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To Compare the Efficacy of Pretreatment with Three Different Doses of Intravenous Thiopentone to Alleviate Local Pain on Propofol Injection in Patients Undergoing Procedures under General Anaesthesia: A Prospective Double Blind Randomized Study

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Abstract: Our aim was to compare three different doses of thiopentone pretreatment (0.25mg/kg, 0.5mg/kg, 0.75mg/kg) in alleviating local pain on propofol injection and to look for any adverse outcomes on thiopentone pretreatment. 138 patients were allocated into three different groups (A, B, C) of 46 each using random number table method. Patients in group A, B and C received 0.25mg/kg, 0.5mg/kg and 0.75mg/kg thiopentone respectively, diluted in 2ml normal saline after occluding the venous drainage by applying tourniquet at middle of forearm. After 60 seconds, tourniquet was removed and 1/4th of total calculated dose of propofol (0.625mg/kg) was administered slowly over 5 seconds. Pain was graded using a four-point verbal rating scale and sedation using Ramsay sedation scale. Within 24 hours after surgery, the injection site was checked for pain, edema, and wheal and flare response. We found that there were statistically significant differences in incidence (p value < 0.0001) as well as severity (p value = 0.001) of pain on propofol injection among the groups. Our study also showed significant variation in incidence and severity of pain in females compared to males (p value = 0.03). Significant differences were also observed in Ramsay sedation scores among the groups (p value < 0.0001). However, no significant difference was found in pain score with regards to age (p value = 0.72) and no injection site reactions as pain, edema, wheal, flare were observed within 24hours of procedure. Our conclusion was that pretreatment with 0.75mg/kg thiopentone is highly effective in attenuating the incidence and severity of pain on propofol injection.
Keywords: Propofol, thiopentone, tourniquet, four point verbal rating scale, Ramsay sedation score.

INTRODUCTION

Propofol is the most popular intravenous anaesthetic drug for induction and sedation in current practice. It is associated with pleasant sleep, rapid recovery and little postoperative nausea [1-4]. However, pain at the site of injection is an important problem. It causes pain and discomfort on injection in 28%–90% of patients [5]. Among 33 clinical problems, propofol induced pain ranked seventh when both clinical importance and frequency were considered [6, 7].

Pain on propofol injection has two components: Immediate and delayed pain. Immediate pain on propofol injection is attributed to a direct irritant effect of the drug by stimulation of venous nociceptive receptors or free nerve endings with central transmission of nerve impulse by myelinated A-delta fibres. This effect is probably associated with the free concentration of propofol. The delayed pain of propofol injection has an onset latency of 10-20 seconds and is probably mediated by indirect action on the endothelium. Propofol is believed to release bradykinin by activation of the kallikrein-kinin system, which induces venous dilation and hyperpermeability, thereby probably promoting contact between free propofol and free nerve endings within the vascular wall, resulting in pain. Prostanoids, particularly prostaglandin E2 has been recently found to be released in plasma after intravenous administration of propofol and could also be involved in this process [8, 9, 10, 11].

Strategies to reduce the incidence of pain on injection include adding lignocaine to propofol, cooling or warming propofol, diluting the propofol solution, injection of propofol into a large vein and pretreatment with IV injection of lignocaine, ondansetron, metoclopramide, an opioid, magnesium or thiopentone with or without tourniquet; all have been tried with variable results.

Use of lignocaine is most extensively studied and is the most widely used technique to reduce the pain associated with injection of propofol [12, 13, 14, 15, 16]. A recent study has reported that pretreatment with thiopentone 0.25 mg/kg was as effective as lignocaine in attenuating pain induced by propofol [17].

Mechanisms of reduction of pain on propofol injection by thiopentone may include, change in concentration of free propofol due to physical properties of thiopentone such as its alkalinity or lipid solubility, co-administration of subanaesthetic doses of thiopentone may inhibit the perception of pain and finally, thiopentone may also block the release of bradykinin, resulting in reduced pain on propofol injection [9, 18, 19].

We aim to compare 3 different doses of thiopentone pretreatment (0.25mg/kg, 0.5mg/kg, and 0.75mg/kg) in alleviating local pain on propofol injection and to look for any adverse outcomes on thiopentone pretreatment.

MATERIALS AND METHODS

After obtaining consent from the institution's ethics committee, this prospective randomized study was conducted in a double blind fashion. All patients had undergone a pre-anaesthetic assessment preoperatively as per standard guidelines along with routine and special investigations whenever indicated. They were explained about the procedure and an informed consent was obtained and was advised fasting over 8 hours.

138 patients were allocated into three different groups (A, B and C) of 46 each using random number table method

Inclusion criteria

Patients aged between 18 to 55 years belonging to ASA physical status I and II undergoing elective surgery under general anaesthesia (with or without tracheal intubation).

Exclusion criteria

Patient's refusal, ASA physical status ≥ III, emergency surgeries, patient with difficulty in communication, history of allergy to propofol or thiopentone, patients who had received analgesics or sedatives within 24 hour prior to surgery and pregnant women.

On arrival in the operation room, 18G cannula was inserted into a vein on dorsum of monodominant hand and normal saline solution was attached. Routine monitoring included noninvasive blood pressure, ECG, peripheral oxygen saturation, capnography in all patients and special monitoring according to the type and duration of surgery.

Patients in group A, B and C received 0.25mg/kg, 0.5mg/kg and 0.75mg/kg thiopentone respectively, diluted in 2ml normal saline after occluding the venous drainage by applying tourniquet at middle of forearm. After 60 seconds, tourniquet was removed and $1/4^{th}$ of total calculated dose of protocol (0.625mg/kg) was administered slowly over 5 seconds. During the protocol injection, patients were continuously observed for vocal response, facial grimacing, arm withdrawal or tears suggesting severe pain. If these signs and symptoms were absent then patients had been questioned after 15 seconds regarding the presence of pain or discomfort.

One anesthesiologist prepared pretreatment drugs and a second anesthesiologist who was unaware of group assignment, assessed the level of pain and sedation. Pain was graded using a four-point verbal rating scale and sedation using Ramsay sedation scale.

Four point verbal rating scale

Pain score	Description
0 (No pain)	No pain reported even after questioning
1 (Mild Pain)	Pain reported only in response to questioning without any behavioural signs
2 (Moderate pain)	Pain reported in response to questioning and accompanied by a behavioural sign or pain reported spontaneously without questioning
3 (Severe pain)	Strong response or response accompanied by facial grimacing, arm withdrawal or tears

Ramsay sedation scale

Ramsay 1	Anxious, agitated, restless
Ramsay 2	Cooperative, Oriented, tranquil
Ramsay 3	Responsive to command only
Ramsay 4	Brisk response to light glabellar tap or loud auditory stimulus
Ramsay 5	Sluggish response to light glabellar tap or loud auditory stimulus
Ramsay 6	No response to light glabellar tap or loud auditory stimulus

Following this, remaining dose of propofol was administered and standard anaesthesia induction was carried out as indicated. Within 24 hour after surgery, the injection site was checked for pain, edema, and wheal and flare response.

STATISTICAL ANALYSIS

Sample size calculation was done using statistical analysis software STATA 12. As per previous studies, incidence of pain after IV propofol injection was 70%. We had expected a 40% reduction in pain after therapy. Taking power of study to be 90% and alpha error of 0.05, we needed 46 patients in each group. Descriptive statistics were presented. The quantitative variables were represented as mean and standard deviation along with minimum and maximum ranges and categorical variables were presented in the form of number percentages. Chi square for trend test was applied to find out the primary outcome in the study. One way ANOVA was used to find out the differences in demographics. All the statistical calculations were done using STATA 12 statistical software, Texas USA. P value < 0.05 was considered significant.

RESULTS

All the demographic characteristics were comparable in all the three groups (p value > 0.05). Significant differences were observed in the incidence of pain on propofol injection among the groups (p value < 0.0001). Percentages of patients complaining of pain in group A, B and C were 71.74%, 10.87% and 0% respectively as shown in table 1.

Table 2 shows statistically significant difference in severity of pain scores among the groups (p value = 0.001). Pain scores were mild in 72.72% and moderate in rest 27.27% patients in group A. In group B, pain scores were mild in 100% cases. In group C no patient had complained of pain.

Table 3 shows significant differences in sedation scores among the groups (p value < 0.0001). In group A, Ramsay sedation scores were 1 (in 69.57%) and 2 (in 30.43%). In group B, scores were 2 (in 78.26%) and 3 (in 21.74%). In group C, scores were 2 (in 13.04%), 3 (in 69.57%) and 4 (in 17.39%).

Significant differences were observed in pain scores in relation to gender as shown in table 4 (p value = 0.03 and correlation coefficient=0.18). Incidence of pain on propofol injection was higher in females (32%) compared to males (22.22%). Severity of pain was also higher in females (20% complained of mild pain and 12% of moderate pain) compared to males (all 22.22% complained of mild pain only).

Age and pain scores revealed no statistically significant differences in our study as shown in table 5 (p value = 0.72 and correlation coefficient= -0.03). No complications such as pain, edema, wheal and flare were observed at injection site within first 24 hours of the procedure.

Table-1: Assessment of pain score during IV injection of Propofol

	Group A (N= 46)	Group B (N= 46)	Group C (N= 46)
Pain	33 (71.74%)	5 (10.87%)	0
No pain	13 (28.26%)	41 (89.13%)	46 (100%)
P value	< 0.0001		

Table-2: Categorization of pain score during IV injection of Propofol

Pain Score	Group A (N= 33)	Group B (N=5)	Group C (N=0)
Mild Pain	24 (72.72%)	5 (100%)	0
Moderate Pain	9 (27.27%)	0	0
P value	0.001		

Table-3: Assessment of Sedation score

Ramsay sedation Score	Group A (N= 46)	Group B (N= 46)	Group C (N= 46)
1	32 (69.57%)	0	0
2	14 (30.43%)	36 (78.26%)	6 (13.04%)
3	0	10 (21.74%)	32 (69.57%)
4	0	0	8 (17.39%)
P value	< 0.0001		

Table-4: Correlation of pain score with gender

Pain Score	Male (N= 63)	Female (N= 75)
No pain	49 (77.78%)	51 (68.00%)
Mild pain	14 (22.22%)	15 (20.00%)
Moderate pain	0	9 (12.00%)
Severe pain	0	0
P value	0.03	
Correlation coefficient	0.18	

Table-5: Correlation of pain score with age

Age Category	Pain (N=38)	No pain (N= 100)
18- 25	6 (15.79%)	17 (17.00%)
26 – 35	17 (44.74%)	32 (32.00%)
36 – 45	8 (21.05%)	28 (28.00%)
46 – 55	7 (18.42%)	23 (23.00%)
P value	0.72	
Correlation coefficient	-0.03	

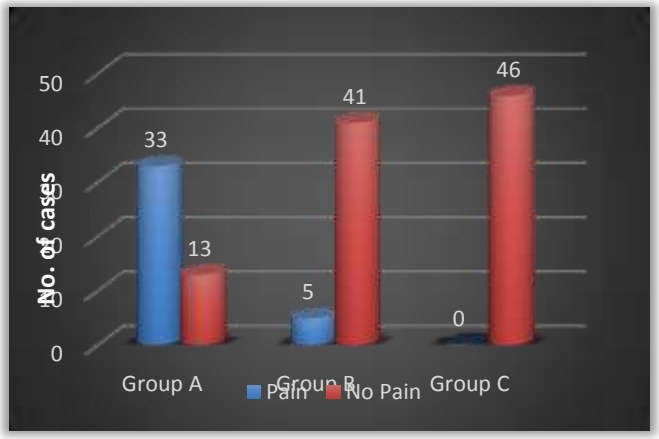

Fig-1: Assessment of pain score during IV injection of Propofol

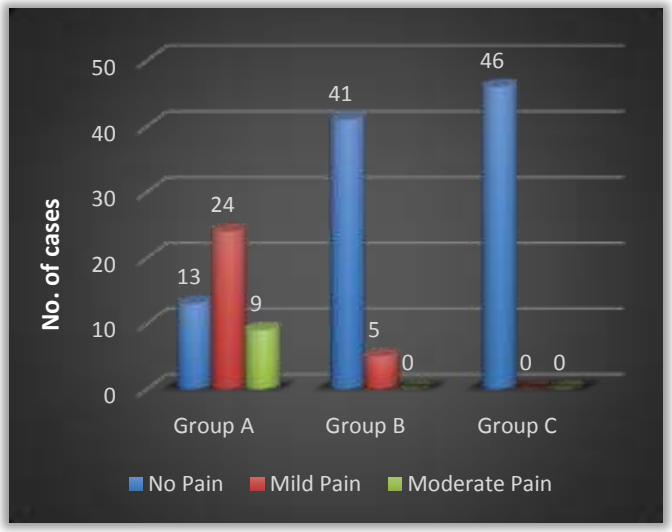

Fig 2: Categorization of pain score during IV injection of Propofol

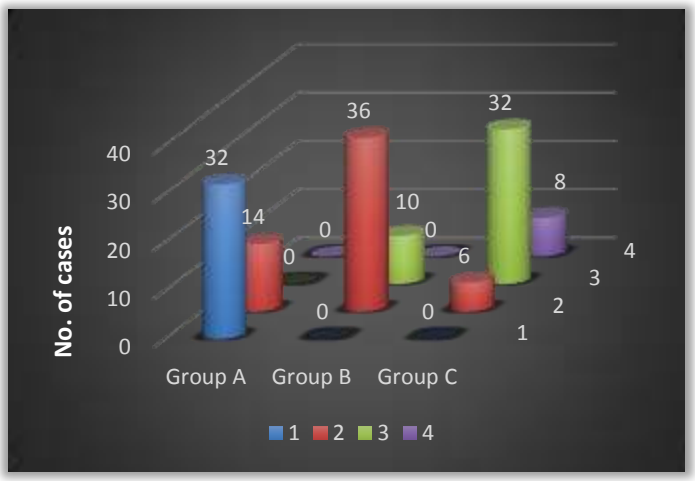

Fig 3: Comparison of Sedation score

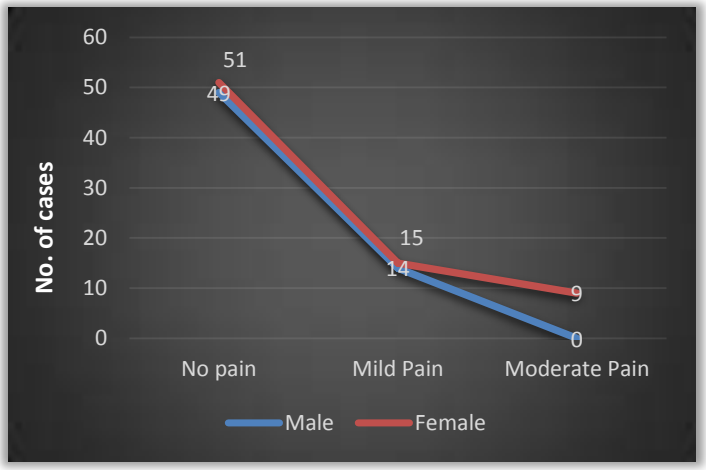

Fig-4: Correlation of severity of pain with gender

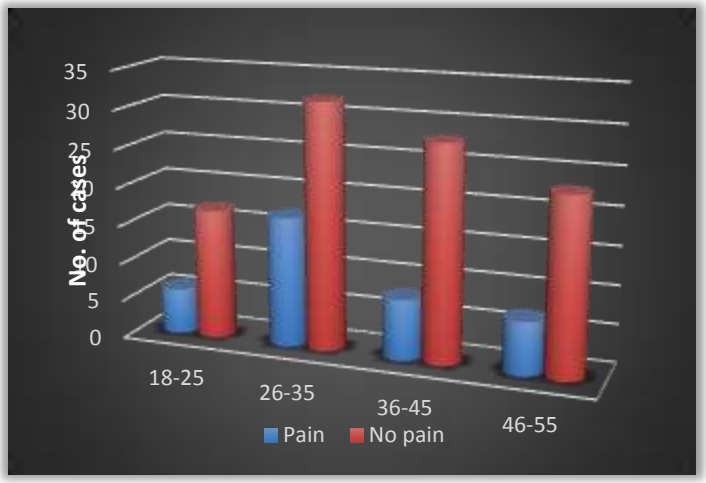

Fig-5: Correlation of pain score with age

DISCUSSION

Propofol is known to cause pain or discomfort on injection. Several methods have been tried for the reduction of pain on propofol injection based on proposed mechanisms with varying degrees of success. Use of lignocaine has been most extensively studied and very commonly used to prevent pain on propofol injection. A study done by Agarwal A *et al*. concluded that thiopentone 0.25 mg/kg pretreatment was as effective as lignocaine 40mg pretreatment in reducing

pain induced by propofol injection. However, pretreatment with thiopentone in a dose of 0.5mg/kg with venous occlusion for 60 seconds was most effective in attenuating pain induced by propofol injection but it still causes pain in 3% patients [17].

Our study aimed to evaluate the efficacy of pretreatment with 3 doses of thiopentone (0.25mg/kg, 0.5mg/kg and 0.75mg/kg) for attenuating pain associated with propofol injection after venous occlusion at forearm for 60 seconds prior to propofol injection and to look for any adverse outcomes such as oversedation, pain, edema, wheal and flare at the site of injection.

The study revealed significant differences in incidence (p value < 0.0001) as well as severity (p value = 0.001) of pain scores among the three groups. We observed that thiopentone pretreatment in a dose of 0.75mg/kg completely abolishes pain on propofol injection. Despite a high Ramsay sedation score with higher doses of thiopentone pretreatment, none of our patients had adverse events such as loss of airway reflexes or rapid fall in oxygen saturation needing immediate tracheal intubation. We also found a strong correlation between gender and pain score (p value = 0.03 and correlation coefficient=0.18). However, age had no significant correlation with pain score in our study (p value = 0.72 and correlation coefficient= -0.03).

Agarwal A *et al*. observed much lower incidence of pain in their study compared to our study with 0.25mg/kg and 0.5mg/kg thiopentone pretreatment respectively. This is probably due to different composition in propofol with lipid emulsion used in their study [17].

Lee TW *et al*. also found that incidence of pain was significantly lower in thiopentone pretreatment group than control group (p < 0.001) as well as lignocaine group (p < 0.03). However they have used much higher dose of thiopentone (100mg / 1.5mg/kg approximately) which could have significant sedative effect which was not evaluated [20].

Pollard RC *et al*. in their study mixed propofol with lignocaine in one group and with thiopentone in other group. They observed that incidence of pain was significantly lower (p = 0.006) in the group receiving propofol thiopentone mixture (14%) compared to those receiving propofol lignocaine mixture (35%) [21].

In contrast to our results, Haugen RD et al compared the efficacy of thiopentone 50 mg (approximately 0.8 mg/kg) pretreatment with lignocaine 40 mg and had found that thiopentone only reduced the severity of propofol pain, whereas lignocaine reduced both the incidence and severity of pain [22].

Stella L *et al*. found that dose of thiopentone required to produce unconsciousness in 20%, 50% and 80% patients were 2mg/kg, 2.2mg/kg and 2.4mg/kg respectively. These doses were much higher than the maximum dose of thiopentone used in our study for pretreatment. Hence, thiopentone pretreatment dose of 0.75mg/kg can be safely administered to patients [23]. Contrary to our result Lee TW *et al*. observed no significant correlation between gender and pain scores [20].

CONCLUSION

Our study reveals that pretreatment with 0.75mg/kg thiopentone is highly effective in attenuating the incidence and severity of pain on propofol injection. This dose produces greater levels of sedation compared to patients receiving lower doses of thiopentone. However, no adverse events including loss of airway reflexes or sudden desaturation have been encountered in any of our studied patients. A strong correlation has been observed between gender and propofol induced pain, females being more sensitive to it. None of our patients have had complains such as pain, edema, wheal and flare at injection site, a day after the surgical procedure. Based on our results, we strongly recommend routine use of 0.75mg/kg thiopentone pretreatment to mitigate pain on propofol injection. However, larger randomized controlled trials are needed to validate our findings.

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