Comparative evaluation of the effect of remifentanil and 2 different doses of esmolol on pain during propofol injection
A double-blind, randomized clinical consort study

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Abstract
Background: Propofol is associated with pain during injection, which is stressful to patients. The present study was designed to investigate the analgesic effect of pretreatment with remifentanil and esmolol in minimizing propofol injection pain, compared with placebo.

Methods: In a randomized, double-blind, prospective trial, 120 patients, scheduled for elective dental surgery under general anesthesia, were randomized to 1 of the 4 treatment arms (n = 30 each) receiving normal saline, remifentanil 0.35 μg/kg, esmolol 0.5 mg/kg, and 1 mg/kg before administration of propofol. During injection of 1% propofol 0.5 mg/kg, pain was evaluated by a 4-point score (0 = none, 1 = mild, 2 = moderate, 3 = severe). Any adverse effects such as hypotension and bradycardia were recorded during the perioperative periods.

Results: In all, 120 patients completed this study. There were no significant differences in terms of demographic data. The incidence of pain on injection of propofol was 11 (36.7%) with remifentanil 0.35 μg/kg, 12 (40%) with esmolol 0.5 mg/kg, and 11 (36.7%) with esmolol 1 mg/kg, compared with 25 (83.3%) with normal saline (respectively, P < 0.05). There were no significant differences in the incidence of pain between groups with remifentanil 0.35 μg/kg, and esmolol 0.5 mg/kg and 1 mg/kg. There were no emergence reactions such as hypotension and bradycardia in all groups.

Conclusions: Pretreatment with esmolol 0.5 mg/kg and 1 mg/kg and remifentanil 0.35 μg/kg equally decreased pain during propofol injection.

Abbreviations: LCT = long-chain triglyceride, MCT = medium-chain triglyceride, NMDA = N-methyl-d-aspartate.

Keywords: esmolol, injection, intravenous, pain, propofol, remifentanil

1. Introduction

Propofol is a short-acting intravenous hypnotic agent, which is widely used for sedation and general anesthesia. However, pain during injection of propofol can occur in up to 80% of patients, which can be very stressful to patients.\(^{1–3}\) Many methods including cooling or diluting the propofol solution or the concomitant use of drugs such as methylene blue, pregabalin, or magnesium sulfate have been used to reduce this pain.\(^{1–3}\) However, these treatments cannot alleviate the pain, which remains a challenge. It was reported that aqueous free propofol could be responsible for injection pain. Therefore, propofol long-chain triglycerides (LCTs)/medium-chain triglycerides (MCTs) were introduced to minimize injection pain, which has less concentration of aqueous free propofol than propofol-LCT.\(^{4}\) This new formulation of propofol is more expensive than standard propofol. However, pain on injection still occurs despite use of propofol-LCT/MCT.\(^{5,6}\)

Remifentanil is a potent, short-acting intravenous opioid. Pretreatment with small dose of remifentanil has been demonstrated to be effective in reducing pain from propofol injection without side effects.\(^{7,8}\) Esmolol, a short-acting β1 adrenergic receptor antagonist, is widely used to reduce cardiovascular stress response to laryngoscopy and tracheal intubation.\(^{9–11}\) It was shown that perioperative infusion of esmolol reduced anesthetic requirement for surgery\(^ {12}\) and postoperative analgesic consumption.\(^{13,14}\) Recently, it was reported that pretreatment with esmolol 0.5 mg/kg has analgesic effect on rocuronium injection pain without side effects.\(^ {14}\)

The present study was designed to compare the analgesic effect of pretreatment with remifentanil 0.35 μg/kg, and esmolol 0.5 mg/kg and 1 mg/kg in minimizing pain during injection of propofol-LCT, compared with placebo.

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The authors have no competing interests to disclose.

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2. Methods

2.1. Patients and exclusion criteria
In all, 120 patients aged 18 to 70 years, American Society of Anesthesiologists physical status I and II, scheduled for elective dental surgery requiring general anesthesia were included. We excluded patients who have cardiac, neurologic or psychiatric problem, patients who had analgesic or sedative agents within 24 hours before surgery, and patients requiring a rapid sequence induction.

2.2. Anesthesia and data collection
The present study was approved by the Ethics Committee of Kyungpook National University Hospital (KNUH 2013–05–003–001) and informed written consent was obtained from all patients. This study was registered in the ClinicalTrials. GOV (NCT01885364). Premedication was not given. On arrival in the operating room, electrocardiogram, noninvasive blood pressure, and pulse oximetry were measured, and a 22-gauge catheter was inserted into a dorsal vein of the patient’s nondominant hand. Using a computer-generated table, patients were randomized to 1 of the 4 treatment arms (n = 30 each) receiving normal saline, remifentanil 0.35 mg/kg, esmolol 0.5 mg/kg and 1 mg/kg as pretreatment. A study-blinded nurse prepared pretreatment substance using identically coded syringes at room temperature. Pretreatment substances were injected over 10 seconds. Thirty seconds after injection of pretreatment drug, patients received propofol-LCT 0.5 mg/kg at rate of 0.5 mL/sec using syringe pump. A study-blinded anesthesiologist measured score of injection pain of propofol using a 4-point scale (0 = none [negative response to questioning], 1 = mild pain [pain reported in response to questioning only, without any behavioral sign], 2 = moderate pain [pain reported in response to questioning and accompanied by a behavioral sign, or pain reported simultaneously without questioning], 3 = severe pain [strong vocal response or response accompanied by facial grimacing, arm withdrawal or tears]).[2] Thereafter, propofol-LCT 1.5 mg/kg and rocuronium 0.8 mg/kg were administered for tracheal intubation, and anesthesia was maintained with desflurane 4% to 7% in 50% N₂O/O₂. Emergence reactions associated with pretreatment substances such as hypotension and bradycardia were recorded. In the present study, the incidence and severity of pain after propofol injection was the primary outcome, and all other variables were secondary outcomes.

2.3. Sample size
On the basis of previously published data,[1] we estimated the incidence of pain during propofol injection in the placebo group to be around 80%. A 40% difference (80%–40%) between placebo group and treatment groups would be considered of clinical significance. Using a 2-tailed test of the proportions with α error of 0.05 and β error of 0.8, 30 patients per group were required to detect such difference.

2.4. Statistical analysis
Data were analyzed using statistical software (SPSS, version 23.0 for Windows; SPSS, Chicago, IL). The factorial analysis of variance was used for age and weight. Fisher exact test or the chi-square test was used for sex, incidence of pain, and incidence of side effects. P < 0.05 was considered to indicate statistical significance. SPSS (version 16.0) was used for statistical analysis.

3. Results
In all, 120 patients completed the study (Fig. 1). There was no difference in demographic data between groups (Table 1). The overall incidence of pain after propofol injection is demonstrated in Table 2. The incidence of pain during propofol injection was significantly reduced with remifentanil 0.35 µg/kg (36.7%), esmolol 0.5 mg/kg (40%) and 1 mg/kg (36.7%), compared with placebo group (83.3%) (respectively, P < 0.05). In addition, pretreatment with remifentanil (3.3%), and esmolol 0.5 mg/kg (3.3%) and 1 mg/kg (3.3%) significantly decreased the incidence...
of severe injection pain, compared with placebo (26.7%), respectively, P < 0.05. There were no emergence reactions associated with pretreatment substances such as hypotension and bradycardia in all groups.

4. Discussion

This study showed that pretreatment with remifentanil 0.35 μg/kg, and esmolol 0.5 mg/kg and 1 mg/kg, was equally effective to reduce pain during propofol injection, compared with placebo. Propofol formulated in a lipid emulsion is widely used in various clinical procedures. But propofol is associated with high incidence of pain after propofol injection, which can generally be reduced by pretreatment with a small dose of opioids halved the incidence of injection pain. By a systemic review and meta-analysis in 2011, both propofol-LCT/MCT and propofol-LCT had similar incidence of pain from propofol injection. By pretreatment substances such as remifentanil and esmolol can cause dose-dependent decrease in blood pressure and heart rate. Therefore, a placebo group was included to investigate the adverse effect of the pretreatment substances. In the present study, there were no emergence reactions associated with pretreatment with remifentanil 0.35 μg/kg and 1 mg/kg and remifentanil 0.35 μg/kg equally decreased pain during propofol injection.

The incidence of pain when propofol was injected into the veins can reach as high as 80%. It was considered unethical to use placebo in this study. Pretreatment substances such as remifentanil and esmolol can cause dose-dependent decrease in blood pressure and heart rate. Therefore, a placebo group was included to investigate the adverse effect of the pretreatment substances. In the present study, there were no emergence reactions associated with pretreatment with remifentanil 0.35 μg/kg and 1 mg/kg and remifentanil 0.35 μg/kg equally decreased pain during propofol injection.

5. Conclusions

In conclusion, pretreatment with esmolol 0.5 mg/kg and 1 mg/kg, and remifentanil 0.35 μg/kg were equally effective in reducing pain during injection of propofol without adverse effects.
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