

Comparative study between 2 different doses of pregabalin and lidocaine on pain following propofol injection

A double-blind, randomized clinical consort study

Eunkyung Choi, MD^a, Donggyeong Kim, MD^a, Younghoon Jeon, MD^{b,*}

Abstract

Background: Propofol, an intravenous anesthetic, often causes pain on injection, which can be very distressful to patients. We investigated the analgesic effect of pregabalin on pain following propofol injection, compared with lidocaine.

Methods: In a randomized, double-blind, prospective trial, 120 patients were randomized into 3 groups of 40 each; who received oral placebo and intravenous lidocaine 40mg with venous occlusion for 1 minute (group L, n=40), oral pregabalin 75 mg and intravenous normal saline with venous occlusion for 1 minute (group LP, n=40), and oral pregabalin 150 mg and intravenous normal saline with venous occlusion for 1 minute (group HP, n=40) as pretreatment, followed by administration of 1% propofol 0.5 mg/kg. Pain intensity was measured on a 4-point scale (0=no, 1=mild, 2=moderate, and 3=severe pain). Any side effects associated with pretreatment substances were recorded during the first 24 hours after surgery.

Results: A total of 120 patients completed this trial. Demographic data were similar between groups. The incidence of pain following propofol injection was significantly reduced in group HP (50%) and group L (55%) compared with group LP (92.5%) ($P < 0.05$, respectively). The incidences of moderate pain in group HP (12.5%) and group L (15%) were significantly decreased compared with group LP (37.5%; both, $P < 0.05$). There were no significant differences in the incidence of side effects such as headache and dizziness between groups.

Conclusion: Pretreatment with oral pregabalin 150 mg and intravenous lidocaine 40 mg with venous occlusion equally reduced pain from propofol injection.

Abbreviations: GABA = gamma-amino butyric acid, LCT = long-chain triglycerides, MCT = medium-chain triglycerides.

Keywords: injection, lidocaine, pain, pregabalin, propofol

1. Introduction

Propofol (2, 6-diisopropylphenol) is a widely used intravenous anesthetic agent to induce general anesthesia.^[1] However, pain following propofol injection is one of distressful adverse effects of propofol, which occurs in 60% to 80% of patients receiving propofol via peripheral vein on the dorsum of hand.^[2-4] Several methods including pretreatment with lidocaine with venous

occlusion or premixed lidocaine with propofol have been tried to attenuate pain during propofol injection. Among these methods, pretreatment with lidocaine with venous occlusion is the most effective method in preventing pain following propofol injection.^[5,6] However, unfortunately this treatment could not abolish the pain. It is reported that the amount of free propofol in the aqueous phase of the emulsion is positively associated with injection pain. Therefore, propofol long-chain triglycerides (LCT)/medium-chain triglycerides (MCT) was introduced in attempts to prevent injection pain by reducing the concentration of aqueous-free propofol.^[7] However, pain can occur up to 47% during injection of propofol-LCT/MCT.^[8] It was demonstrated that pretreatment with lidocaine with venous retention before injection of propofol LCT or lidocaine premixed in propofol LCT were more effective in reducing pain than a more expensive reformulation of propofol-LCT/MCT.^[8,9]

Pregabalin, a synthetic molecule derived from gamma-amino butyric acid (GABA) inhibitor, has anticonvulsant and analgesic effects. Pregabalin is recommended as first-line treatments for neuropathic pain disorders.^[10,11] In addition, this agent is known to be effective for treatment of incisional inflammatory pain. Many studies demonstrated that preoperative administration with pregabalin effectively decreased pain severity and opioid requirement after various surgeries.^[12,13] However, up to date, there is no study about the effect of pregabalin on pain following propofol injection. Therefore, we evaluated the effect of pretreatment with oral pregabalin 75 and 150 mg on pain from

Editor: Kazuo Hanaoka.

The authors have no conflicts of interest to disclose.

^a Department of Anesthesiology and Pain Medicine, School of Medicine, Kyungpook National University Hospital, ^b Department of Anesthesiology and Pain Medicine, School of Dentistry, Kyungpook National University, Daegu, Republic of Korea.

* Correspondence: Younghoon Jeon, 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).

Copyright © 2016 the Author(s). Published by Wolters Kluwer Health, Inc. This is an open access article distributed under the terms of the Creative Commons Attribution-Non Commercial-No Derivatives License 4.0 (CCBY-NC-ND), where it is permissible to download and share the work provided it is properly cited. The work cannot be changed in any way or used commercially without permission from the journal.

Medicine (2016) 95:51(e5153)

Received: 9 September 2016 / Received in final form: 17 September 2016 /

Accepted: 26 September 2016

<http://dx.doi.org/10.1097/MD.00000000000005153>

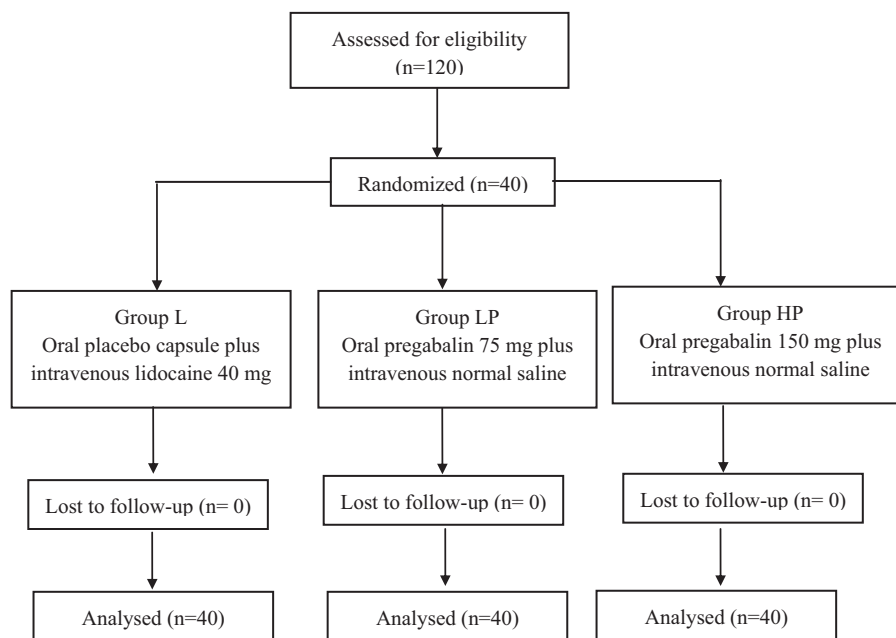


Figure 1. Flow diagram of the study.

propofol injection, compared with intravenous lidocaine 40 mg with venous occlusion.

2. Methods

2.1. Patients and exclusion criteria

A total of 120 patients (20–60 years) with American Society of Anesthesiologists physical status I or II were studied. Patients with a history of adverse response to any drugs, renal or cardiac disease, neurologic deficits and psychiatric disorders, active alcohol or drug usage, or intake of any sedatives, analgesics, or anticonvulsants within 24 hours before surgery were excluded.

2.2. Anesthesia and data collection

The present study was approved by the Ethics Committee of Kyungpook National University Hospital (KNUH 2015-03-037-001), and informed written consent was obtained from all patients. This study was registered in the ClinicalTrials.GOV (NCT02668094).

Using a computerized randomization table, patients were randomly assigned to 1 of 3 groups (Fig. 1). The lidocaine group (group L, $n=40$) received oral placebo capsules containing sugar, pregabalin 75 mg group (group LP, $n=40$) received oral pregabalin 75 mg, and pregabalin 150 mg group (group HP, $n=40$) received oral pregabalin 150 mg at 2 hours before the anesthetic induction, respectively. The placebo and pregabalin were provided in identical white capsules by a pharmacist who was not involved in this study.

Preanesthetic sedative or analgesic was not administered. On arrival at the operating room, standard monitoring devices including noninvasive blood pressure, electrocardiogram, and pulse oximetry were applied, and a 22-ga cannula was placed into the vein on the dorsum of the nondominant hand. After venous occlusion using a rubber tourniquet, patients in group LP and HP received 2 mL of normal saline and patients in group L received 2 mL of 2% lidocaine intravenously, respectively. A physician who

was not involved in this study prepared identically coded syringes. After 1 minute, venous occlusion was released and propofol 0.5 mg/kg was administered at the rate of 0.5 mL/s using syringe pump.^[14,15] Pain following propofol injection was assessed by a study blinded anesthesiologist using a 4-point scale: 0=no (negative response to questioning), 1=mild pain (pain reported only in response to questioning without any behavioral signs), 2=moderate pain (pain reported in response to questioning and accompanied by a behavioral signs or pain reported spontaneously without questioning), and 3=severe pain (strong vocal response or response accompanied by facial grimacing, arm withdrawal, or tears).^[14,15] Thereafter, propofol 1.5 mg/kg was administered for induction of anesthesia. After loss of an eyelash reflex, rocuronium 0.8 mg/kg was injected and tracheal intubation was performed. Anesthesia was maintained by a mixture of air and oxygen supplemented with sevoflurane and continuous infusion of 0.05 to 0.3 $\mu\text{g}/\text{kg}/\text{min}$ of remifentanyl. During the first 24 hours after surgery, any side effects (e.g., dizziness, drowsiness, and visual disturbance) were assessed by a blinded investigator.

In this study, the incidence of pain during propofol injection was primary outcome, and secondary outcomes were adverse effects of pretreatment substances.

2.3. Sample size

Based on the literatures, the incidence of pain following propofol injection is assumed as 80%.^[2–4] When a 50% reduction in pain is considered as a clinically significant endpoint, calculated minimum sample size for each group was 40 patients with a type I error of 0.05 and a test power of 80%.

2.4. Statistical analysis

Data analysis was performed using statistical software (SPSS, version 18.0 for Windows; SPSS, Chicago, IL). One-way analysis of variance was used for continuous variables. The incidences and the severities of pain following propofol injection were compared

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

| Characteristics | Treatment group | | |
|-----------------|-----------------|-----------|-----------|
| | L (n=40) | HP (n=40) | LP (n=40) |
| Age, y | 36.2±12.7 | 41.4±12.9 | 37.3±14.0 |
| Male/female, n | 29/11 | 25/15 | 22/18 |
| Weight, kg | 66.0±12.6 | 65.4±13.4 | 63.8±13.0 |
| Height, cm | 170.4±7.7 | 166.2±7.6 | 167.7±8.9 |

Treatment group: L = lidocaine, HP = pregabalin 150mg, and LP = pregabalin 75mg. Data presented as mean±standard deviation or number.

between groups with Fisher exact test or the Mann–Whitney U test, respectively. Statistical significance was accepted at $P < 0.05$.

3. Results

A total of 120 patients completed this study (Fig. 1). There were no statistical differences in demographic data (Table 1). The overall incidence of propofol injection pain was significantly decreased in group L (55%) and group HP (50%), compared with group LP (92.5%) ($P < 0.05$, respectively). The incidences of moderate pain in group L (15%) and group HP (12.5%) were significantly decreased, compared with group LP (37.5%; both, $P < 0.05$). The incidences of severe injection pain in patients receiving pregabalin 75, 150 mg, and lidocaine were 12.5%, 0%, and 0%, respectively, but there were no significant differences in the incidences of severe pain between groups (Table 2). There were no significant differences in the incidence of adverse effects such as dizziness and drowsiness during 24 hours after operation between groups (Table 3).

4. Discussion

In this study, pretreatment with oral pregabalin 150mg was significantly effective in attenuating pain on propofol injection, compared to pretreatment with oral pregabalin 75 mg. Pregabalin 150 mg was compatible with intravenous lidocaine 40 mg with venous retention for preventing propofol injection pain. There were no differences in the incidence of side effects such as headache, dizziness, and drowsiness between groups.

Lipid emulsion propofol is commonly used for sedation and induction of general anesthesia. But pain from propofol injection is one of the most common adverse effects, which often distresses patients.^[3,6] The exact mechanism of pain on propofol injection is unclear. The pain following propofol injection is thought to

Table 2
Pain during propofol injection.

| Severity | Treatment group | | |
|-------------------------------------|-----------------|-----------|-----------|
| | L (n=40) | HP (n=40) | LP (n=40) |
| None | 18 (45)* | 20 (50)* | 3 (7.5) |
| Mild | 16 (40) | 15 (37.5) | 17 (42.5) |
| Moderate | 6 (15)* | 5 (12.5)* | 15 (37.5) |
| Severe | 0 | 0 | 5 (12.5) |
| Overall incidence of injection pain | 22 (55)* | 20 (50)* | 38 (92.5) |

Treatment group: L = lidocaine, HP = pregabalin 150 mg, and LP = pregabalin 75 mg. Data are presented as number of patients (proportion, %).

* Statistically significant difference between group L and group HP compared with group LP ($P < 0.05$).

Table 3
Side effects.

| Side effects | Treatment group | | |
|--------------|-----------------|-----------|-----------|
| | L (n=40) | HP (n=40) | LP (n=40) |
| Dizziness | 3 (7.5) | 7 (17.5) | 5 (12.5) |
| Drowsiness | 2 (5.0) | 3 (7.5) | 5 (12.5) |

Treatment group: L = lidocaine, HP = pregabalin 150 mg, and LP = pregabalin 75 mg. Data are presented as number of patients (proportion, %).

arise from direct stimulation of nociceptive receptors or free nerve ending in the vessels by free propofol molecules.^[5,6] In addition, free propofol activates the kallikrein kinin system which releases inflammatory factors such as bradykinin, resulting in increase of permeability and dilation of vein. In this bradykinin-modified vein, contacts between free propofol and free nerve ending increases, leading to pain on injection.^[7,16] Pretreatment with various drugs including lidocaine, opioid, and nitroglycerin have been tried for the prevention of injection pain. By a systematic review conducted in 2000, pretreatment with lidocaine 40 mg plus venous occlusion was suggested as the most effective intervention for preventing pain on propofol injection.^[5] Pretreatment with lidocaine plus venous occlusion decreases injection pain by local anesthetic effect on vein and stabilizing the kinin cascade. However, this cannot completely alleviate pain following propofol.^[5] Propofol LCT/MCT which contains lower concentration of free propofol than standard propofol was introduced to reduce injection pain.^[7] However, despite of pretreatment with lidocaine, pain still occurs during injection of propofol-LCT/MCT.^[8,9,17] In the previous study, when pre-mixed with lignocaine, there was no difference in the incidence of pain between propofol LCT and propofol LCT/MCT.^[17]

The fundamental mechanism of action of pregabalin is the reduction of release of calcium by binding to $\alpha_2\text{-}\delta$ subunit of calcium channels, which inhibit excitatory neurotransmitter including glutamate and increase neuronal GABA levels.^[18] In addition, it was found that opioid spinal pathway is involved in the analgesic actions of pregabalin in mice.^[19] Recently, it has been used as a multidimensional analgesia for postoperative pain in various surgeries including dental, laparoscopic cholecystectomy, and spine surgery.^[20–22]

Orally administered pregabalin is rapidly absorbed with maximum plasma concentrations attained with 1.3 hours and has a bioavailability of 90% with elimination half-life of 6 hours.^[23] Therefore, in the present study, oral pregabalin was administered 2 hours before general anesthesia. Dizziness and drowsiness are common side effects of pregabalin.^[24,25] The previous studies demonstrated that premedication with pregabalin 150 mg could be optimal dose for improving postoperative analgesia without an increase of adverse effects.^[26,27] In the present study, pretreatment with 150 mg pregabalin was effective in reducing propofol injection pain, which was comparable with pretreatment with lidocaine 40 mg with venous retention. In addition, there was no significant differences in the incidence of side effects of pregabalin such as drowsiness and dizziness between groups.

The present study had some limitations. First, placebo group was not examined to determine the baseline incidence of pain following propofol injection. Pain during propofol injection is a common clinical problem.^[3,5,6] Therefore, in this study, it was considered unethical that patients given propofol did not receive prophylactic analgesics. Second, in this study, premedication was

not administered, which could affect pain on injection of propofol. The incidence of postoperative recall of this pain was about 50% to 87% if sedative or anxiolytic premedication was not given.^[8,28] The recall of pain during injection of propofol can decrease patient's satisfaction with anesthetic care.^[8] Therefore, another study will be required to investigate the postoperative recall for this pain.

In conclusion, pretreatment with oral pregabalin 150 mg and intravenous lidocaine 40 mg with venous occlusion equally reduced pain from propofol injection.

References

- [1] Dundee JW. New i.v. anaesthetics. *Br J Anaesth* 1979;51:641–8.
- [2] Nathanson MH, Gajraj NM, Russell JA. Prevention of pain on injection of propofol: a comparison of lidocaine with alfentanil. *Anesth Analg* 1996;82:469–71.
- [3] Tan CH, Onsieng MK. Pain on injection of propofol. *Anaesthesia* 1998;53:468–76.
- [4] Agarwal A, Ansari MF, Gupta D, et al. Pretreatment with thiopental for prevention of pain associated with propofol injection. *Anesth Analg* 2004;98:683–6.
- [5] King SY, Davis FM, Wells JE, et al. Lidocaine for the prevention of pain due to injection of propofol. *Anesth Analg* 1992;74:246–9.
- [6] Picard P, Tramèr MR. Prevention of pain on injection with propofol: a quantitative systematic review. *Anesth Analg* 2000;90:963–9.
- [7] Babi J, Doenicke V, Monch V. new formula of propofol in an LCT/MCT emulsion: approach to reduce pain on injection. *Eur Hosp Pharm* 1995;1:15–21.
- [8] Schaub E, Kern C, Landau R. Pain on injection: a double-blind comparison of propofol with lidocaine pretreatment versus propofol formulated with long-and medium-chain triglycerides. *Anesth Analg* 2004;99:1699–702.
- [9] Adam S, van Bommel J, Pelka M, et al. Propofol-induced injection pain: comparison of a modified propofol emulsion to standard propofol with premixed lidocaine. *Anesth Analg* 2004;99:1076–9.
- [10] Gilron I, Watson CP, Cahill CM, et al. Neuropathic pain: a practical guide for the clinician? *CMAJ* 2006;175:265–75.
- [11] Jeon YH. Herpes zoster and postherpetic neuralgia: practical consideration for prevention and treatment. *Korean J Pain* 2015;28:177–84.
- [12] Mishriky BM, Waldron NH, Habib AS. Impact of pregabalin on acute and persistent postoperative pain: a systematic review and meta-analysis. *Br J Anaesth* 2015;114:10–31.
- [13] Lam DM, Choi SW, Wong SS, et al. Efficacy of pregabalin in acute postoperative pain under different surgical categories: a meta-analysis. *Medicine (Baltimore)* 2015;94:e1944.
- [14] Ambesh SP, Dubey PK, Sinha PK. Ondansetron pretreatment to alleviate pain on propofol injection: a randomized, controlled, double-blinded study. *Anesth Analg* 1999;89:197–9.
- [15] Jeon Y. Reduction of pain on injection of propofol: combination of nitroglycerin and lidocaine. *J Anesth* 2012;26:728–31.
- [16] Nakane M, Iwama H. A potential mechanism of propofol-induced pain on injection based on studies using nafamostat mesilate. *Br J Anaesth* 1999;83:397–404.
- [17] Varghese E, Krishna HM, Nittala A. Does the newer preparation of propofol, an emulsion of medium/long chain triglycerides cause less injection pain in children when premixed with lignocaine? *Paediatr Anaesth* 2010;20:338–42.
- [18] Gajraj NM. Pregabalin: its pharmacology and use in pain management. *Anesth Analg* 2007;105:1805–15.
- [19] Kaygisiz B, Kilic FS, Senguleroglu N, et al. The antinociceptive effect and mechanisms of action of pregabalin in mice. *Pharmacol Rep* 2015;67:129–33.
- [20] Hill CM, Balkenohl M, Thomas DW, et al. Pregabalin in patients with postoperative dental pain. *Eur J Pain* 2001;5:119–24.
- [21] Esmat IM, Farag HM. Comparative study between paracetamol and two different doses of pregabalin on postoperative pain in laparoscopic cholecystectomy. *Saudi J Anaesth* 2015;9:376–80.
- [22] Kim JC, Choi YS, Kim KN, et al. Effective dose of peri-operative oral pregabalin as an adjunct to multimodal analgesic regimen in lumbar spinal fusion surgery. *Spine (Phila Pa 1976)* 2011;36:428–33.
- [23] Bockbrader HN, Radulovic LL, Posvar EL, et al. Clinical pharmacokinetics of pregabalin in healthy volunteers. *J Clin Pharmacol* 2010;50:941–50.
- [24] White PF, Tufanogullari B, Taylor J, et al. The effect of pregabalin on preoperative anxiety and sedation levels: a dose-ranging study. *Anesth Analg* 2009;108:1140–5.
- [25] Finnerup NB, Jensen TS. Clinical use of pregabalin in the management of central neuropathic pain. *Neuropsychiatr Dis Treat* 2007;3:885–91.
- [26] Fujita N, Tobe M, Tsukamoto N, et al. A randomized placebo-controlled study of preoperative pregabalin for postoperative analgesia in patients with spinal surgery. *J Clin Anesth* 2016;31:149–53.
- [27] Cegin MB, Soyoral L, Yuzkat N, et al. Pregabalin administered as an anxiolytic agent in ultrasound-guided infraclavicular block: a controlled, double-blind, dose-ranging trial. *Eur Rev Med Pharmacol Sci* 2016;20:568–74.
- [28] Fletcher JE, Seavell CR, Bowen DJ. Pretreatment with alfentanil reduces pain caused by propofol. *Br J Anaesth* 1994;72:342–4.