J Anesth (2005) 19:273–276
DOI 10.1007/s00540-005-0331-3

Journal of
Anesthesia

Original articles

How to decrease pain at rapid injection of propofol: effectiveness of flurbiprofen

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Abstract
Purpose. Many studies have been conducted on how to decrease propofol injection pain, but none has been completely successful. In the present study, the most effective method was investigated by adding lidocaine or a nonsteroidal antiinflammatory drug or by changing the solvent.
Methods. A total of 250 patients scheduled for general anesthesia were divided into five groups. Anesthesia was induced with intravenous administration of flurbiprofen 50 mg followed immediately by propofol in a long-chain triglyceride (LCT) 2 mg·kg^{-1} (flurbiprofen group, n = 50), flurbiprofen 50 mg followed by propofol LCT 2 mg·kg^{-1} 1 min later (flurbiprofen 1 group, n = 50), 2% lidocaine 40 mg followed immediately by propofol LCT 2 mg·kg^{-1} (lidocaine group, n = 50), propofol LCT 2 mg·kg^{-1} alone (LCT group, n = 50), or propofol in a mixture of medium-chain triglyceride (MCT) and LCT 2 mg·kg^{-1} (MCT/LCT group, n = 50). Pain at injection was assessed 10 and 20 s after starting the propofol infusion.
Results. The numbers of patients with severe and mild pain were larger in the order: LCT group (10 and 31 patients, respectively) > flurbiprofen 1 group (3 and 19) ≥ MCT/LCT group (1 and 14) ≥ lidocaine group (2 and 11) > flurbiprofen group (0 and 0).
Conclusions. Flurbiprofen 50 mg i.v. just before propofol injection completely abolished propofol injection pain. When it was administered 1 min before propofol injection it was less effective.

Key words Propofol · Injection pain · Flurbiprofen · Lidocaine

Introduction

Propofol injection pain is not serious but it is a major problem with a high incidence (up to 90%) [1]. Many studies have suggested ways to decrease propofol injection pain, such as mixing it with lidocaine [2], cooling the propofol to 4° [3], diluting the propofol [4], or pretreatment with various drugs, including lidocaine [5], opioid [6], thiopental [7], ketorolac [8], or nafamostat [9]. The best method reported was to use a tourniquet and lidocaine 0.5 mg·kg^{-1} i.v. before propofol injection [5]. Various propofol formulations in mixtures of medium-chain triglyceride (MCT) and long-chain triglyceride (LCT) (propofol MCT/LCT) induces less injection pain than the original propofol formulation (propofol LCT) [10], but even these trials could not completely abolish the pain.

Flurbiprofen, a nonsteroidal antiinflammatory drug (NSAID), administered before surgery was reported to have a postoperative analgesic effect (i.e., preemptive analgesic effect) [11]. Therefore, if prior administration of flurbiprofen could decrease propofol injection pain, this method would have double benefits: decreased propofol injection pain and preemptive analgesia. The present study was performed to investigate the effects of flurbiprofen on propofol injection pain in comparison with the methods used previously.

Methods

After the approval of the protocol by the ethics committee of the hospital and informed consent from the patients, 250 patients aged 20–70 years with American Society of Anesthesiologists (ASA) physical status I or II and requiring general anesthesia were enrolled in this study. Those who had vascular diseases, habituation of analgesics, sedatives, or antianxiety drugs, or allergic diseases were excluded from the study. They were divided into five groups at random by a random number table.

Midazolam 2–3 mg and atropine 0.2–0.5 mg were administered intramuscularly 30 min before entering the

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Received: January 7, 2005 / Accepted: April 30, 2005

Table 1. Demographic data

Parameter	LCT group	Lidocaine group	Flurbiprofen group	Flurbiprofen 1 group	MCT/LCT group
Age (years)	53 ± 14	50 ± 16	48 ± 15	46 ± 14	51 ± 15
Sex (male/female)	8/42	11/39	10/40	11/39	9/41
Body weight (kg)	58 ± 13	62 ± 14	57 ± 16	55 ± 13	60 ± 12
Surgery (no.)					
Body surface	40	39	40	35	39
Shoulder	4	3	5	8	4
Spine	6	8	5	7	7

Results are the Mean ± SD or number of the patients
LCT, long-chain triglyceride; MCT, medium-chain triglyceride
LCT group: propofol LCT 2 mg·kg^{-1} only; lidocaine group: 2% lidocaine 40 mg followed immediately by propofol LCT 2 mg·kg^{-1}; flurbiprofen group: flurbiprofen 50 mg followed immediately by propofol LCT 2 mg·kg^{-1}; flurbiprofen 1 group: flurbiprofen 50 mg followed by propofol LCT 2 mg·kg^{-1} 1 min later; MCT/LCT group: propofol MCT/LCT 2 mg·kg^{-1}

Table 2. Patients with injection pain

Degree of pain	LCT group	Lidocaine group	Flurbiprofen group	Flurbiprofen 1 group	MCT/LCT group
Severe	10	2*	0*	3*	1*
Mild	31	11*,†	0*	19*,†	14*,†
None	9	37*,†	50*	28*,†	35*,†

*$P < 0.05$ vs. LCT group; †$P < 0.05$ vs. flurbiprofen group
Results are the number of patients. Total number was 50 in each group

operating room as routine premedication. A 20-gauge catheter was inserted into a superficial radial vein of the left hand, and lactated Ringer's solution was infused at 100 ml·h^{-1}. Under 100% oxygen inhalation with a mask, flurbiprofen (Ropion; Kaken Pharmaceutical, Tokyo, Japan) 50 mg in 10 s followed immediately by propofol LCT 2 mg·kg^{-1} (Diprivan 1% prefilled syringe; AstraZeneca, Osaka, Japan) (flurbiprofen group, $n = 50$), flurbiprofen 50 mg in 10 s followed by propofol LCT 2 mg·kg^{-1} 1 min later (flurbiprofen 1 group, $n = 50$), 2% lidocaine 40 mg followed immediately by propofol LCT 2 mg·kg^{-1} (lidocaine group, $n = 50$), propofol LCT 2 mg·kg^{-1} alone (LCT group, $n = 50$), or propofol MCT/LCT 2 mg·kg^{-1} (1% propofol "Maruishi"; Maruishi Pharmaceutical, Osaka, Japan) (MCT/LCT group, $n = 50$) was administered intravenously in 5 s. All drugs were used at room temperature. Disposalble syringes (Nipro, Osaka, Japan) were used for drug injection except for propofol LCT, which was provided in a prefilled glass syringe.

Pain at injection of propofol was assessed 10 and 20 s after the start of propofol infusion as no pain, mild pain (pain reported only in response to questioning without behavioral signs), or severe pain (pain reported spontaneously accompanied by a behavioral sign such as arm withdrawal or facial grimacing). More severe pain between 10 and 20 s was recorded.

Statistical analysis was performed with the factorial analysis of variance for age and body weight, and the chi-square test for sex, type of surgery, and the number of the patients with injection pain. $P < 5\%$ was considered statistically significant.

Results

The backgrounds of the patients were not different among the five groups (Table 1). The total numbers of the patients with severe and mild pain were larger in the order: LCT group > flurbiprofen 1 group ≥ MCT/LCT group ≥ lidocaine group > flurbiprofen group. The number of the patients with severe pain was largest in the LCT group. The flurbiprofen group had no patients with pain. The lidocaine group, Flurbiprofen 1 group, and MCT/LCT group had no statistically significant differences in the number of the patients with severe or mild pain (Table 2).

Discussion

Flurbiprofen 50 mg followed immediately by propofol completely abolished propofol injection pain in this study. However, a 1-min interval between flurbiprofen and propofol decreased its effect to the same level as preinjection of lidocaine and changing the solvent from LCT to MCT/LCT.

Intramuscular midazolam was administered as a premedication to all patients. However, it is reported that

midazolam premedication had no effect on the incidence of propofol injection pain [12].

Regarding propofol injection pain, first, the phenol may cause immediate pain from a local irritant effect on the vein. Then after 10–20 s, by indirect action on the endothelium, lipid activates the kallikrein-kinin system and releases bradykinin. This then produces venous dilation and hyperpermeability, which increases the contact between the aqueous phase of propofol and free nerve endings resulting in pain on injection [13]. Considering these mechanisms, abolishing propofol injection pain may be achieved by decreasing the aqueous phase of propofol or propofol in contact with nerve endings, inhibiting the kallikrein-kinin system or bradykinin release, or a local anesthetic effect.

Propofol MCT/LCT has less aqueous phase of propofol than propofol LCT; thus, propofol MCT/LCT induces less injection pain than propofol LCT [10]. The present results are consistent with those results. Agarwal et al. noted that pretreatment with thiopental was effective for preventing propofol injection pain [7]. probably by changing the concentration of free aqueous propofol. However, thiopental itself sometimes induces injection pain, and one patient still complained of pain in their study [7].

Pretreatment with nafamostat, a kallikrein inhibitor, before propofol injection decreased injection pain [9]. However, nafamostat is expensive.

Many studies used lidocaine 40 mg i.v., and the incidence of propofol injection pain decreased to 20%–30% [6, 7, 14]. In the present study also, lidocaine induced propofol injection pain in 26% of the patients. Adding lidocaine to propofol is effective for decreasing propofol injection pain to the same degree as intravenous lidocaine [15]. The addition of lidocaine to propofol results in the coalescence of oil droplets, which finally proceeds to a visible layer [16]. Therefore, it is not recommended.

Propofol, when drawn up in a disposal syringe, may lead to the formation of irritants [17]. Propofol strips the silicone lubricant from the inside barrel of the plastic syringe. In the present study, a disposable syringe was used for propofol MCT/LCT, whereas a prefilled glass syringe was used for propofol LCT. Therefore, some of the injection pain induced by propofol MCT/LCT might depend on the reaction with the disposable syringe.

Application of many analgesics other than local anesthetics to decrease propofol injection pain have been investigated. For instance, pretreatment with intravenous ketorolac reduced propofol injection pain [8]. Ketorolac is a potent cyclooxygenase inhibitor that blocks prostaglandin production [18]. Therefore, the authors thought that the mechanism of propofol injection pain might be through the cyclooxygenase pathway.

Flurbiprofen, the other NSAID available for intravenous administration, was reported to have no effect on propofol injection pain [19], which is inconsistent with the results of the present study. Karasawa et al. [19] administered flurbiprofen 10 min before propofol injection. The most interesting result of our study is that flurbiprofen administered just before propofol LCT completely abolished propofol injection pain but that a 1-min interval between flurbiprofen and propofol LCT lessened this effect. The 1-min interval may wash out flurbiprofen from the injection site. Thus, the difference between the flurbiprofen group and the flurbiprofen 1 group is whether flurbiprofen existed at the propofol injection site.

The mechanism of analgesia may be twofold. Flurbiprofen may be given as a solution with soybean oil and egg lecithin containing 50 mg flurbiprofen (Ropion). The lipid in Ropion might create a layer on the intima of the vein, preventing propofol–intima contact. Another possible mechanism is that the lipid in Ropion may combine with propofol, with the result that there is decreased free propofol in aqueous phase. Further study is necessary to elucidate the mechanism.

Flurbiprofen administered before surgery is reported to induce better postoperative analgesia than that administered after surgery [11]. Although postoperative analgesia was not examined in the present study because the purpose was to investigate propofol injection pain, administration of flurbiprofen just before propofol injection might be useful for both abolishing propofol injection pain and decreasing postoperative pain. In conclusion, flurbiprofen 50 mg i.v. just before propofol injection is strongly recommended for abolishing propofol injection pain.

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