

## PAINLESS INJECTION OF PROPOFOL: PRETREATMENT WITH

— Ketamine vs Thiopental, Meperidine, and Lidocaine —

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### Abstract

Propofol, a commonly used anesthetic, often causes pain on injection. Several methods have been described to reduce this pain, however, complete inhibition has not been achieved.

Our randomized, placebo controlled, double blind study has been conducted to compare the analgesic efficacy of iv pretreatment of ketamine, meperidine, thiopental, lidocaine to minimize the injection pain of propofol.

125 patients ASA I and II were randomly allocated into 5 groups and received.

Group K, ketamine 0.4 mg/kg;

Group T, thiopental 0.5 mg/kg;

Group M, meperidine 0.4 mg/kg;

Group L, lidocaine 1 mg/kg;

Group S, saline 3 ml.

All pretreatment drugs were made into 4 ml solutions and were accompanied by manual venous occlusion for 1 min, followed by tourniquet release and slowly IV administration of propofol.

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Pain was assessed with a four point scale. All treatment groups had a significantly lower incidence of pain than placebo group ( $p < 0.05$ ). However, it has been observed that pretreatment with ketamine was the most effective in attenuating pain associated with propofol injection ( $p < 0.05$ ). For painless injection of propofol, routine pretreatment with ketamine 0.4 mg/kg along with venous occlusion is recommended.

### **Key words**

Pain, injection, propofol, ketamine, meperidine, thiopental.

### **Introduction**

Propofol is a rapidly acting IV agent used widely for induction and maintenance of anesthesia<sup>1</sup>. It has many advantages and a low incidence of side effects. A well known drawback is pain during injection, although its pH and osmolality are close to those of blood<sup>2</sup>. Several methods have been described to reduce this pain, one of the most common is mixing with lidocaine<sup>3</sup>. However, complete inhibition has not been achieved<sup>4</sup>.

The present study was designed to compare the most effective analgesic to prevent pain caused by propofol injection using ketamine, thiopental, meperidine, and lidocaine.

### **Methods and Materials**

After approval of the Ethics Committee, written informed consent was obtained from 125 patients (ASA I, II) adult patients scheduled for elective surgery lasting 1-2 hours. The study was conducted in a double-blind randomized fashion. No patient received premedication on arrival to the operating room.

22G catheter was placed into largest vein on the dorsum of the hand under local anesthesia, and attached to normal saline infusion. Before induction of anesthesia, patients were told that they would receive IV

anesthetic that may cause pain in the forearm. The patients were instructed to inform the investigator of the amount of pain that they have experienced by using 4 point scale 0 = no pain, 1 = mild pain, 2 = moderate pain 3 = severe pain.

After the patient understood the instruction, monitoring was applied using ECG, NIBP, pulse oximeter.

IV fluids was stopped. The arm with IV line was elevated for 15 seconds for gravity drainage of venous blood. A manual tourniquet was placed on the upper arm to produce a venous occlusion. The study drugs were randomly prepared in an unlabeled syringe for pretreatment and handed to the anesthesiologist who was blind to identity the drug. All study drugs were kept at room temperature and used within 30 minutes of preparation.

The 125 patients were allocated into 5 groups:

Group K (25 patients): received ketamine 0.4 mg/kg

Group T (25 patients): received thiopental 0.5 mg/kg

Group M (25 patients): received meperidine 0.5 mg/kg

Group L (25 patients): received lidocaine 2% 1m/kg

Group S (25 patients): received saline 3 ml

All study drugs were made into 4 ml volume with addition of normal saline.

All injections were given at a rate of 0.5 ml/sec. one minute after injection of study drugs, the tourniquet was released, followed by IV injection of 1/4 of the total calculated dose of propofol at rate of 0.5 ml/sec. The induction does of propofol (propofol 1%) was 2.5 mg/kg.

Paitents were asked during administration of the study drugs, and every 10 sec during induction with propofol regarding the presence of pain or discomfort using 4 point scale:

0 = no pain,

1 = mild pain (pain reported only in response to question without any behavioural signs),

2 = moderate pain (pain reported spontaneously, or in response to question, accompanied by a behavioral sign; facial grimacing);

3 = severe pain (strong vocal response, or response accompanied by facial grimacing, arm withdrawal, or tears).

Assessment of pain was conducted by a second, independent anesthesiologist who was unaware of group assignments.

Mean arterial pressure (MAP), heart rate (HR) were recorded preoperatively, after administration of the study drugs, and after propofol administration.

Inspection of the injection site was carried up immediately after injection of the study drugs, during operation and at 6 hours. Presence or absence of edema, wheals erythema, or itching at the injection site, was noted, and recorded.

After assessment of pain, induction of anesthesia was continued with propofol. Tracheal intubation was facilitated with cisatracurium, and anesthesia was maintained with inhaled technique supplemented with fentanyl.

### *Statistical Analysis*

The results were analyzed by using analysis of variance for demographic data, Manny-Whitney-Wilcoxon ranked sum test, and one way analysis of variance for propofol pain scores,  $X$  analysis for the incidence of side effects. A  $p$  value  $<0.05$  was considered statistically significant.

### **Results**

There were no significant demographic differences between the five groups (Table 1).

Table 1  
Demographic Data

	Group K	Group T	Group M	Group L	Group S
Age (yr)	39.9 ± 13.6	40.1 ± 14.1	47.7 ± 20.1	46.2 ± 26.7	39.9 ± 13.6
Weight (kg)	65.6 ± 7.2	58.8 ± 5.3	72.9 ± 5.7	62.4 ± 8.8	57.6 ± 4.7
male/female (n)	14/11	13/12	13/12	14/11	12/13
ASA grade I/II	21/4	19/6	22/3	18/7	22/3

Values for age and weight are expressed as mean ± SD

Group K = Ketamine 0.4 mg/kg,

Group T = Thiopental 0.5 mg/kg,

Group M = Meperidine 0.5 mg/kg,

Group L = Lidocaine 1 mg/kg,

Group S = Saline 3 ml.

There was no significant difference between the treatment groups.

### Incidence of Side Effects (Table 2)

The incidence of injection pain was 8% (2 of 25) in the thiopental group and 24% (6 of 25) in the meperidine group. However this difference did not reach statistical significance. The incidence of skin reaction was significantly high in the meperidine group compared to the thiopental group (40% versus 8%). No Skin erythema and/or wheals were observed in the other study drugs (Table 2).

Table 2  
The incidence of side effects of the pretreatment drugs

Groups	Pain on injection		Skin reaction	
	n	(%)	n	(%)
Group K	0	(0)	0	(0)
Group T	2	(8)	2	(8)
Group M	6	(24)*	10	(40)*
Group L	0	(0)	0	(0)
Group S	0	(0)	0	(0)

n = 25 in each of the five groups.

\* P < 0.05 compared with control (Group S).

Group K = Ketamine 0.4 mg/kg, Group T = Thiopental 0.5 mg/kg, Group M = Meperidine 0.5 mg/kg, Group L = Lidocaine 1 mg/kg, Group S = Saline 3 ml.

After propofol injection, the mean blood pressure in the ketamine group decreased insignificantly compared to the preoperative levels but was significantly higher compared to the other groups (Table 3). However, in the other 4 groups MAP values significantly decreased after propofol injection (Table 3, Fig. 1). The heart rate in all the groups decreased insignificantly compared to the preoperative levels as shown in (Table 3, Fig. 2).

*Table 3*  
*Mean arterial blood pressure (MAP) and heart rate (HR) just before induction, after injection of study drugs, and after propofol injection*

	<b>K Group</b> <b>(n = 25)</b>	<b>T Group</b> <b>(n = 25)</b>	<b>M Group</b> <b>(n = 25)</b>	<b>L Group</b> <b>(n = 25)</b>	<b>S Group</b> <b>(n = 25)</b>
<u>Before induction</u>					
MAP (mmHg)	97.12 ± 14.3	92.1 ± 18	95.76 ± 13.9	98.4 ± 10.6	99.9 ± 13.3
HR (beat min)	83.4 ± 13.3	81.4 ± 16.2	85.6 ± 14.2	84.2 ± 10.3	86.9 ± 11.7
<u>After injection of study drugs</u>					
MAP (mmHg)	93.6 ± 4.9	94.4 ± 5.8	90.9 ± 4.5	92.6 ± 50.3	94.4 ± 5.8
HR (beat min)	81.4 ± 6.4	82.5 ± 7.8	80.8 ± 6.6	83.3 ± 8.2	85.2 ± 3.9
<u>After propofol injection</u>					
MAP (mmHg)	85.6 ± 6.9 <sup>†</sup>	76.5 ± 10.5 <sup>*</sup>	77.6 ± 13.5 <sup>*</sup>	75.8 ± 8.3 <sup>*</sup>	74.4 ± 9.2 <sup>*</sup>
HR (beat min)	77.9 ± 11.1	73.8 ± 12.7	74.6 ± 13	75.1 ± 11.4	76.4 ± 14.9

Values are expressed as mean ± SD

\* P < 0.05 inter group comparison before induction and after propofol injection.

† P < 0.05 K Group significance versus T Group, M Group, and L Group.

K Group = ketamine group, T Group = thiopental group, M Group = meperidine group, L Group = lidocaine group, S Group = saline group.

Fig. 1  
Mean arterial pressure changes

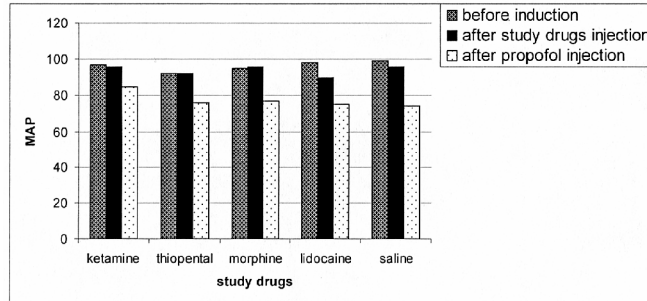
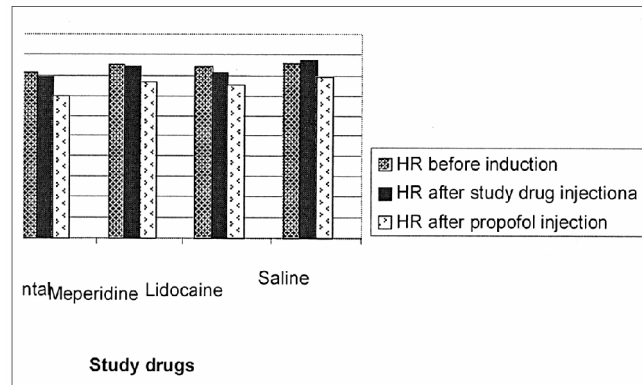


Fig. 2  
Heart rate changes



The incidence of pain during propofol injection in the various groups is shown in Table 4 & Fig. 3.

Table 4  
Incidence of pain during injection of propofol

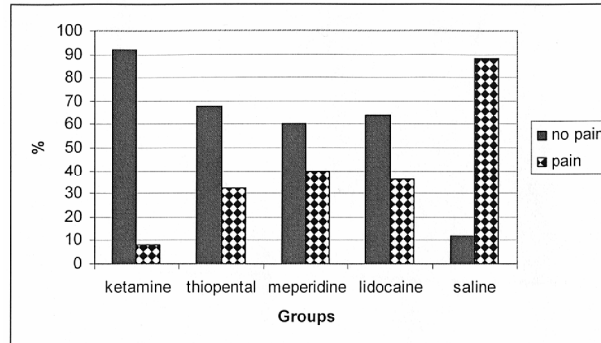
Pain	K Group (n = 25) %		T Group (n = 25) %		M Group (n = 25) %		L Group (n = 25) %		S Group (n = 25) %	
	None	23 <sup>*†</sup>	92	17 <sup>*</sup>	68	15 <sup>*</sup>	60	16 <sup>*</sup>	64	3
Mild	1	4	5	20	5	20	4	16	3	12
Moderate	1	4	3	12	1	4	2	8	7	28
Severe	0	0	0	0	4	16	3	12	12	48
Total	2	8	8	32	10	40	9	36	22	88

\* P < 0.05 intergroup comparison between control and other study groups.

K Group = ketamine group, T Group = thiopental group, M Group = meperidine group,

L Group = lidocaine group, S Group = saline group.

Fig. 3  
Incidence of pain  
during injection of  
propofol



Pretreatment with thiopental 0.5 mg/kg, meperidine 0.5 mg/kg and lidocaine 1 mg/kg were equally effective in attenuating pain during IV injection of propofol ( $P > 0.05$ ). Propofol pain was markedly reduced in the ketamine group 0.4 mg/kg when compared with other study groups ( $p < 0.05$ ).

The incidence of severe pain was more in the control group compared to Group M and Group L (48%, 16%, and 12% respectively).

## Discussion

Propofol is the most commonly used IV anesthetic<sup>5</sup>. Although it has an excellent recovery profile (i.e., fast and smooth emergence, infrequent incidence of post operative nausea and vomiting), its use is associated with pain on injection, increased triglyceride levels, and the potential for microbial contamination<sup>6,7</sup>.

Pain on injection of propofol occurs in 30%-90% of patients<sup>8</sup>. Pain results not only from a direct irritant effect on the vein wall, but an indirect effect too. The lipid solvent for propofol activates the plasma kallikrein-kinin system, that produces bradykinin which modify the injected local vein. This modification of the local vein may increase the contact between the aqueous phase propofol and the free nerve endings of the vessel, resulting in aggravation of propofol-induced pain<sup>9</sup>. This was further supported by Iwama et al., who demonstrated that

pretreatment with nafamost, a kallikrein inhibitor, inhibited injection pain of propofol<sup>10</sup>.

In our study, it has been observed that pretreatment with ketamine 0.4 mg/kg was the most effective in attenuating pain associated with propofol injection when compared to thiopental, meperidine and lidocaine.

### *Ketamine*

Ketamine is an iv anesthetic that produces minimal cardiovascular or respiratory depression. Ketamine, is a non-competitive blocker of glutamate NMDA receptors. In the sub-anesthetic doses, ketamine possesses analgesic properties<sup>11</sup>. Finck et al suggested that ketamine analgesia may be mediated by  $\mu$  or  $\delta$  opioid receptors<sup>12</sup>. However, Smith et al. suggested that ketamine may be  $\mu$  antagonist and a  $k$  agonist<sup>13</sup>. In contrast to opioids, the effect of ketamine is not antagonized by naloxone<sup>14</sup>. Electrophysiological studies of ketamine analgesia show dissociation between the lateral and medial pathways of pain processing (concerned with sensory and affective processing respectively)<sup>15</sup>. Ketamine is characterized clinically by an indifference to pain rather than diminution in pain intensity. In addition, it was suggested that ketamine analgesia might result from local anesthetic action<sup>16</sup>. Earlier studies suggested that the analgesic effects of small dose ketamine complement the sedation provided by propofol during monitored anesthesia care<sup>17</sup>. Thus the combination of propofol and ketamine has the potential to provide better sedation with less toxicity. Combination of propofol and ketamine produces superior analgesia than propofol alone, improve spontaneous ventilation, and hasten the postoperative recovery<sup>18</sup>.

Mortero RF et al. studied the effect of co-administration of propofol (9.8 mg/ml) and small dose ketamine (0.98 mg/ml). They concluded that co-administration of both drugs improves propofol-induced hypoventilation, produces positive mood effects, and may improve post

operative analgesia<sup>19</sup>.

Our results showed that pretreatment with ketamine 0.4 mg/kg was the most effective in attenuating pain associated with propofol injection (92% patients had no pain). Our results are similar to Barbi et al. In their study, they used 0.5 mg/kg ketamine in pediatric patients<sup>21</sup>. However, in a study conducted by Tan et al. ketamine was as effective as lidocaine in attenuating pain during propofol injection. In their study they used 10 mg of ketamine prior to propofol administration without application of tourniquet<sup>20</sup>.

Propofol induces a decrease in the arterial blood pressure after induction of anesthesia. This is due to the decrease in the peripheral vascular resistance, inhibition of both the sympathetic activity and myocardial contractility. Administration of ketamine before propofol has the advantage of producing a non-significant decrease in the arterial pressure compared to preoperative level. However, in other study groups, there was a significant decrease in blood pressure after administration of propofol compared to the preoperative level. This could be explained by the positive effect of ketamine on sympathetic stimulation leading to increase in myocardial contractility and vascular resistance, which in turn leads to increase arterial pressure<sup>22</sup>.

Our findings were similar to those of Furya et al. They found that IV administration of 0.5 mg/kg ketamine 1 minute before propofol, attenuates arterial pressure changes during induction of anesthesia. However, they did not investigate the effect of ketamine on pain during propofol injection.

### *Lidocaine*

Lidocaine has been shown to be effective in minimizing the pain especially when used with tourniquet. Importantly, after reviewing more than 6000 patients in a trial for prevention of pain caused by propofol injection, lidocaine 0.5 mg/kg given with a rubber tourniquet before propofol injection; was very effective in attenuating the pain<sup>23</sup>. In our

study, 64% in the lidocaine group had no pain compared to 84% in the control group.

### *Thiopental*

The mechanism by which thiopental reduces pain on injection of propofol is unclear. However, the physical properties such as its alkalinity or lipid solubility may affect the concentration of free aqueous propofol, which is responsible for propofol pain<sup>24</sup>. Thiopental may prevent the release of bradykinin, which cause venous dilatation and hyper permeability resulting in aggravation of pain. Administration of sub-anesthetic doses of thiopental may inhibit the perception of pain<sup>25</sup>.

Our results showed that propofol pain was not reduced markedly in the thiopental group 0.5 mg/kg (17 of 25 had no pain) when compared to lidocaine group (16 of 25 had no pain). These results are similar to Tobias et al who compared the incidence and severity of pain associated with administration of a mixture of propofol/thiopental 50%:50% versus a mixture of propofol with lidocaine<sup>26</sup>. This was in contrast to the study by Agarwal et al., in which propofol pain was more effectively reduced with thiopental 0.5 mg/kg when compared to lidocaine.

### *Opiates*

Trials with opiates such as fentanyl, alfentanil, tramadol, and pethidine, for relieving pain during propofol injection, were done. Fletcher et al., found that IV alfentanil 1 mg given 15 seconds before propofol administration was effective in reducing the incidence and severity of pain. Meperidine may have dual mechanism of action<sup>27</sup>. The primary clinical effect of meperidine is mediated via peripheral opioid receptors<sup>28</sup>. Meperidine has a local anesthetic effect, which could be related to its structural similarity to cocaine and tetracaine<sup>29</sup>. However, in one trial concomitant use of naloxone did not reduce meperidine's efficacy, suggesting that its peripheral analgesic effect is not mediated by opioid receptors<sup>30</sup>. Our results are in agreement with those reported

by Pang et al., and Mok et al who showed that meperidine 40 mg and lidocaine 60 mg were equally effective in reducing the injection pain of propofol<sup>31,32</sup>.

### *Side Effects*

There was a high incidence of pain and skin erythema/wheals during injection of pethidine (24% and 40% of patients respectively). However, the incidence of pain skin erythema/wheals in the thiopental group was 8% of the patients. This was due to histamine release. However, all of skin reaction disappeared within on hour.

In conclusion, the best prevention of propofol injection pain is ketamine 0.4% mg/kg given with a rubber tourniquet on minute before the injection of propofol. Ketamine has the advantage of attenuating arterial pressure changes during the induction of anesthesia with propofol. Pethidine is not recommended as a method to decrease the pain during propofol injection due to the high incidence of pain and skin reaction caused by histamine release.

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