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ORIGINAL ARTICLE

Reduction of pain on injection of propofol: combination of nitroglycerin and lidocaine

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Abstract
Purpose Pain on propofol injection is a common adverse effect. This study examined the effect of a combination of nitroglycerin and lidocaine on pain during propofol injection compared to lidocaine alone.
Methods In a double-blind, prospective trial, 90 patients scheduled to undergo elective plastic surgery were allocated randomly to three groups, to receive lidocaine 20 mg ($n = 30$), a combination of lidocaine 20 mg and nitroglycerin 0.1 μg/kg ($n = 30$), or normal saline as a placebo ($n = 30$), with venous occlusion for 1 min, followed by the administration of 25 % of the total calculated dose of propofol (2 mg/kg) into a dorsal hand vein. The pain intensity during the propofol injection was assessed using a four-point scale (0 = none, 1 = mild, 2 = moderate, 3 = severe). Hemodynamic variables–mean arterial pressure and heart rate–were measured during the preoperative and intraoperative periods.
Results A significantly higher proportion of patients in the placebo group (83 %) experienced pain compared to the lidocaine and combination groups (43 and 7 %, respectively; both, $P < 0.01$). The incidence of pain in the combination group was lower than that in the lidocaine group ($P < 0.01$). The pain score (median) was lower in the lidocaine (0) and combination (0) groups than in the placebo group (2); ($P < 0.01$). The hemodynamic variables were similar in the three groups.
Conclusion A combination of nitroglycerin 0.1 μg/kg and lidocaine 20 mg with venous occlusion for 1 min was more effective than lidocaine 20 mg alone in decreasing pain during propofol injection.

Keywords Lidocaine · Nitroglycerin · Propofol · Pain

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Introduction

Propofol is a popular anesthetic induction drug, but pain is one of the most common side effects during propofol injection. During the induction of anesthesia, 80–90 % of patients experienced pain on propofol injection when a vein on the dorsum of the hand was used [1–3]. This was sometimes quite distressing to the patients [1–3].

A number of methods have been used to prevent injection pain, including varying the injection speed and carrier fluid, varying the dilution temperature, or the concomitant use of drugs [3–6]. One well-accepted technique is lidocaine pretreatment with a rubber tourniquet on the forearm [6]. However, despite the use of this treatment, pain on injection of propofol was not abolished completely and it continues to be a problem [3–5]. Therefore, combination therapy has been suggested for the prevention of pain on injection of propofol [3, 7].

In previous studies, nitroglycerin increased analgesic efficacy when added to a range of analgesics [8–10]. However, a topical nitroglycerin ointment combined with intravenous lidocaine did not have any additional pain reduction effect during propofol injection compared to the effect of intravenous lidocaine alone [11]. Therefore, the present study examined the analgesic effect of a combination of nitroglycerin and lidocaine administered intravenously, compared to lidocaine alone during propofol injection in a dorsal hand vein.

Patients, materials, and methods

After obtaining approval from the Ethics Committee of Kyungpook National University Hospital and patient informed consent, this study enrolled 90 patients aged 19–60 years, American Society of Anesthesiologists (ASA) physical status I and II, scheduled for elective plastic surgery under general anesthesia. Patients with cardiovascular, hepatic, or renal problems; patients who had received analgesic or sedative medications within 24 h before the surgery; patients with neurological deficits or psychiatric disorders; and patients requiring a rapid sequence induction were excluded.

Premedication was not given. Upon the patient's arrival at the operating room, a 20-G intravenous catheter was inserted into the dorsum of the nondominant hand. Routine monitoring included an electrocardiogram, noninvasive blood pressure, and pulse oximetry. The administration of Ringer's lactate as a carrier fluid was stopped before the administration of any study drugs or test substances.

Using a sealed envelope technique, patients were allocated randomly to three groups: to receive lidocaine 20 mg, lidocaine 20 mg plus nitroglycerin 0.1 μg/kg, or normal saline as a placebo. An anesthesiologist not involved in this study prepared identically coded syringes. If the volume to be administered was less than 3 ml, saline was added to a total volume of 3 ml. The patients received the study drugs after the application of a rubber tourniquet around the forearm. The study drug was injected over ten seconds and venous occlusion was maintained for 1 min. Immediately after the venous occlusion had been relieved, room-temperature propofol was injected through a catheter. The induction dose of propofol was 2 mg/kg, and the patients received 25 % of the total calculated dose of propofol, which is known to induce significant pain intensity without exerting depression in consciousness [12, 13]. After administering 25 % of the total calculated dose of propofol at a rate of 0.5 ml/s through a syringe pump, a study-blinded investigator evaluated the level of pain on the injection of propofol. 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 signs), 2 = moderate pain (pain reported in response to questioning and accompanied by a behavioral sign, or pain reported simultaneously with a behavioral sign, but without questioning), 3 = severe pain (strong vocal response or response accompanied by facial grimacing, arm withdrawal, or tears) [12, 13]. Subsequently, the induction of anesthesia was continued with the remainder of the calculated propofol dose. After the loss of the eyelash reflex, the patients were intubated after the administration of rocuronium 1.0 mg/kg. Anesthesia was maintained with sevoflurane 2–3 % and nitrous oxide 50 % in oxygen. Hemodynamic variables–mean arterial pressure (MAP) and heart rate (HR)–were measured before application of the tourniquet, after injection of the total calculated propofol dose, and every 5 min after intubation. Within 24 h after surgery, the injection site was checked by a blinded investigator for any complications such as pain, edema, or a wheal and flare response.

Statistical analyses were conducted using SPSS for Windows software program version 12.0 (SPSS….). The data were expressed as means ± SD, numbers (%), or medians where appropriate. The incidence of pain in patients receiving placebo was estimated to be approximately 80 % from other studies [1, 12, 13]. A 40 % (from 80 to 40 %) decrease in the treatment group would be of clinical importance. Based on an α error of 0.05 and a β error of 0.2, a minimum sample size of 30 patients per group was estimated to be needed to detect a difference. The groups were compared with regard to the demographic data (age, weight, and height) and 25 % of the total calculated dose of propofol, using Student's *t*-test. The incidence and intensity of propofol-induced pain on injection and side effects in the three groups were compared using Fisher's exact test and the Mann–Whitney *U*-test, respectively. The hemodynamic variables in the three groups were compared using a one-way analysis of variance (ANOVA) test. A P value of <0.05 was considered significant.

Results

A total of ninety participants completed the study. The age, weight, height, gender, and 25 % of the calculated propofol dose (2 mg/kg) for induction were similar in the three groups (Table 1). Table 2 lists the overall incidence and severity of pain during the propofol injection. The incidence of pain at the injection site was significantly higher in the control group [25 patients (83 %)], compared to that in the lidocaine group and combination groups [13 (43 %) and 2 (7 %) respectively; both, $P < 0.01$]. The incidence of pain was significantly lower in the patients receiving the lidocaine and nitroglycerin combination, compared to that in the patients receiving lidocaine alone ($P < 0.01$). The pain score (median) was less in the lidocaine (0) and combination (0) groups than that in the placebo group (2); ($P < 0.01$). The hemodynamic variables were similar in the three groups. There were no adverse effects, such as pain, edema, or a wheal and flare response at the injection site, within the first 24 h after surgery in any of the three groups.

Table 1 Patient demographics

	Saline ($n = 30$)	Lidocaine ($n = 30$)	Lidocaine/nitroglycerin ($n = 30$)
Age (years)	45 ± 14.5	48 ± 14.5	50 ± 13.5
Sex (male/female)	14/16	13/17	14/16
Height (cm)	167.9 ± 7.5	165.1 ± 5.8	166.3 ± 7.1
Weight (kg)	65.5 ± 8.4	63.7 ± 8.7	63.6 ± 7.1
Initial propofol dose (mg)[a]	32.8 ± 4.2	31.9 ± 4.3	31.8 ± 3.6

Values are means ± SD or numbers

[a] Initial dose = 25 % of calculated propofol dose (2 mg/kg) during induction of anesthesia

Table 2 Pain on injection of propofol

	Saline ($n = 30$)	Lidocaine ($n = 30$)	Lidocaine/nitroglycerin ($n = 30$)
Patients with pain (%)	25 (83)	13 (43)*	2 (7)*,†
Pain score (median)	2	0*	0*
Grading of pain			
None (0)	5 (17)	17 (57)*	28 (93)*,†
Mild (1)	4 (13)	8 (27)	2 (7)
Moderate (2)	11 (37)	4 (13)	0 (0)*
Severe (3)	10 (33)	1 (3)*	0 (0)*

Values are numbers (%) or medians

* $P < 0.01$ versus saline, † $P < 0.01$ versus lidocaine

Discussion

This study demonstrated that a combination of nitroglycerin and lidocaine, or lidocaine alone, reduced the overall incidence of pain during propofol injection compared to that with a placebo. In addition, the combination of nitroglycerin and lidocaine was more effective than lidocaine alone in preventing the pain.

Propofol is commonly used to induce anesthesia, but the pain upon injection is one of the most notable adverse effects. The precise mechanism of the pain during injection of propofol is unknown. The pain probably results from either direct irritant effects or from indirect effects through activation of the plasma kinin cascade [14, 15]. The peripheral veins are innervated with polymodal nociceptors that mediate the responses to an injection that causes pain [16]. Free propofol in the aqueous phase of an emulsion activates the kallikrein-kinin system in plasma [15, 16]. Therefore, because of the liberation of bradykinin, the peripheral vein becomes permeable. In this vein, the aqueous phase of propofol contacts free nerve endings outside the endothelial layer of the vessel and causes pain on injection [17].

Lidocaine, which is commonly used to reduce pain on propofol injection, may act via a local anesthetic effect on the vein and stabilize the kinin cascade [18]. The presence of a tourniquet gives lidocaine more time to achieve its peripheral anesthetic actions. In the present study, 13 (43 %) patients in the lidocaine group reported pain with the propofol injection, a finding which is consistent with previous studies [3, 4].

The analgesic effect of a small dose (<6 mg daily) of nitroglycerin has been reported in a range of clinical situations [8, 9]. Therefore, nitroglycerin 0.1 μg/kg was chosen in the present study. A topical nitroglycerin ointment added to lidocaine premixed with propofol did not decrease pain on propofol injection, compared to lidocaine premixed with propofol [11]. However, nitroglycerin 200 μg added to lidocaine for intravenous regional anesthesia was reported to improve sensory and motor block, tourniquet pain, and postoperative analgesia, without side effects [10]. Nitric oxide (NO) derived from nitroglycerin causes an increase in the intracellular concentration of cyclic guanosine monophosphate, which induces pain modulation in the central and peripheral nervous systems [8, 19, 20]. NO can also induce an antinociceptive effect through the direct stimulation of peripheral fibers, mimicking the actions of locally applied acetylcholine [20]. In addition, the topical application of nitroglycerin has analgesic and anti-inflammatory effects exerted by blocking hyperalgesia and the neurogenic component of inflammatory edema [21]. In the present study, using a venous occlusion method, the intravenous administration of nitroglycerin 0.1 μg/kg added to lidocaine significantly reduced the incidence of pain on propofol injection, compared to the effect of lidocaine alone. Nitroglycerin causes venodilatation that might promote the distribution of lidocaine to nerves [10]. The intravenous administration of nitroglycerin with a venous occlusion method appears to be more effective than the topical application of nitroglycerin in producing venous dilation.

Pain from propofol injection was reported to occur in 80–90 % of patients when the injection was given in the hand [1–3]. In the present study the inclusion of a placebo group was considered to be unethical. However, because nitroglycerin with rapid onset and short duration can cause dose-dependent adverse effects such as hypotension or tachycardia [19, 23], we included a placebo group to examine the side effect of the study drugs. Nitroglycerin (1.5–2.5 μg/kg) was used to blunt the hemodynamic response to endotracheal intubation [22]. However, in various circumstances, a low dose (<6 mg daily) of nitroglycerin has an analgesic effect without causing hemodynamic changes [8, 9]. In the present study, there were no significant hemodynamic changes with nitroglycerin 0.1 μg/kg, a dose which is compatible with that used in previous studies [8, 9].

There were some limitations in this study. First, in previous studies, 81–96 % of patients without premedication recalled pain on injection of propofol [1, 24]. This might affect the patient's satisfaction about anesthetic care. In the present study, the recall of this pain after anesthesia was not measured. Therefore, another study will be needed to examine the recall of this pain. Second, the analgesic effect of nitroglycerin alone on pain during the injection of propofol was not investigated, because it had been shown that a topically applied nitroglycerin ointment was ineffective in reducing propofol injection pain [11]. However, in contrast to that finding, topical application of a nitroglycerin ointment was shown to cause analgesia and to reduce edema in patients with thrombophlebitis [21]. Therefore, further studies will be needed to investigate the analgesic effect of nitroglycerin alone, when administered intravenously, on propofol injection pain.

In conclusion, a combination of nitroglycerin 0.1 μg/kg and lidocaine 20 mg, administered with a venous occlusion method for 1 min, was more effective than lidocaine 20 mg alone in decreasing pain on propofol injection.

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