Comparison of Effect of Premixed Lidocaine in Propofol With or Without Ketorolac Pretreatment With Placebo on Reducing Pain on Injection of Propofol: A Prospective, Randomized, Double-Blind, Placebo-Controlled Study in Adult Korean Surgical Patients

Jinseok Yeo, MD; Younghoon Jeon, MD; Youngsoo Kim, MD; Jaehyun Ha, MD; and Woonyi Baek, MD

Department of Anesthesiology and Pain Medicine, School of Medicine, Kyungpook National University, Daegu, Republic of Korea

ABSTRACT

BACKGROUND: Pain on injection of propofol is a common adverse event.

OBJECTIVE: The aim of this study was to investigate the effect of a combination of ketorolac pretreatment and premixed lidocaine in propofol compared with placebo on propofol injection pain.

METHODS: In this prospective, randomized, double-blind, placebo-controlled study, Korean patients scheduled for elective plastic surgery were randomized to 1 of 3 groups. Group A received 15 mg ketorolac in saline IV as pretreatment. Groups B and C received 3 mL saline IV as pretreatment. Sixty seconds after pretreatment, groups A and B received a mixture of lidocaine 1% in propofol 1% at a 1:10 ratio and group C received propofol 1% alone. Pain during propofol injection was assessed on a 4-point scale (0 = none, 1 = mild, 2 = moderate, 3 = severe).

RESULTS: Ninety patients (41 men, 49 women; mean age, 41.7 years; mean weight, 63 kg) completed the study. The overall incidence of pain on propofol injection was significantly lower in groups A (16.7%) and B (36.7%) than in group C (83.3%; both, P < 0.001). There was no significant difference in the incidence of pain between groups A and B. However, the patients in group A reported a significantly lower incidence of moderate (0% vs 33.3%; P < 0.001) and severe pain (0% vs 20%; P = 0.024) compared with those in group C. There were no significant differences in the incidences of moderate and severe pain between the B and C groups.

CONCLUSIONS: In this Korean population, premixed lidocaine in propofol with or without ketorolac pretreatment was associated with significantly less pain when compared with placebo. The combination of ketorolac pretreatment and premixed lidocaine in propofol was more effective in decreasing the incidence of moderate or severe pain compared with placebo. (Curr Ther Res Clin Exp. 2009;70:351–358) © 2009 Excerpta Medica Inc.

KEY WORDS: propofol, complication, pain, lidocaine, ketorolac.
INTRODUCTION

Propofol is a popular anesthetic induction drug that can cause considerable discomfort or pain on injection.\textsuperscript{1,2,3} During induction of anesthesia, \textasciitilde 37.5\% to \textasciitilde 90.0\% of patients experience pain on propofol injection when a vein on the dorsal of the hand is used. Many methods have been proposed to reduce the incidence of pain on propofol injection, including varying injection speed and carrier fluid, adjusting dilution temperature, and adding other concomitant drugs.\textsuperscript{4-8}

Peripheral veins are innervated with polymodal nociceptors that mediate the responses to an injection that cause pain.\textsuperscript{9} Pain on injection of propofol can be immediate or delayed. Immediate pain may result from a direct irritant effect, whereas delayed pain may be caused by an indirect effect via kinin cascade.\textsuperscript{10,11} A high concentration of free propofol in the aqueous phase of an emulsion activates the kallikrein-kinin system in plasma, liberating bradykinin. Bradykinin acts on the local vein to dilate it and make it permeable. In this bradykinin-modified vein, the aqueous phase of propofol may contact more free nerve endings outside the endothelial layer of the vessel, causing pain.\textsuperscript{12}

Although the exact cause of propofol injection pain remains unknown, the direct irritant effect of propofol and the activation of the plasma kallikrein-kinin cascade have been suggested.\textsuperscript{13,14} Some research has theorized that pain on propofol injection may be reduced by administration of an NSAID and venous occlusion of the forearm with a tourniquet for 2 minutes before injection.\textsuperscript{13,14} It was theorized that venous occlusion was necessary to keep the NSAID in the vein long enough to produce the postulated localized antiprostaglandin effect and reduce the release of kininogens.\textsuperscript{13,14} However, although the venous occlusion technique allows time for the NSAID to mediate its analgesic effect at the peripheral site, increasing the tourniquet time may result in greater discomfort to the patient.\textsuperscript{15}

One well-accepted technique is the use of a premixture of lidocaine in propofol.\textsuperscript{7,8,16} Mixing lidocaine with propofol has been reported to reduce injection pain.\textsuperscript{7,8,16} Lidocaine may act by local anesthetic effect on the vein and by stabilizing the kinin cascade.\textsuperscript{7} However, the incidence of pain has been reported to be between 25.7\% and 48.9\% despite the addition of lidocaine.\textsuperscript{7,8,16,17}

Yamakage et al\textsuperscript{16} reported that premixing lidocaine in propofol did not decrease free propofol concentration, suggesting that lidocaine acts mainly through inhibition of pain transmission. King et al\textsuperscript{16} observed that 20 mg of lidocaine premixed in 200 mg propofol significantly reduced the incidence of injection pain from 73\% to 32\%. Tan and Hwang\textsuperscript{8} reported that the incidence of propofol injection pain was reduced to 25.7\% in their study population using a mixture of lidocaine 1\% and propofol 1\% at a 1:10 ratio.

A few studies have investigated the effect of ketorolac in preventing pain on propofol injection. Kotorolac, a potent cyclooxygenase inhibitor that blocks prostaglandin production, is widely used for postoperative analgesia.\textsuperscript{18} Yull et al\textsuperscript{14} reported that the incidence of severe pain due to propofol injection was reduced by administration of 10 mg ketorolac with venous occlusion for 2 minutes. The same dose of ketorolac without venous occlusion did not decrease the incidence of pain. Huang et al\textsuperscript{19} observed that pretreatment with either 15 or 30 mg ketorolac without venous occlusion
achieved the same pain relief effect of ketorolac 10 mg IV with venous occlusion. However, injection pain still occurred at a rate of 23.3%.

Recently, combination treatment with partially effective drugs has been suggested for the prevention of injection pain.\textsuperscript{15,17,20} No studies were identified that assessed the efficacy of the combination of ketorolac pretreatment and premixture of lidocaine in propofol on preventing pain on injection. Therefore, this study was designed to investigate the analgesic effect of the combination of ketorolac pretreatment without a tourniquet and premixed lidocaine in propofol, compared with premixed lidocaine in propofol alone (positive control group) and placebo (negative control group) during propofol injection.

**PATIENTS AND METHODS**

This prospective, randomized, double-blind, placebo-controlled study was approved by the Institutional Review Board of Kyungpook National University Hospital, Daegu, Republic of Korea, and was conducted between December 2008 and January 2009. Eligible patients were scheduled for elective plastic surgery under general anesthesia and met American Society of Anesthesiologists Physical Status Classification I (no organic, physiologic, biochemical, or psychiatric disturbance) or II (mild to moderate systemic disturbance that may or may not be related to the reason for surgery). Written informed consent was obtained. Patients who had sensitivity to NSAIDs or propofol; were currently taking NSAIDs; or had asthma, a coagulation disorder, or renal or cardiac problems were excluded. The study was limited to adult patients aged 18 to 75 years.

After arrival in the operating room, a 20 G intravenous catheter was inserted on the dorsum of the nondominant hand and a 3-way tap was directly connected to the catheter. Administration of Ringer’s lactate 5 mL/kg/h was started after injection of study drugs or test substances. Patient monitoring consisted of pulse oximetry, ECG, and noninvasive blood pressure.

Patients were randomized to 1 of 3 groups using a sealed-envelope technique in the preoperative holding area. Ninety sealed envelopes, each containing the name of 1 of the 3 treatment groups, were prepared before the initiation of the study. An anesthesiologist who was not involved in this study selected an envelope for each patient. Patients in group A received 15 mg ketorolac plus 2.5 mL 0.9% saline IV (total volume 3 mL) as pretreatment, based on dosing used in a previous study.\textsuperscript{19} Patients randomized to groups B and C received 3 mL 0.9% saline IV as pretreatment. All pretreatment substances were injected over 15 seconds and were administered 60 seconds before propofol injection. The running carrier fluid was stopped before any study drugs or test substances were administered.

Sixty seconds after pretreatment, propofol 2 mg/kg was administered at a rate of 2.5 mg/s. Patients in groups A and B received 2 mg/kg of premixed lidocaine 1% in propofol 1% in a 1:10 ratio at a rate of 990 mL/h by an infusion pump. Patients in group C received 1% propofol alone at a rate of 900 mL/h.\textsuperscript{17}

The dose of premixed lidocaine in this study was determined based on previous research.\textsuperscript{8,16,17} Because the addition of lidocaine may lead to destabilization of the
propofol solution in a dose- and time-dependent manner, the mixture was used within 30 minutes of preparation. An anesthesiologist who was not involved in this study prepared the drugs before injection at room temperature and programmed the infusion pumps in the absence of the blinded observer. The infusion pump was completely hidden from the blinded observer's view by an opaque cover.

The same blinded investigator evaluated the level of pain on injection of propofol during the study. Pain scores were recorded using a verbal rating 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). If there was no spontaneous complaint of pain 10 seconds after the start of the injection, patients were repeatedly asked if they felt any pain in the arm until they could not respond. The anesthesia was continued with an appropriate technique at the discretion of the attending anesthesiologist. Patients were monitored every 8 hours for 24 hours after surgery for adverse events at the injection site (eg, pain, edema, wheal, flare response) by an anesthesiologist blinded to the patient's group assignment.

Statistical Analyses

Based on identified published studies, we estimated the incidence of pain in patients receiving placebo to be ~80%. We considered a reduction in the incidence of pain by half (from 80% to 40%) to be clinically significant. Based on an error of 0.05 and a error of 0.2, a minimum sample size of 30 patients per group was estimated to be necessary to detect a significant difference. Statistical analyses were performed with factorial ANOVA for age, weight, and height, and with the test for sex and incidence of pain. Pain intensity scores were compared using the Kruskal-Wallis test. Significance was established at . The number needed to treat was calculated. Data were expressed as mean (SD), number (%), or median, as appropriate. All statistical analyses were conducted using SPSS software version 12.0 (SPSS Inc., Chicago, Illinois).

RESULTS

A total of 90 patients, 41 men and 49 women aged 19 to 60 years (mean age, 41.7 years; mean weight, 63 kg), were enrolled. Groups were similar with regard to age, weight, height, gender, and American Society of Anesthesiology Physical Status Classification (Table I). The overall incidence and severity of pain on propofol injection in the 3 groups is shown in Table II. The incidence of pain was significantly lower in patients in group A (16.7%) or B (36.7%) than in group C (83.3%; both, ). The median pain score was 0 in groups A and B compared with a median pain score of 2 in group C (both, ). There was no significant difference in the incidence of pain between groups A and B. The combination of ketorolac pretreatment and premixed lidocaine (group A) had a significantly lower incidence of moderate (0% vs 33.3%; ) and severe pain (0% vs 20%; ) compared with those in the placebo group (group C). However, there were no significant differences
### Table I. Demographic characteristics of Korean patients undergoing elective plastic surgery (N = 90).*

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Group A (Ketorolac + Lidocaine + Propofol) (n = 30)</th>
<th>Group B (NS + Lidocaine + Propofol) (n = 30)</th>
<th>Group C (NS + Propofol) (n = 30)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, mean (SD), y</td>
<td>42.0 (8.5)</td>
<td>42.5 (13.0)</td>
<td>40.5 (14.4)</td>
</tr>
<tr>
<td>Sex, no. (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>18 (60)</td>
<td>19 (63)</td>
<td>12 (40)</td>
</tr>
<tr>
<td>Male</td>
<td>12 (40)</td>
<td>11 (37)</td>
<td>18 (60)</td>
</tr>
<tr>
<td>Weight, mean (SD), kg</td>
<td>63 (11.7)</td>
<td>62 (7.4)</td>
<td>64 (7.4)</td>
</tr>
<tr>
<td>Height, mean (SD), cm</td>
<td>167 (8.4)</td>
<td>167 (10.0)</td>
<td>165 (7.9)</td>
</tr>
<tr>
<td>ASA physical status, no. (%)</td>
<td>17 (57)</td>
<td>16 (53)</td>
<td>20 (67)</td>
</tr>
<tr>
<td>I</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>II</td>
<td>13 (43)</td>
<td>14 (47)</td>
<td>10 (33)</td>
</tr>
</tbody>
</table>

NS = normal saline; ASA = American Society of Anesthesiologists.
*No significant between-group differences were observed.

### Table II. Incidence of pain on injection of propofol in Korean patients undergoing elective plastic surgery (N = 90).

<table>
<thead>
<tr>
<th>Variable</th>
<th>Group A (Ketorolac + Lidocaine + Propofol) (n = 30)</th>
<th>Group B (NS + Lidocaine + Propofol) (n = 30)</th>
<th>Group C (NS + Propofol) (n = 30)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients with pain, no. (%)</td>
<td>5 (16.7)*</td>
<td>11 (36.7)*</td>
<td>25 (83.3)</td>
</tr>
<tr>
<td>Pain score, median (range)</td>
<td>0 (0–1)*</td>
<td>0 (0–3)*</td>
<td>2 (0–3)</td>
</tr>
<tr>
<td>Grading of pain, no. (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>None (0)</td>
<td>25 (83.3)*</td>
<td>19 (63.3)*</td>
<td>5 (16.7)</td>
</tr>
<tr>
<td>Mild (1)</td>
<td>5 (16.7)</td>
<td>6 (20.0)</td>
<td>9 (30.0)</td>
</tr>
<tr>
<td>Moderate (2)</td>
<td>0*</td>
<td>4 (13.3)</td>
<td>10 (33.3)</td>
</tr>
<tr>
<td>Severe (3)</td>
<td>0†</td>
<td>1 (3.3)</td>
<td>6 (20.0)</td>
</tr>
</tbody>
</table>

NS = normal saline.
*P < 0.001 versus group C.
†P = 0.024 versus group C.
in the incidences of moderate (13.3% vs 33.3%) and severe pain (3.3% vs 20.0%) between groups B and C. The estimated number needed to treat to reduce pain on propofol injection in groups A and B was 1.5 and 2.1, respectively, compared with group C. There were no adverse events such as pain, edema, wheal, or flare at the injection site within 24 hours after surgery in any of the groups.

DISCUSSION

Although various methods to decrease pain on propofol injection have been investigated, there is no single method that entirely prevents this adverse event. Therefore, treatment with a combination of partially effective drugs has been suggested.\textsuperscript{15,17,20} In this study, combination therapy was more effective in decreasing the incidence of moderate or severe pain compared with placebo. There was no significant difference in the incidence of pain between the groups receiving the premixture of lidocaine in propofol with or without ketorolac pretreatment. Both groups had significant reduction in pain compared with placebo. However, the group pretreated with ketorolac (group A) had a greater reduction in the incidence of moderate and severe pain compared with placebo (group C).

Previous research has suggested that increasing the dose of an NSAID may provide more control of propofol injection pain.\textsuperscript{23} Therefore, the analgesic effect of increasing the dose of ketorolac in combination with lidocaine premixture on propofol injection pain should be investigated.

These findings should be considered within the context of the limitations of this study. First, we included the premixed lidocaine group as a positive control and the placebo group as a negative control. However, the difference in infusion rate of propofol between the groups may have affected the incidence of pain. Second, the sample size of this study was relatively small, and the exclusion criteria may limit the ability to extrapolate the results beyond the selected population.

CONCLUSIONS

In this Korean population, premixed lidocaine in propofol with or without ketorolac pretreatment was associated with significantly less pain when compared with placebo. The combination of ketorolac pretreatment and premixed lidocaine in propofol was more effective in decreasing the incidence of moderate or severe pain compared with placebo.

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REFERENCES


**Address correspondence to:** Younghoon Jeon, MD, Department of Anesthesiology and Pain Medicine, School of Medicine, Kyungpook National University, 200 Donduk-ro, Jung-gu, Daegu, 700-721, Republic of Korea. E-mail: jeon68@knu.ac.kr