

Reduction of propofol injection pain by utilizing the gate control theory

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Background: Propofol is the most commonly using intravenous hypnotic for the induction and maintenance of general anesthesia. However, pain on propofol injection is a well known adverse event. Currently, acute and chronic pain can be controlled by utilizing the "gate control" theory.

Methods: Patients were randomized to receive lidocaine (0.5 mg/kg; Group L), touch on IV injection site (Group T), combination lidocaine (0.5 mg/kg) and touch on IV injection site (Group B), or normal saline (Group S) with venous occlusion for 1 minute, followed by administration of propofol (0.5 mg/kg) into the largest dorsal vein of the hand. Immediately after administering propofol, an investigator blinded to the group assignments asked the patient about pain at the injection site and assessed pain intensity using a 4-point verbal rating scale (0 = none, 1 = mild, 2 = moderate, 3 = severe).

Results: A significant decrease in the incidence of pain on propofol injection was achieved in group L (37%) and group B (23%) compared to either group T (80%) and group S (83%) ($P < 0.001$). But, the incidence of moderate and severe pain was significantly lower in group L (7%), group T (20%) and group B (0%) when compared to group S (53%) ($P < 0.05$).

Conclusions: Light touch and rubbing reduced pain, although while, they did not reduce the incidence of pain, they reduced the intensity of pain. This method might be considered as an alternative to other treatments but may be contraindicated for use with other drugs. (Korean J Anesthesiol 2011; 61: 288-291)

Key Words: Lidocaine, Pain, Propofol, Touch.

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Introduction

Propofol is the most commonly using intravenous hypnotic for the induction and maintenance of general anesthesia. However, pain on injection of propofol is a well known adverse event [1]. Its incidence has been reported from 28% to 90% [2]. Macario et al. [1] concluded that propofol injection pain ranked number 7 among 33 low morbidity clinical outcomes. For the reduction of pain on injection of propofol, several studies have been performed using pharmacologic and nonpharmacologic methods [3]. But, none of these has achieved the complete elimination of pain. Pretreatment with lidocaine with a rubber tourniquet occluding the proximal part of the arm has been reported to be the most effective in minimizing propofol injection pain [4].

Currently, acute and chronic pain can be controlled by using the “gate control” theory [5]. “Gate control” theory of pain was introduced by Melzack and Wall in the 1965 [6]. This theory proposed that stimulation of A beta fibers which are stimulated by touch and vibration, modulate the dorsal horn “gate” and therefore the nociceptive input from the periphery could be reduced [7]. The present study was conducted to evaluate the efficacy of touching and rubbing of IV injection site on propofol injection. We also investigated whether a combination of touching and rubbing of the IV injection site with IV administration of lidocaine, preceded by venous occlusion was associated with additional analgesic efficacy compared with either treatment alone.

Materials and Methods

This prospective, randomized, single-blinded, placebo controlled study was conducted at our hospital. Verbal informed consent was obtained from all patients before enrollment. 120 patients aged 16 to 73 years, who were scheduled to undergo elective otolaryngologic surgery with general anesthesia and were American Society of Anesthesiologists physical status of I–III, were enrolled. Patients who have experienced adverse responses to propofol or lidocaine were excluded from the study. Patients were not allowed to receive analgesics or sedative drugs 24 hours prior to surgery. No patient received preanesthetic medication. No patient had hepatic, renal, cardiac problems, neurologic deficits and psychiatric disorders. On arrival to the operating room, a 20-gauge intravenous cannula was inserted into the largest dorsal vein of the patient’s nondominant hand and Ringer’s lactate solution was administered at a rate of 10 ml/kg/h. Patients were randomly assigned to 4 groups (n = 30/group) that received either: lidocaine (0.5 mg/kg, IV; Group L), saline (3 ml) with touching on the IV injection site (Group T), lidocaine (0.5 mg/kg, IV) with touching on the IV injection site

(Group B) or saline (3 ml; Group S). If the volume of lidocaine to be administrated was < 3 ml in group L and B, normal saline was injected at a total volume of 3 ml. Solutions were prepared by an independent anesthesiologist and investigator that did not know the contents of the solutions. All patients underwent venous occlusion for 1 minute and the prepared drug (lidocaine or saline) was injected over 10 seconds. After the occlusion was stopped, propofol (0.5 mg/kg, at room temperature, 23°C) was delivered through the intravenous cannula at the rate of 1 ml/sec. In group T and B, the injection site was gently touched and rubbed on proximal part of the IV injection site 3 times per second with the palm of the hand during propofol injection. Immediately after administering propofol, an investigator who was blinded to group assignment asked the patient about pain at the injection site and assessed pain intensity using a 4-point verbal rating scale (VRS), with 0 = no pain (negative response to questioning); 1 = mild pain (pain reported only in response to questioning without any behavioral signs); 2 = moderate (accompanied by a behavioral signs or sign reported spontaneously without questioning); and 3 = severe pain (strong vocal response or response accompanied by facial grimacing, arm withdrawal, or tears) [8]. The overall incidence of pain (mild, moderate, or severe) on injection of propofol was assessed in each group. Thereafter, anesthesia was induced with propofol (2 mg/kg). After the loss of consciousness, rocuronium bromide (0.6 mg/kg) was administered for muscle relaxation and to facilitate tracheal intubation. Two minutes after rocuronium bromide injection, the trachea was intubated and anesthesia was maintained with desflurane (4.0% to 8.0% inspired concentration) and nitrous oxide (50% in oxygen) with controlled ventilation. Patients were monitored for 24 hours postoperatively for adverse events (pain, edema, wheal, and inflammation) at the injection site.

All statistical analyses were performed with statistical software (SPSS, version 12.0 for Windows; SPSS, Chicago, Illinois). Continuous variables were expressed as mean ± standard deviation or median and categorical variables as frequencies, or percentage. Demographic data were analyzed using ANOVA for continuous variables and the chi-squared test for categorical variables. The chi-square test was used to analyze the incidence of pain and severe pain between groups. The Fisher’s exact test was also applied when the distribution of data was not normal. The Kruskal-Wallis rank test was used to analyze the difference in the median pain score. Analysis of tendency by the linear and linear trend analysis with chi-squared test was used to assess the differences in the mean pain intensity score. P value of less than 0.05 was deemed statistically significant.

Results

A total of 120 patients completed the study. Each group comprised 30 patients. No patient was excluded from the study. Demographic characteristics including age, sex, height, and weight are presented in Table 1. No significant differences were observed among the 4 groups. The overall incidence of pain on injection of propofol was 37% (11/30) in group L, 23% (7/30) in group B, 80% (24/30) in group T, and 83% (25/30) on group S. There were significant differences on the incidence of pain in group L and group B compared with group T or group S ($P < 0.001$). There is no difference on the incidence of pain between groups T and S. But, there was a significant difference in the incidence of moderate and severe pain with 7% (2/30) in group L, 20% (6/30) in group T and 0% (0/30) in group B compared with 53% (16/30) in group S ($P < 0.05$). There is no significant differences between group L and group T by fisher's exact test ($P = 0.254$). But, a difference existed between group B and group T by a Fisher's exact test ($P = 0.024$). With respect to the median pain scores, they were less in groups L, T and B than in group S ($P < 0.05$) (Table 2). The pain intensity score showed a tendency to decrease in groups T, L and B compared with group S ($P < 0.05$; Table 2).

Discussion

Our results showed that touch and rubbing was not efficacious on the incidence of pain on propofol injection. However, moderate and severe pain expressed by the pain intensity score was significantly decreased by either lidocaine pretreatment or touching and rubbing of the IV injection site at the time of propofol injection.

The mechanism of pain on the injection of propofol is not fully understood. However, the triggering of the kinin cascade system is thought to be a possible cause [9]. Several methods have been studied for the prevention of propofol injection pain. Nonpharmacologic methods including injection into a large vein, slow injection of propofol, diluting the propofol solutions, and cooling or warming of propofol have been

Table 1. Demographic Data of the Patients in This Study

	Group L (n = 30)	Group T (n = 30)	Group B (n = 30)	Group S (n = 30)
Age (yr)	39.3 (17.3)	37.0 (14.1)	41.1 (16.4)	34.2 (15.7)
Sex (M/F)	16/14	15/15	16/14	15/15
Height (cm)	163.4 (5.4)	165.3 (6.8)	166.2 (9.6)	164.1 (8.0)
Weight (kg)	58.1 (11.1)	60.2 (10.7)	64.9 (10.9)	58.7 (12.3)

Values are shown as mean (SD) or number of patients. Group L: lidocaine, 0.5 mg/kg, Group T: touch on IV injection site, Group B: lidocaine, 0.5 mg/kg + touch on IV injection site, Group S: saline, 3 ml.

studied [9-11]. Pharmacologic methods have been investigated including pretreatment with IV injection of local anesthetics (lidocaine, procaine, prilocaine) [9,12-14], dexamethasone [15], metoclopramide [16], aspirin or NSAIDs [17-20] and opioids (Fentanyl, Alfentanyl, Remifentanyl) [21-25]. The most common method is to mix lidocaine with propofol [9]. The mechanism of action of lidocaine in reducing propofol injection pain is unclear, but it is thought as its local anesthetic effect on the vein and stabilization of the kinin cascade [9]. Lidocaine appears to have its maximum effect when administered as a pretreatment with a venous tourniquet occluding the proximal part of the arm [3], but, it is contraindicated in patients with allergy to lidocaine.

In the present report, we showed touching and rubbing is an alternative method for decreasing pain on injection of propofol: this procedure seems to have no drawbacks. The effect could be explained by the "gate control" theory that was introduced by Melzack and Wall in 1965 [6]. They proposed that A delta and C nerve fibers stimulated by pain and A beta nerve fibers stimulated by touch, pressure and vibration carry information from the site of injury to two terminus including the substantia gelatinosa and the second order transmission neurons in the spinal dorsal horn. Signals from both A delta, C nerve and A beta nerve fibers excite the second order transmission neurons and when the output of the second order transmission cells exceeds a critical level, pain begins. The action of inhibitory interneurons located in substantia gelatinosa inhibits activation of the second order transmission cells. The second order transmission cells are the gate on pain, and inhibitory interneurons located in substantia gelatinosa can close the gate. When A delta, C nerve and A beta nerve fibers were activated by a noxious event, they excite the second order transmission cell and also act on inhibitory interneurons located in substantia gelatinosa. The inhibitory effect of substantia gelatinosa neuronal activity is increased by A beta and decreased by A

Table 2. Incidence and Intensity of Propofol Injection Pain

	Group L (n = 30)	Group T (n = 30)	Group B (n = 30)	Group S (n = 30)
Incidence of pain	11 (36.7)*	24 (80.0)	7 (23.3)*	25 (83.3)
Median pain score	0 [†]	1 [†]	0 [†]	2
Pain intensity score	†	†	†	
0 (None)	19 (63.3)	6 (20.0)	23 (76.7)	5 (16.7)
1 (Mild)	9 (30.0)	18 (60.0)	7 (23.3)	9 (30.0)
2 (Moderate)	2 (6.7)	4 (13.3)	0 (0.0)	10 (33.3)
3 (Severe)	0 (0.0)	2 (6.7)	0 (0.0)	6 (20.0)

Values are shown as the number of patients (%). Group L: lidocaine, 0.5 mg/kg, Group T: touch on IV injection site, Group B: lidocaine, 0.5 mg/kg + touch on IV injection site, Group S: saline, 3 ml. * $P < 0.05$ versus Group S by chi-square test. [†] $P < 0.05$ versus Group S by Kruskal-Wallis rank test. † $P < 0.05$ versus Group S by chi-square test, linear and linear trend analysis.

delta and C nerve activities. Therefore, the A delta and C nerve fibers impede the inhibitory interneurons located in substantia gelatinosa (tending to open the gate) while the A beta nerve fibers excite the inhibitory interneurons located in substantia gelatinosa (tending to close the gate) [7]. This theory has been provided as the theoretical base for the clinical effects of neuromodulatory techniques ranging from transcutaneous electrical nerve stimulation to spinal cord stimulation and acupuncture [6].

The findings of the present study must be considered within the context of its limitations. First, a newer formulation of propofol, which contains 10% fat emulsion consisting of long-chain triglyceride and medium-chain triglyceride, is associated with less pain on injection: this is not used at our institution because of cost. Second, the sample size of the study was relatively small despite a sufficient number of patients per the results of the power analysis. Future researchers should consider these limitations.

The results of this study may provide important information about a nonpharmacologic method that reduces pain on injection of propofol. Only light touch and rubbing can reduce pain. Although, light touch and rubbing can't reduce incidence of pain, it can reduce pain intensity. This method might be considered as an alternative while it is difficult or contraindicated for use with other drugs.

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