compared by $\chi^2$ or Fisher’s Exact test, as appropriate. A $P$-value $\leq 0.05$ was considered significant (two-tailed). Whenever significant discrepancies in the frequency of pain and adverse effects appeared, each group was compared separately with others so as to analyze the differences with Bonferroni correction when appropriate. A corrected $P$-value of 0.05 was considered significant. All statistical analyses were performed with Statistical Package for Social Sciences version 13.0 software (SPSS, Inc., Chicago, IL, USA).

3. Results

Of the 192 children who were originally enrolled in the study, 6 children were excluded from the final analysis because of a disconnection of venous cannulation (three children) and distress prior to propofol injection (three children), which rendered pain assessment impossible. Hence, data from 186 patients are presented. No significant differences in demographic data, duration of surgery, or duration of recovery were noted among the 4 groups (Table 1).

The frequency of propofol injection pain (pain score of 2 or more) in Group S (39/46, 84.8%) was higher than in Group K1 (26/46, 56.5%), Group K3 (8/47, 17.0%), and Group K5 (7/47, 14.9%), respectively ($P < 0.001$).

Pain severity in Group S was significantly higher than it was in Groups K1, K3, and K5 ($P < 0.001$, respectively). Most pain (76.1%) in Group S was moderate or severe. Furthermore, the frequency of moderate and severe pain in Group K1 (21.8%), Group K3 (6.4%), and Group K5 (4.3%) was significantly ($P < 0.001$, respectively) reduced compared with that in Group S (76.1%). Pain severity in Group K1 was significantly higher than in Groups K3 and K5 ($P = 0.001$ and $P < 0.001$, respectively). There were no significant differences in frequency or severity of pain between Groups K3 and K5 ($P = 0.778$ and $P = 0.847$, respectively). The median score in different groups is shown in Table 2; Group S had the highest median score, or 2 ($P < 0.001$).

Changes in HR during induction of anesthesia were less than 20% in all children. During induction of anesthesia, 5 of 46 Group S children (10.9%) developed hypotension.
Ketamine and pediatric profocol injection pain

Table 3 Characteristics of induction of anesthesia

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Group S (n = 46)</th>
<th>Group K1 (n = 46)</th>
<th>Group K3 (n = 47)</th>
<th>Group K5 (n = 47)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Propofol dose (mg/kg)</td>
<td>4.0 ± 1.2 *</td>
<td>3.9 ± 1.3 *</td>
<td>4.0 ± 1.4 *</td>
<td>3.4 ± 1.0</td>
</tr>
<tr>
<td>Duration of induction (sec)</td>
<td>40.4 ± 13.1 *</td>
<td>39.8 ± 10.8 *</td>
<td>40.5 ± 14.0 *</td>
<td>34.0 ± 9.7</td>
</tr>
</tbody>
</table>

Data are means ± SD.

Group S received normal saline 15 seconds before propofol injection; Group K1 received 0.1 mg/kg of ketamine 15 seconds before propofol injection; Group K3 received 0.3 mg/kg of ketamine 15 seconds before propofol injection; Group K5 received 0.5 mg/kg of ketamine 15 seconds before propofol injection.

* P < 0.05 vs Group K5.

frequency of desaturation in Group S, Group K1, Group K3, and Group K5 was 13%, 10.9%, 8.5%, and 12.8%, respectively (P > 0.05; Table 2).

The doses of propofol used for induction were lower in Group K5 than those in Group S, Group K1, and Group K3 (P = 0.028, P = 0.03, and P = 0.022, respectively). The induction durations were less in Group K5 than in Groups S, K1, and K3 (P = 0.010, P = 0.018, and P = 0.008, respectively; Table 3).

One 6-year old girl in Group K5 had postanesthesia emergence agitation during recovery. No study patient from any group suffered from laryngospasm during induction of anesthesia.

4. Discussion

Pretreatment with ketamine at a dose of 0.1 mg/kg significantly reduced the frequency of propofol injection pain compared with control. Furthermore, increasing the dose of ketamine to 0.3 or 0.5 mg/kg significantly reduced the severity of propofol injection pain without increasing side effects such as laryngospasm in pediatric patients.

Propofol (2, 6-diisopropyl phenol) injection pain is a clinical issue [8]. Physical and pharmacological approaches have been proposed to reduce propofol injection pain. These attempts include pretreatment or premixture of propofol with lidocaine [4,9], ketamine [3,4], thiopental sodium [10], N2O [11], opioid [12], cooling [13], diluting the propofol solution [14], or changing the propofol formulation [15]. However, none of these strategies is very effective in eliminating the pain completely.

Propofol injection pain is associated with kinin release due to the direct irritation of venous endothelia [16]. As a noncompetitive N-Methyl-D-aspartate (NMDA) receptor antagonist [17], ketamine may attenuate pain caused by propofol through the blockade of NMDA receptor activation either in the vascular endothelium or in the central nervous system. When administered for IV regional anesthesia, ketamine has potent analgesic and local anesthetic properties [18]. The application of ketamine at small doses for reducing propofol-associated injection pain has been reported both in adults [2,5,6] and in children [3,4]. In adults, the incidence of propofol injection pain was 26% ~ 46.7% after pretreatment with ketamine without venous occlusion. In contrast, 8% of children had propofol injection pain after ketamine injection [3]. The different dosages of ketamine used in pediatric (0.5 mg/kg) [3] and adult (0.1 - 0.2 mg/kg) patients may have contributed to this discrepancy.

One limitation of previous studies is that the effect of a lower dose of ketamine such as 0.1 or 0.2 mg/kg was not investigated. Therefore, we performed this study to determine the appropriate dose of ketamine for reducing propofol injection pain during induction of anesthesia.

The frequency of propofol injection pain was 14.9% after pretreatment with ketamine at a dose of 0.5 mg/kg in the current study, which was higher than the 8% noted in a previous study [3]. The most likely explanations for the differences in the frequency of pain during propofol injection between our study and the previous study are: different study protocols used. In the earlier study, ketamine was injected 45 seconds before the propofol injection [3], while in our study ketamine was injected 15 seconds before the propofol injection. Also, the median age of patients was 9 years in the previous study [3] and 5 years in our study. Propofol injection pain is more likely to occur in younger patients as a result of the smaller size of the accessible veins [7].

Ketamine may induce dose-related analgesia and unconsciousness. The analgesic effect of ketamine usually occurs at smaller doses, while the anesthetic effect usually occurs at higher doses [19]. The doses of propofol given for induction were smaller in Group K5 than in the other groups. Furthermore, induction duration was less in Group K5 than in the other groups. It is likely that a 0.5 mg/kg ketamine dose may have some central effects. Indeed, one child in Group K5 experienced emergence agitation.

Ketamine dose is one of the important factors that affect the frequency of emergence agitation in children. Ketamine is associated with adverse psychological effects and several other side effects at significantly higher doses [20]. The small doses of ketamine used in the current study may have accounted for the very low frequency of these side effects. In the control group, 5 children experienced hypotension after propofol injection. However, there was no hypotension in the ketamine groups. One explanation is that ketamine may activate the sympathetic nervous system. As a consequence, BP was increased [21,22], which may have abolished the hypotensive effect of the propofol injection in our study.
One limit of the current study was the absence of a tourniquet. Although venous occlusion with a rubber tourniquet provided a useful model for exclusion of a central effect [23], children do not tolerate a tourniquet. We were thus unable to rule out the possible central role of ketamine in reducing propofol injection pain [24,25].

In summary, pretreatment with ketamine at a dose of 0.3 mg/kg reduces the frequency and intensity of propofol injection without significant adverse effects.

References
