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Comparative Benefit of Preemptively Applied Thiopental for Propofol Injection Pain: the advantage over lidocaine

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ABSTRACT

Propofol is one of the most frequently applied intravenous anesthetics for the induction of general anesthesia. However, pain on injection of this agent is a considerable problem in daily anesthesia practice because of its severity. Administration of lidocaine prior to propofol injection is a standard technique for reducing the pain on injection. However, this method provides insufficient pain relief. To evaluate whether pretreatment with an ultra-short acting barbiturate, thiopental, is more effective than with lidocaine, a randomized and single-blinded trial was conducted. Patients (20–65 years old, n = 137) were allocated into six groups, and applied with physiological saline, thiopental (25, 50, 75, or 100 mg), or lidocaine (40 mg) at 30 second prior to propofol injection (1 mg/kg, 1200 ml/h). The patient was interviewed about the degree of pain just after propofol was totally injected. Both thiopental (≥ 25 mg) and lidocaine decreased the severity of pain in comparison with physiological saline as evaluated by a six-graded pain score. Lidocaine failed to influence the incidence of pain (from 86% to 55%), although thiopental significantly decreased it to 40% (25 mg), 21% (50 mg), 12% (50 mg), and 0% (100 mg), respectively. Thiopental (≥ 50 mg) decreased both the severity and incidence of pain more effectively than lidocaine. A Hill plot analysis of these data, after rearrangement by patient's body weight, estimated that the half-effective dose (ED_{50}) and the ED_{99} of this drug to block pain on injection of propofol were 0.6 and 1.4 mg/kg, respectively.

Key words: *Thiopental, Lidocaine, Propofol, Pain on injection*

Propofol, an oil-in-water emulsion of 1,6-diisopropylphenol, is an intravenous general anesthetic with rapid onset and elimination half-life. Because of this pharmacokinetic feature, propofol is used for the induction as well as the maintenance of general anesthesia. However, the administration of propofol is frequently associated with severe pain on injection[16]. Administration of lidocaine prior to or simultaneously with the injection of propofol is a standard technique recommended by the manufacturer to reduce propofol injection pain, and it is now used by many practitioners[1]. However, this method does not provide sufficient relief from injection pain.

From our preliminary trial, pretreatment with a small dose of thiopental was supposed to be more beneficial than lidocaine. The aim of this study was thus to evaluate the comparative effect of thiopental against lidocaine in relieving propofol injection pain.

PATIENTS AND METHODS

After approval by the local review board, the pain on induction of general anesthesia by using propofol was studied in a prospective, randomized, and single-blinded manner. One hundred and eighty patients (20–65 years old), scheduled for elective surgery under general anesthesia, were allocated into six groups by using randomly sorted case-cards after receiving their written informed consent. Patients with asthma, liver or renal dysfunction, and cardiac disease were pre-excluded. The groups comprised: T0, physiological saline (2 ml) was intravenously administrated at 30 second before the commencement of propofol injection (1 mg/kg, 1200 ml/h); T25, same as T0 except that 25 mg thiopental was administrated instead of physiological saline; T50, pretreatment with 50 mg thiopental; T75, with 75 mg thiopental; T100, with 100 mg thiopental; and L40, with 40 mg lidocaine

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(30 patients each). Neither a hypnotic nor an opioid analgesic was premedicated. After the patient's arrival at the operating room, an 18-gauge plastic cannula was inserted into a cephalic vein. A local anesthetic was not used for the venipuncture. When the catheterization to the cephalic vein was difficult, the patient was excluded from the study. The patient was interviewed about injection pain just after the total dose of propofol was injected. The propofol injection pain was scored as follows: 1, patient was asleep before the interview; 2, no complaint of pain according to the interview; 3, complaint of pain according to the interview; 4, complaint of pain spontaneously before the interview; 5, complaint of pain with an agonized face; and 6, complaint of pain with an agonized movement of the injected arm.

To further evaluate the dose-effect relationship between the preemptively applied thiopental and the incidence of pain (pain score > 2) or of sleep (pain score = 1) after the propofol injection, data were rearranged into six groups according to the dose of thiopental per body weight (approximately 0, 0.5, 1, 1.5, 2, and 2.5 mg/kg). Sigmoid dose (mg/kg)-response (%incidence) curves were drawn by fitting data to a Hill plot using least squares.

Statistical analysis.

Data were expressed as mean ± S.D.. Multiple comparison of pain score was performed by using the Kruskal-Wallis test. The following group-to-group comparison was performed by using the Mann-Whitney's U test. The incidence of pain or of sleep was compared by using a chi-squire test. A value of p less than 0.05 was considered as significant.

RESULTS

Twenty patients were excluded from this study because the catheterization to a cephalic vein was difficult. The severity as well as the incidence of pain on propofol injection to seven patients, allocated in the T0 group, was beyond the expectation of the investigators. Thus, the T0 group was removed from the random allocation after the seven patients participated. Thereafter, the remaining 137 patients were evaluated for propofol injection pain (Table 1). No statistical difference in age, height, and body weight was observed among groups ($p < 0.05$). Pretreatment with 25 mg thiopental (T25) or 40 mg lidocaine (L40) before the injection of propofol decreased the injection pain score as compared with physiological saline (T0). These results indicated that both thiopental and lidocaine inhibited the severity of pain on injection of propofol. The injection pain score in the groups pretreated with 50 mg (T50) and 75 mg (T75) thiopental was significantly lower than in T0 or L40. The pain score in the group pretreated with 100 mg thiopental (T100) was lower than in T0, T25, T50, or L40. These results indicated that preemptive thiopental dose-dependently decreases the severity of pain on injection of propofol, and that pretreatment at a dose equal to or higher than 50 mg is more effective than 40 mg lidocaine. The incidence of pain (Pain score > 2) in the absence of preemptive active drugs was 86%. Pretreatment with thiopental dose-dependently decreased the incidence of pain as well as the severity of pain, as shown above. On the other hand, there was no statistical difference in the incidence of pain between L40 and T0. The incidence of pain in T50, T75 and T100 was lower than in L40. No patient was asleep before the interview about pain in T0 or L40. In contrast, 20%–52% of patients fell asleep after pretreatment with thiopental. Even pretreatment with 25 mg thiopental significantly increased the incidence of sleep as compared with pretreatment with lidocaine. Table 1 also shows that the incidence of sleep by preemptive thiopental was dose-dependent.

Data from T0 - T100 were then regrouped by the dose of thiopental per body weight to perform Hill plot analyses (Fig. 1). Only one individual in 29 patients, to whom thiopental at a dose of 1.45 ± 0.13 mg/kg was applied preemptively, complained of pain on injection of propofol. No patient com-

Table 1. Patient demographic of pain on injection of propofol

Group	(n)	Injection Pain Score						The incidence of	
		1	2	3	4	5	6	Pain	Sleep
T0	(7)	0	1	1	1	2	2	86%	0%
T25*	(25)	5	10	6	1	1	2	40%*	20%#
T50*#	(28)	7	15	3	1	1	1	21%*#	25%#
T75*#	(25)	10	12	0	2	0	1	12%*†#	40%*#
T100*†‡#	(23)	12	11	0	0	0	0	0%*†‡#	52%*†‡#
L40*	(29)	0	13	7	5	2	2	55%	0%

Injection pain score: 1, asleep before the interview for pain; for pain; 2, no complaint of pain; 3, complaint of pain according to the interview; 4, before the interview; 5, with an agonized face; and 6, with an agonized movement of injected arm.

Significant difference in the pain score, the incidence of sleep or of pain: from *T0; †T25; ‡T50; or #40 ($p < 0.05$).

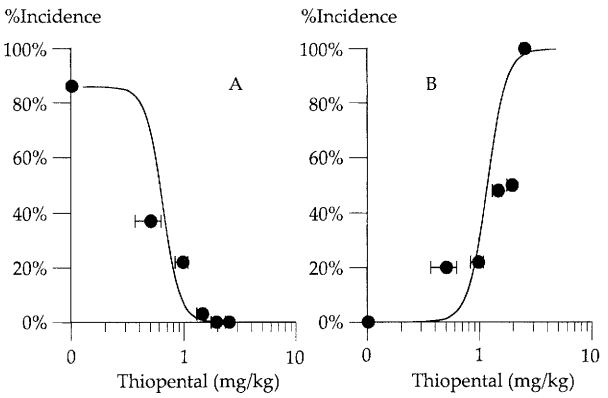

Fig. 1. Effects of preemptive thiopental per body weight on the incidence of sleep or pain induced by propofol injection. Thiopental at a dose of 0 mg, 25 mg, 50 mg, 75 mg, or 100 mg was preemptively applied at 30 second prior to the injection of propofol (1 mg/kg, 1200 ml/h). Data were rearranged into six groups according to the applied dose of thiopental per body weight (mg/kg) and shown as mean ± SD. The number of patients in each group was: 7 (0 mg/kg); 30 (0.50 ± 0.13 mg/kg); 32 (0.97 ± 0.13 mg/kg); 29 (1.45 ± 0.13 mg/kg); 6 (1.93 ± 0.16 mg/kg); and 4 (2.51 ± 0.15 mg/kg), respectively. The incidence of pain (A) or sleep (B) was plotted against the dose of thiopental (mg/kg). Hill plot analyses were performed to calculate and draw sigmoid dose (mg/kg)-response (%incidence) curves.

plained of pain to whom thiopental was applied at 1.93 ± 0.16 mg/kg (n = 6) or at 2.51 ± 0.15 mg/kg (n = 4). A Hill plot analysis revealed that the half-effective dose (ED_{50}) and the ED_{99} of preemptive thiopental to block the pain on injection of propofol were 0.6 and 1.4 mg/kg, respectively (Fig. 1A). The ED_{50} and the ED_{99} of preemptive thiopental against the incidence of asleep were also calculated to be 1.2 and 2.9 mg/kg, respectively (Fig. 1B).

DISCUSSION

Pain on propofol injection is a considerable problem in daily anesthesia practice because of its high incidence (28%–100%) and the severity of this complaint[17]. A single intravenous administration of lidocaine before the propofol injection, as recommended by the manufacturer, is an easy solution to propofol injection pain. However, the efficacy of this method is far from adequate. The reported incidence of pain on propofol injection after lidocaine application still remains high (17.5%–44%)[8,12,14,15]. In the present study, the incidence of propofol injection pain after administration of 40 mg lidocaine was more than 50%. It is also notable that in the preliminary trial for this study the increased administration of lidocaine from 20 mg to 40 mg failed to decrease the propofol injection pain, suggesting that the effect of pretreatment with lidocaine is limited (data not shown). Therefore, the comparative benefit of several drugs against lidocaine has been examined[17]. Of these, preemptive use of an ultra-short acting barbiturate, thiopental, has been evaluated as an alternative choice by several investigators. However, the efficacy of this drug for pain on propofol injection was reported to be controversial. Haugen et al reported that pretreatment with thiopental significantly reduced the severity of pain on injection, although it failed to reduce the incidence of pain[10]. In contrast, Lee et al showed that thiopental reduced the incidence of propofol injection pain as well as its severity, in contrast with the former report[11]. Since these reports examined the effect of thiopental at a single dose, it is suggested that evaluation at multiple doses is required to solve the issue.

In the present randomized trial, we thus applied four different doses of thiopental (25–100 mg) at 30 second prior to intravenous administration of propofol. It has been reported that the site of injection, the size of venous cannula, and the speed of propofol injection influence the pain on propofol injection[17]. To reduce the possible statistical bias among the groups, these factors were standardized in our method. We demonstrated that pretreatment with thiopental (≥ 50 mg) at 30 second prior to intravenous administration of propofol significantly decreased the incidence as well as the severity of pain on injection as compared with lidocaine (40 mg) (Table 1). Our data were then rearranged according to the body weight of patients (Fig. 1). A Hill plot analysis of these rearranged data estimated that the incidence of propofol injection pain was virtually abolished by 1.4 mg/kg thiopental (ED_{99}). The ED_{50} (0.6 mg/kg) as well as the ED_{99} for the incidence of pain relief were two-times lower than those for the incidence of sleep (1.2 and 2.9 mg/kg, respectively), indicating that preemptively applied thiopental inhibits the pain on propofol injection at sub-hypnotizing concentrations.

The mechanism(s) of pain on injection of propofol has not yet been clarified. However, it is known that the onset of pain on propofol injection is often delayed for 10–20 seconds, suggesting that kinin release from the vessel wall is involved[17]. It is likely, therefore, that lidocaine counteracts propofol injection pain through local anesthetic action. A report from Manger and Holak, where the inhibitory effect of lidocaine on propofol injection pain was enhanced by using an arm tourniquet before the application of lidocaine, potently supports this idea[13]. In the present study, no patient fell asleep through the preemptive application of lidocaine before propofol injection. On the other hand, we showed that thiopental dose-dependently increased the incidence of sleep while decreasing the injection pain score. It has been reported that premedication with hypnotics prior to the entry of the patient to the operating room[5,7], or preemptive

use of the intravenous general anesthetic, ketamine, reduced the pain on propofol injection[18]. These drugs, including thiopental, were likely to decrease the pain on propofol induction primarily through the inhibition of the central nervous system rather than the peripheral sensory nerves. However, in contrast with the other hypnotics, it is known that thiopental decreases the threshold of pain sensation[6], suggesting that the site of action of this drug against propofol injection pain is complex. We believe that the interaction of barbiturates and lidocaine with the kinin-induced signal transduction pathway in peripheral sensory neurons has not yet been examined in detail. It is noteworthy, however, that a short-acting barbiturate, pentobarbital, as well as lidocaine, counteracted the kinin-induced release of prostacyclin and nitric oxide from endothelial cells[3,4]. The production and the release of these agents from endothelial cells are regulated by the stimulation of a kinin-receptor, followed by the activation of IP_3-dependent cytosolic Ca^{2+} elevation[2]. Because the proximal part of this signal transduction pathway is involved in the kinin-induced excitation of sensory neurons[9], these experimental findings support our concept, in part, that thiopental inhibited the pain on propofol injection partly through local anesthetic action at the site of injection.

In conclusion, preemptively applied thiopental at 30 second prior to the injection of propofol significantly reduced the incidence and the severity of pain on injection. Thiopental at doses equal to or more than 50 mg was more effective than 40 mg of lidocaine in reducing pain. A Hill plot analysis of these data, after rearrangement by patient's body weight, estimated that a preemptive thiopental at a dose of 1.4 mg/kg virtually blocks the pain on injection of propofol.

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