

Comparative evaluation of the effect of remifentanyl and 2 different doses of esmolol on pain during propofol injection

A double-blind, randomized clinical consort study

Myunghwan Lee, DDS^a, Taegeon Kwon, DDS^a, Sujin Kim, MD^b, Saeyoung Kim, MD^b, Kibum Park, MD^c, Younghoon Jeon, MD^{a,b,*}

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 remifentanyl 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, remifentanyl 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 remifentanyl 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 remifentanyl 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 remifentanyl 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, remifentanyl

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]

Remifentanyl is a potent, short-acting intravenous opioid. Pretreatment with small dose of remifentanyl has been demonstrated to be effective in reducing pain from propofol injection without side effects.^[7,8] Esmolol, a short-acting β_1 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.^[15]

The present study was designed to compare the analgesic effect of pretreatment with remifentanyl 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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^a Department of Oral and Maxillofacial surgery, School of Dentistry, ^b Department of Anesthesiology and Pain Medicine, Kyungpook National University Hospital,

^c Department of Anesthesiology and Pain Medicine, Keimyung University Dongsan Hospital, Daegu, Republic of Korea.

* Correspondence: Younghoon Jeon, Department of Oral and Maxillofacial Surgery, Department of Anesthesiology and Pain Medicine, School of Dentistry, Kyungpook National University, 130 Dongduck-ro, Jung-gu, Daegu 41944, Republic of Korea (e-mail: jeon68@gmail.com).

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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, remifentanyl 0.35 µg/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 remifentanyl 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 remifentanyl (3.3%), and esmolol 0.5 mg/kg (3.3%) and 1 mg/kg (3.3%) significantly decreased the incidence

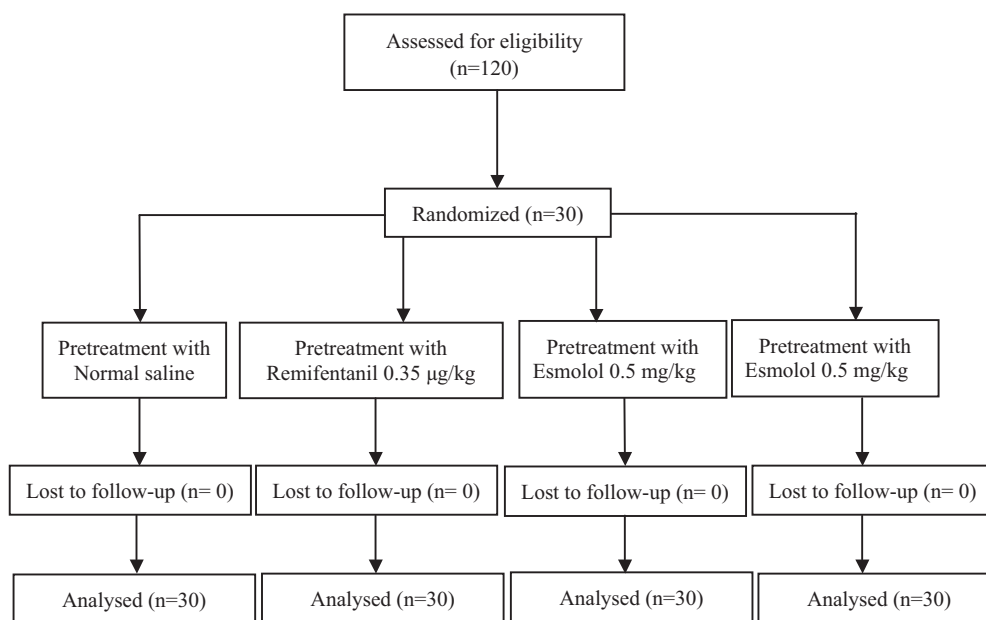


Figure 1. Flow diagram of the study.

Table 1
Demographic characteristics of the study population (n = 120).

	Treatment group			
	Normal saline (n = 30)	Remifentanil 0.35 µg/kg (n = 30)	Esmolol 0.5 mg/kg (n = 30)	Esmolol 1 mg/kg (n = 30)
Age, y	43.5 ± 15.2	42.4 ± 17.2	42.8 ± 17.5	43.1 ± 16.5
Sex (male/female)	13/17	14/16	13/17	12/18
Height, cm	167.8 ± 7.4	165.5 ± 6.8	166.3 ± 7.1	166.8 ± 6.6
Weight, kg	65.5 ± 8.5	63.3 ± 7.5	63.7 ± 7.2	64.2 ± 6.6

All values are expressed as mean ± standard deviation or numbers.

Table 2
Incidence and pain severity during injection of propofol.

Pain severity	Treatment group			
	Normal saline (n = 30)	Remifentanil 0.35 µg/kg (n = 30)	Esmolol 0.5 mg/kg (n = 30)	Esmolol 1 mg/kg (n = 30)
None	5 (16.7%)	19 (63.3%)*	18 (60%)*	19 (63.3%)*
Mild	7 (23.3%)	7 (23.3%)	8 (26.7%)	7 (23.3%)
Moderate	9 (30%)	3 (10%)	3 (10%)	3 (10%)
Severe	8 (26.7%)	1 (3.3%)*	1 (3.3%)*	1 (3.3%)*
Incidence of pain	25 (83.3%)	11 (36.7%)*	12 (40%)*	11 (36.7%)*

All values were expressed as number (%).

* Statistically significant difference compared with normal saline ($P < 0.05$).

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 at injection site, which is often very stressful to patients.^[1–3] The exact mechanism of pain on propofol injection is unknown. The direct exposure of nociceptive receptors or free nerve ending in the vein by free propofol can increase the pain on injection.^[16,17] Propofol-LCT/MCT was specially proposed to decrease injection pain. Varghese et al^[18] reported that when added with lidocaine, both propofol-LCT/MCT and propofol-LCT had similar incidence of injection pain. By a systemic review and meta-analysis in 2011, pretreatment with a small dose of opioids halved the incidence of pain after propofol injection, which can generally be recommended.^[19] The previous study demonstrated that pretreatment with remifentanil 0.35 µg/kg reduced injection pain of propofol by 38.8% without any side effects.^[8,19] In the present study, the incidence of pain from propofol injection was 33.3% in the patients who received remifentanil 0.35 µg/kg, which is consistent with the previous study.^[8]

Esmolol, antagonist of β1 adrenergic receptor, is often used to blunt adrenergic response to perioperative stimuli.^[10–14,20] It was demonstrated that a single injection of esmolol 1 to 2 mg/kg is effective to attenuate the increase of heart rate after intubation without adverse effects.^[10] In the previous studies, intraoperative infusion of esmolol decreased the requirement of opioid and inhalation anesthetic without causing hemodynamic change,^[12] and reduced postoperative analgesic consumption.^[13,14] Up to date, the exact analgesic mechanism of β adrenergic receptor antagonist remains unclear. Adrenal hormone, commonly

known as stress hormone, increases during emotional distress and anxiety, which are associated with activation of hippocampal neurons.^[21,22] β adrenergic receptors are involved in learning-facilitated plasticity in the mammalian hippocampus, which requires activation of N-methyl-D-aspartate (NMDA) receptor.^[23,24] The activation of NMDA receptor in the hippocampus is involved in nociceptive processing, at least, in part. Therefore, esmolol with lipophilic property can decrease adrenergic activity in the hippocampus.^[25] In addition, it was found that esmolol can facilitate inhibitory transmitter release in spinal trigeminal nucleus, which produces analgesic effects.^[26] In the present study, pretreatment with esmolol 0.5 mg/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 vein of the dorsum of hand can reach as high as 80%.^[1,19] Therefore, 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 esmolol 0.5 mg/kg and 1 mg/kg. These results were compatible with the previous studies.^[8,10]

The present study had some limitations. In the present study, premedication, such as sedatives, was not given. This might increase the patient's anxiety and dissatisfaction about anesthetic care.^[27] The previous study showed that 87% of patients who did not receive anxiolytic premedication reported the recall about injection pain after propofol injection.^[28] Therefore, another study is needed to examine the patient's satisfaction about anesthetic care and the incidence of recall for 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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