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Attenuation of propofol induced pain by thiopentone sodium, fentanyl and lignocaine: A comparative study

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Abstract
Propofol is one of the most popular intravenous anaesthetic used for induction and maintenance of anaesthesia and sedation in and outside of operating room. Its role is valuable especially for day care surgeries and with larngeal mask airways. Because of high incidence of pain on propofol injection (POPI) numerous interventions have been tested to prevent this pain including the use of different drugs and physical measures as well as the combination of methods. In this. study the effect of pretreatment with thiopentone sodium, preservative free fentanyl, and preservative free 2% lignocaine on reducing propofol induced pain with 4 point pain scale. A prospective observational study was conducted in Government Medical College, Kottayam in 63 patients (ASA 1 and 2) in the age group of 18-60 years scheduled for elective surgery under general anaesthesia. Selected patients were allocated into 3 groups: Group T, Group F and Group L. Prior to propofol injection, Group T received thiopentone sodium 0.5mg/kg, Group F received preservative free fentanyl 2 mcg/kg and Group L received preservative free lignocaine 1 mg/kg and pain on propofol injection was assessed during induction of anaesthesia. All patients post induction received standard general anaesthesia. The lowest incidences of pain on propofol injection were observed in Group T, whereas Group L and Group F shown the same incidences of pain on propofol injection. There were no statistically significant differences in the pain perceived between three groups, group L, group F and group T (47.7 v/s 47.7% v/s 33.3%, p=0.170) on propofol injection. Thiopentone sodium was not significantly different from lignocaine for reducing pain during injection of propofol in this study. Fentanyl is equally effective as lignocaine in reducing such pain. The pretreatment with preservative free fentanyl and thiopentone sodium reduced the incidence of propofol induced pain similar to preservative free 2% lignocaine.

Keywords: Fentanyl, propofol, thiopentone sodium, lignocaine

Introduction
Propofol is the drug of choice for induction of anaesthesia in million of patients every year because of its rapid onset and short duration of action, easy titration and favorable profile for side effects. However pain on propofol injection is considerable problem in daily anaesthesia practice because of its severity. The incidence of pain due to propofol injection has been reported from 45% to 100% [3-8]. Of the 37 common clinical problems in anesthesia, the pain on propofol injection ranks seventh [9]. The etiology of this pain is unknown, but two reasons have been suggested. First, phenol may cause local pain immediately by stimulation of venous nociceptive receptors [5]. Second, the indirect release of Kininogens from endothelial cells may stimulate pain at the nerve endings between the vessel wall intima and media and cause delayed pain 10-20 seconds later [6]. Controlling and reducing the pain caused by the injection of propofol has always been one of the main challenge to anaesthesiologists and therefore many methods have been used to reduce pain. Studies have suggested the use of different types of opiates, such as Morphine, Pethidine, Fentanyl, Alfentanil, [49] tramadol, [10, 13] changes in injection rate, [14] drug dilution, [15] drug cooling and warming, [16] the use of various propofol solutions, such as the use of propofol Fresenius and Lipuro, [5, 16-18] the use of metoclopramide [50] and ondansetron, [18] and the use of topical anesthetics with the closure of the tourniquet [7]. Because the reduction in propofol pain has beneficial effects on the process of induction of anesthesia, the use of available and effective drug methods that can be used to replace another drug in cases of contraindications prompted us to examine the effects of different drugs on reducing the pain caused by propofol.
Among all the drugs and interventions that can reduce pain on propofol injection, Lignocaine is a commonly used drug because of its effectiveness and easy availability and safety profile for side effects.

Only few reviews on comparing the effect of thiopentone and fentanyl with lignocaine for preventing pain following propofol injection is available. This study is designed to compare the efficacy of thiopentone and fentanyl with lignocaine for preventing pain following propofol injection.

Alizade *et al*. [21] showed that the use of lidocaine 2% (40 mg) in reducing pain caused by propofol injection was more effective than the propofol mixture with 40 mg of lidocaine 2%.

Kazemnezhad *et al*. [23] studied the effect of lidocaine, thiopental, fentanyl, and normal saline on reducing pain incidence and intensity following injection of Propofol Fresenius 1%. In this study, the patients were divided into four groups of Propofol Fresenius 1%, lidocaine, normal saline and thiopental. The results of this study showed that the use of lidocaine and sodium thiopental were more effective than other drugs in reducing pain, especially severe pain caused by propofol injection. Kazemnezhad [26] in another study examined the effect of lidocaine on reducing pain following propofol Lipuro 1% injection, and found that the use of lidocaine 1% in combination with propofol Lipuro reduced pain during injection. Soltani Mohammadi *et al*. [28] in a study concluded that adding thiopental to propofol reduces pain caused by intravenous propofol injection. The mechanism of pain when injecting propofol is not yet well understood. However, it is speculated that a direct stimulus may cause an immediate sensation of pain or an indirect effect that depends on the release of mediators to the onset of pain with delayed onset [2]. Delayed pain (10-20 seconds) results from an indirect effect on the endothelium due to the release of quinogens [38]. Finally, the propofol is a group of drugs that stimulate the skin, mucous membranes, and inner walls of the veins [31]. Vatankhah *et al*. [19] in a study concluded that lidocaine reduced pain during propofol injection, and that lidocaine had a greater effect than hydrocortisone. Therefore, the use of these drugs may be able to reduce the pain caused by propofol injection. Eydi *et al*. [20] in a study reported that lidocaine alone or in combination with nitroglycerin both reduced pain following propofol injection. Khezri. [29] conducted a study concluded that the pretreatment with low-dose ephedrine reduced the incidence rate and intensity of pain during propofol injection, but was not as effective as lidocaine. Safavi *et al*. [29] in a study stated that intravenous injection of magnesium sulfate, lidocaine, and ketamine had almost the same effect in reducing pain during propofol injection. Zahedhossein khan *et al*. [25] in a study concluded that there was no significant difference between lidocaine and ephedrine groups. Movafegh *et al*. [30] in a study stated that metoclopramide reduced the pain caused by propofol injection more than lidocaine. The analgesic effects of lidocaine in reducing pain following propofol injection not only occur because of its topical analgesic effects, but also because of reducing the pH of propofol solution. According to a hypothesis, its reduction causes the propofol solution to migrate to the fat phase and reduces the amount of propofol in the aqueous phase, thereby reducing pain. [37] Soltani Mohammadi *et al*. [28] conducted a study concluded that adding thiopental to propofol reduced pain caused by intravenous propofol injection.Studies on the physicochemical properties of the propofol-thiopental mixture have proven the compatibility of this combination, and found no trace of instability [41-45]. Anil Agarwal *et al*. [11] conducted a study on pretreatment with thiopentone for prevention of pain associated with propofol injection. Result showed that pretreatment with thiopental was most effective in attenuating pain on propofol injection. Safavi *et al*. [27] in a study examined the effects of sufentanil or remifentanil on prevention of pain during propofol injection. Patients were randomly divided into four groups of fentanyl, remifentanil, sufentanil and normal saline. The results of this study showed that the intravenous remifentanil injection (20 µg) one minute before propofol injection compared to intravenous sufentanil (10 µg) more effectively reduces the incidence and intensity of pain during injection. Akhondzade *et al*. [22] in a comparative study examined the analgesic effects of ketamine and fentanyl during propofol injection in patients under general anesthesia. The results showed that fentanyl was more potent in reducing pain than ketamine and normal saline. Despite the half-life of 3-4 hours of this drug, this can be justified compared to other groups, even up to 6 hours after surgery. Although it took 5 to 15 minutes for fentanyl to peak, 72% of patients reported analgesia at the time of propofol injection 45 seconds after receiving the drug.

Table 1: Assessment of pain.47 (McCrirrick and Hunter, 1990)

Pain score	Degree of pain	Response
0	None	Negative response to questioning.
1	Mild	Pain reported in response to questioning only without any behavioural signs.
2	Moderate	Pain reported in response to questioning and accompanied by a behavioural signs or pain reported spontaneously without questioning.
3	Severe	Strong vocal response/ response accompanied by facial grimacing, arm withdrawal or tears.

Materials and Methods

Study Design

Obseravational study

Study period

12 months, December 2021-November 2022

Study setting

Major operation theatre, Department of Anaesthesiology, Government Medical college, Kottayam.

Study population

ASA 1 and ASA 2 patients of age 18 to 60 years undergoing elective surgeries under general anaesthesia in Kottayam Government Medical College during 2021- 2022.

Sample size

$$\text{Formula-}\ \frac{(Z_{\alpha/2} + Z_{\beta})^2 pq(r+1)}{r(p_1-p_2)^2}$$

Z α/2 = standard normal deviate for two-tailed test based on alpha level=1.96
Zβ = standard normal deviate for one-tailed test based on beta level=0.84
r = ratio of controls to cases=1
p1 = proportion of patients in group 1 with pain=39 p2 = proportion of patients in group 2 with pain=3
p= average percentage of the character i.e. pain = $\frac{(p_1+p_2)}{2}$ and q=1-p
[from the study done by Anil Agarwal *et al*. [11]

Sample size - 21 in each group
Inclusion criteria
1. ASA Grade 1 and 2
2. Age between 18 and 60
3. Patients undergoing elective surgeries under general anaesthesia

Exclusion criteria
1. Patients allergic to any drugs
2. Emergency surgery
3. Patients with respiratory, cardiovascular, cerebrovascular, renal disease
4. Pregnant patients

Sampling method
Consecutive sampling

Study procedure
After obtaining the Institutional research methodology and ethical committee approval for the study, subjects will be selected based on inclusion and exclusion criteria. A written informed consent will be taken from patients and required data will be collected preoperatively and pain on propofol injection will be assessed during induction of anaesthesia using a 4 point pain scale.
In the operation theatre, after instituting routine monitoring, an 18G cannula was inserted without local infiltration on the dorsum of non dominant hand of the patient and intravenous fluid 0.9% Nacl will be started. Standard monitors such as ECG, pulse oximeter, non invasive blood pressure will be attached and preoperative heart rate, SPO_2, blood pressure will be obtained.

Prior to propofol either one of the three is given
Group L: Receive preservative free 2% Lignocaine 1 mg/kg IV
Group F: Receive preservative free Fentanyl 2mcg/kg IV over 1-2 min
Group T Receive Thiopentone sodium 0.5mg/kg IV

Patients will be assigned into 3 groups as per the decision taken by the senior consultant. After giving 30% induction dose, patients are asked regarding pain and pain assessed by the investigator using 4 point pain scale. All patients post induction will receive standard GA.
After preoxygenation with 100% O2 for 30 minutes, anaesthesia was induced with rest of propofol (2mg/kg). Endotracheal intubation was done with succinylcholine 2mg/kg. Trachea was intubated by anaesthesiologist in charge of operation theatre with cuffed endotracheal tube of 6.5mm to 7.5mm ID in females and 7.5mm to 8.5mm ID in males. Bilateral air entry was confirmed by five point auscultation and cuff was inflated and endotracheal tube was fixed.
Patients are administered intravenous vecuronium (0.1mg/kg) after tracheal intubation for muscle relaxation. Anaesthesia will be maintained with oxygen and nitrous oxide. Vecuronium is administered as 0.02 mg/kg bolus to maintain muscle relaxation at the end of surgery, patient will be ventilated with 100%oxygen at a flow rate of 6L/mnt. Once patient developed spontaneous breathing effort, neuromuscular blockade will be antagonized with neostigmine 0.05mg/kg and glycopyrolate 0.01mg /kg.
Extubation will be performed when adequate spontaneous ventilation and response to verbal commands are established. Adverse venous reactions like appearance of any tenderness, redness, hardness or cord like sensation over the cannulated vein noted.

Statistical method
Data will be coded and entered in Microsoft Excel sheet will be analysed using SPSS statistical software version 22. Quantitative variables will be summarized using mean and standard deviation (SD) if data follows normality else by using median and interquartile range (IQR). Categorical variables will be summarized using frequency and percentages. To compare quantitative variables between the three groups, we will be performing ANOVA if data follows normality, else by using Kruskal Wallis test. Association of different qualitative variables between the groups will be tested using Chi-square test/Fisher's exact test. $p<0.05$ will be considered as statistically significant.

Results
The study was conducted on 63 patients divided into three groups of 21 patients each using consecutive sampling.

Group L
Patients in group L received 2% preservative-free lignocaine 1mg/kg iv 1 minute prior to 30% induction dose of propofol for general anaesthesia. Preoperative data was collected, and pain on propofol injection was assessed during induction of anaesthesia using 4-point pain scale.

Group F
Patients in group F received preservative-free fentanyl 2mcg/kg iv 1 minute prior to 30% induction dose of propofol for general anaesthesia. Preoperative data was collected, and pain on propofol injection was assessed during induction of anaesthesia using 4-point pain scale.

Group T
Patients in group T received thiopentone Sodium 0.5mg/kg iv 1 minute prior to 30% induction dose of propofol for general anaesthesia. Preoperative data was collected, and pain on propofol injection was assessed during induction of anaesthesia using 4-point pain scale.

Demographic characteristics and comparison between participants in three groups
Gender

Table 2: Comparison of cases in three groups based on gender

Sex	Group			Total
	Lidocaine	Fentanyl	Thiopentone Sodium	
Female	13(61.9%)	13(61.9%)	10(47.6%)	36(57.1%)
Male	8(38.1%)	8(38.1%)	11(52.4)	27(42.9%)
Total	21	21	21	63

Fisher's exact test for sex, p value= 0.690

There was no significance difference between the three groups with respect to sex.

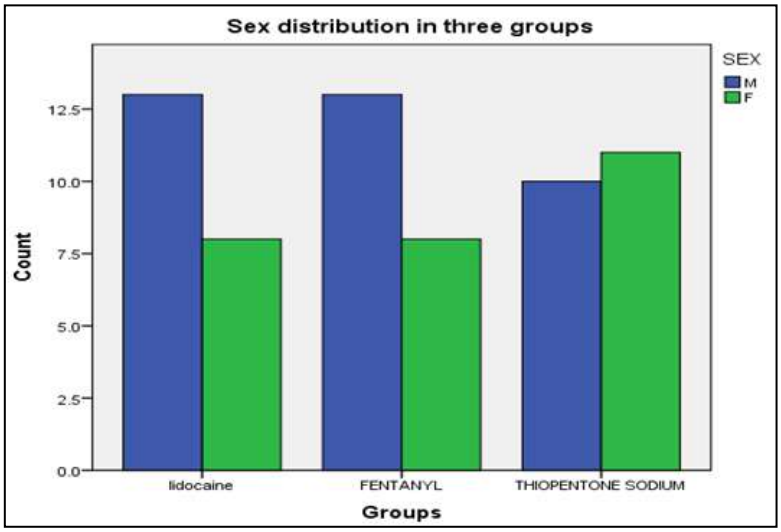

Fig 1: Distribution of cases in three groups based on sex

Age

Table 3: Comparison of cases in three groups based on age

Group	Age		P value (ANOVA)
	Mean	Std. Deviation	
Lidocaine	36.76	12.235	0.598
Fentanyl	31.76	9.110	
Thiopentone Sodium	43.52	7.916	

There is no significant difference between the three groups with respect to age (p=0.598). The mean age of the Group L is 36.76±12.235 years; the mean age of the Group F is 31.76±9.110 and the mean age of Group T is 43.52±7.916 years.

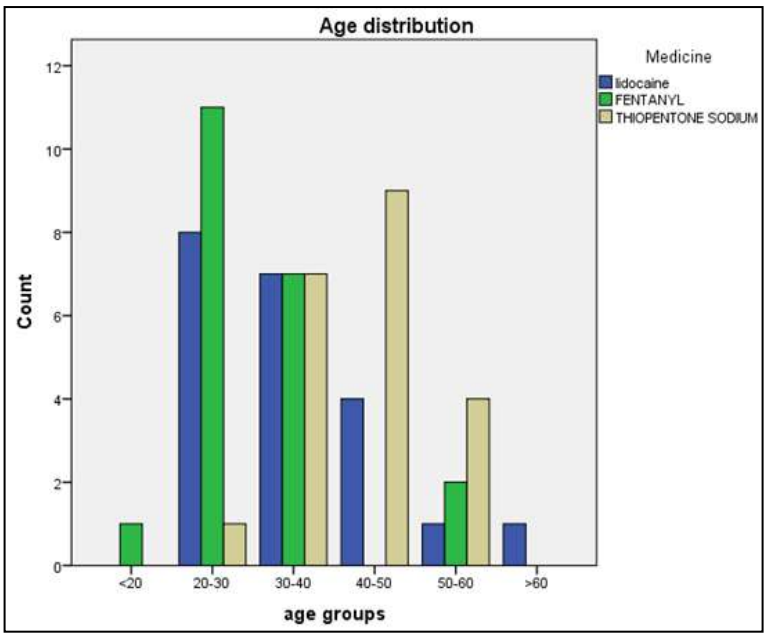

Fig 2: Distribution of cases in three groups based on Age

Weight

Table 4: Comparison of cases in three groups based on weight

Group	Weight		P value(ANOVA
	Mean	Std. Deviation	
Lidocaine	63.71	4.280	0.135
Fentanyl	64.38	7.025	
Thiopentone sodium	72	6.419	

There was no significant difference between the three groups with respect to weight (p=0.135). The mean weight of the Group L is 63.71±4.280 Kg; the mean weight of the Group F is 64.38±.025 and the mean weight of Group T is 72±6.419 Kg.

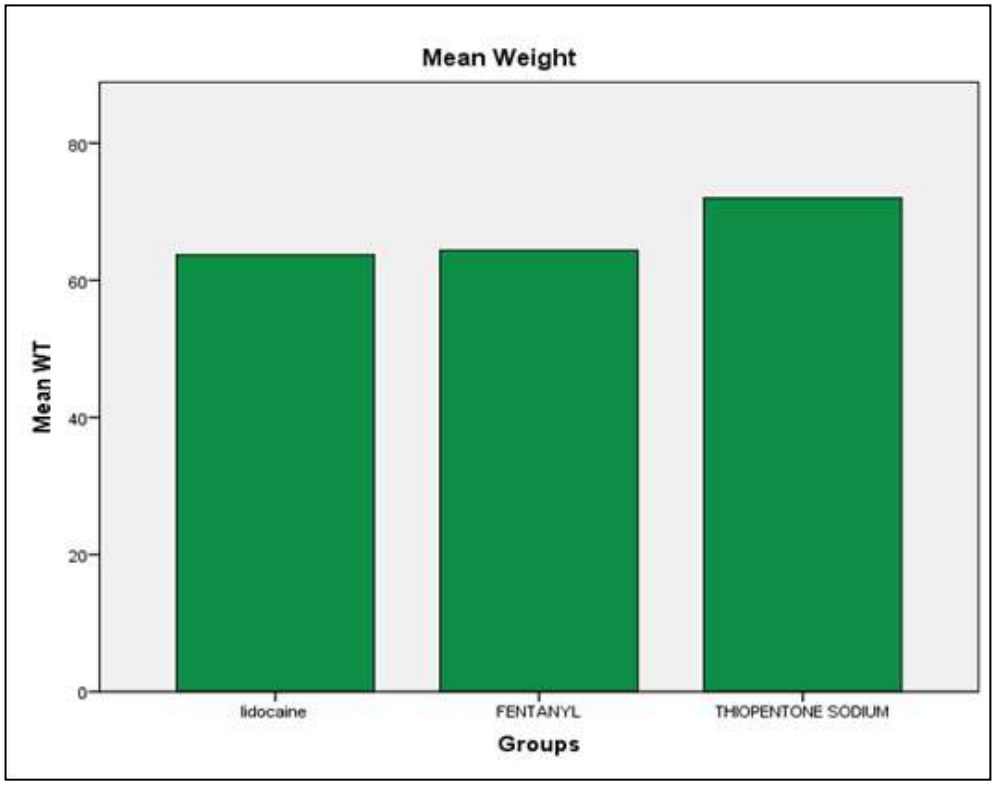

Fig 3: Distribution of cases in three groups based on weight

It was observed that there was no statistically significant difference between the groups with respect to age, weight, sex. Fisher's exact test is used to analyse the independency of sex variable. ANOVA used for age and weight variables. Demographic characteristics, including age, sex and weight in the study group is presented in the tables 1,2,3. No significant differences were observed among the groups.

Hemodynamic variables and comparison between participants in three groups

Heart rate

Table 5: Comparison of cases in three groups based on Heart Rate

Group	Heart Rate		P value(ANOVA
	Mean	Std. Deviation	
Lidocaine	85.57	5.844	0.181
Fentanyl	83.57	6.539	
Thiopentone sodium	81.81	7.075	

There is no significant difference in heart rate between the three groups.

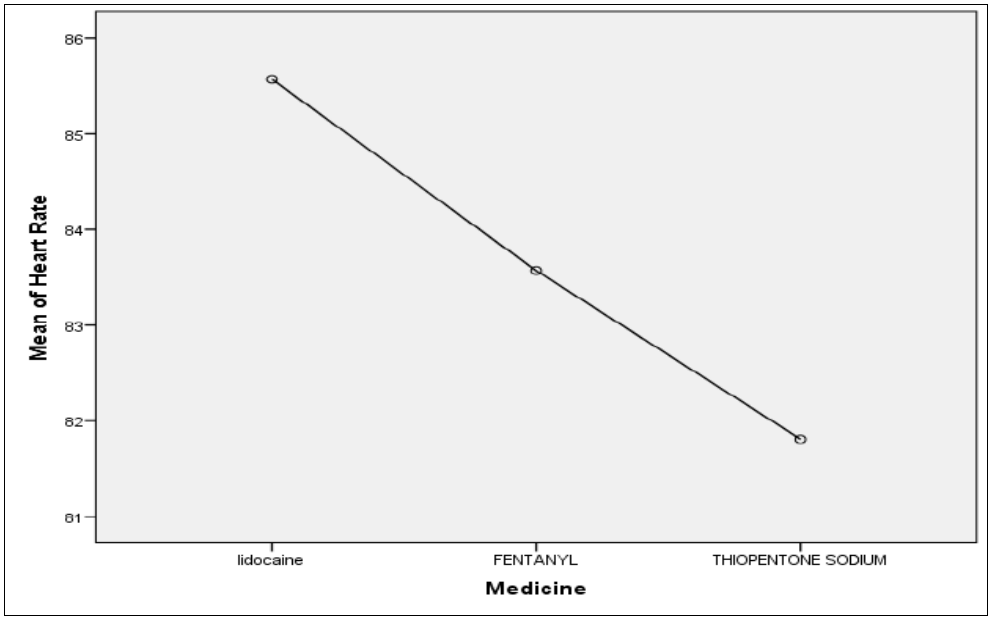

Fig 4: Mean Plot- Heart Rate

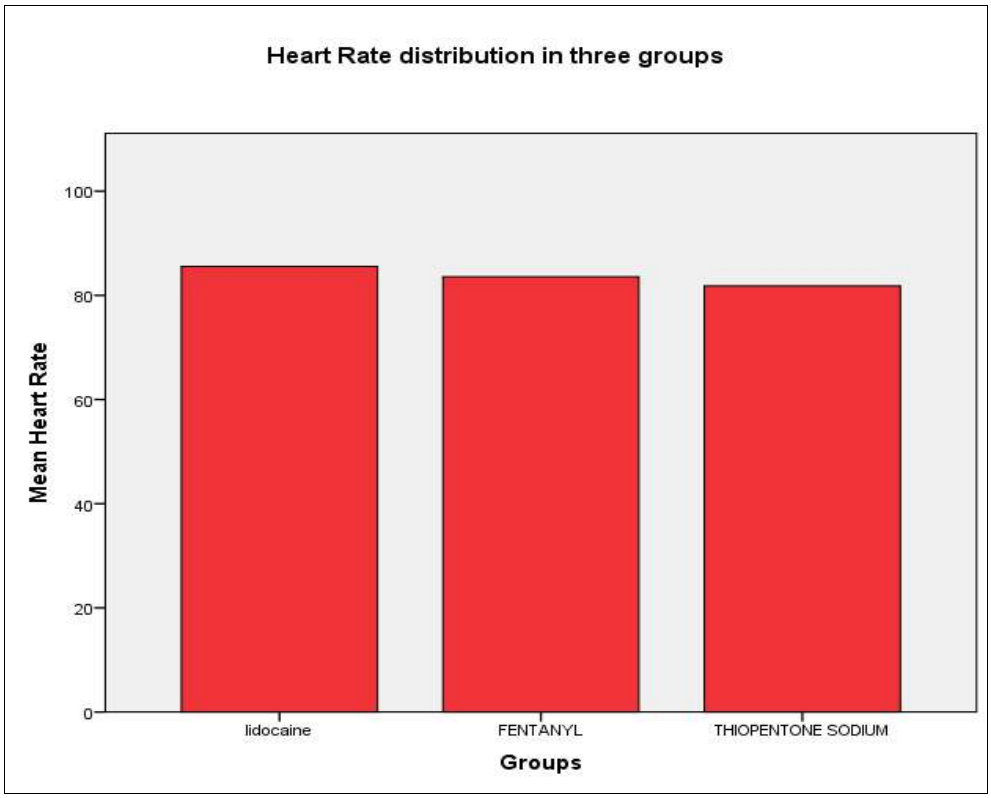

Fig 5: Distribution of cases in three groups based on heart rate

Systolic blood pressure

Table 6: Comparison of cases in three groups based on Systolic Blood Pressure

Group	Systolic Blood Pressure		P value(ANOVA)
	Mean	Std. Deviation	
Lidocaine	127.76	7.245	0.013
Fentanyl	127.86	6.093	
Thiopentone Sodium	135.65	13.683	

There is significant difference in Systolic Blood Pressure (SBP) between the three groups.

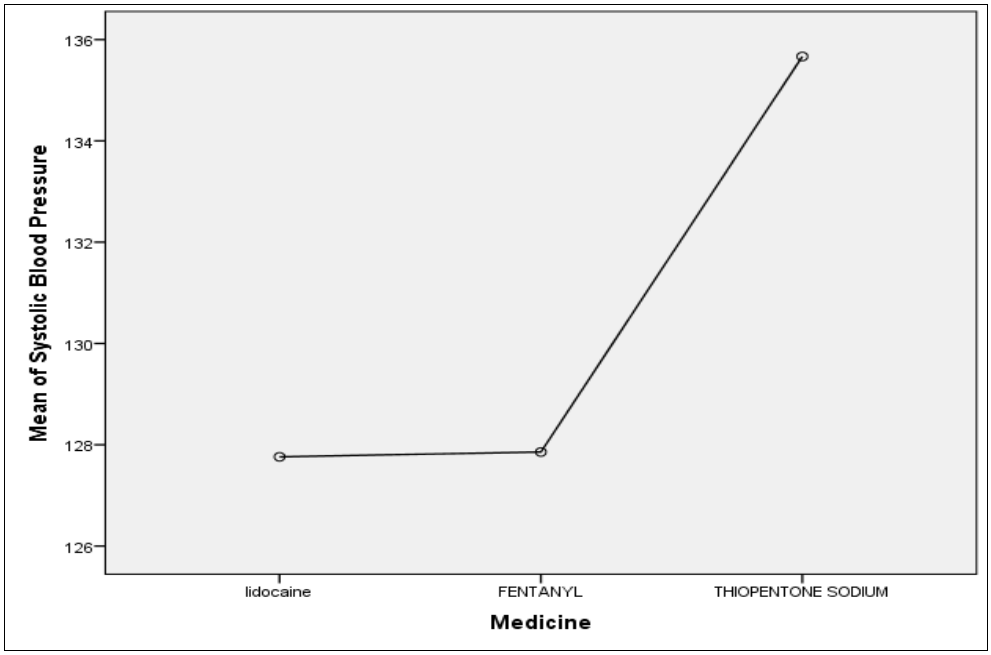

Fig 6: Mean plot- Systolic Blood Pressure

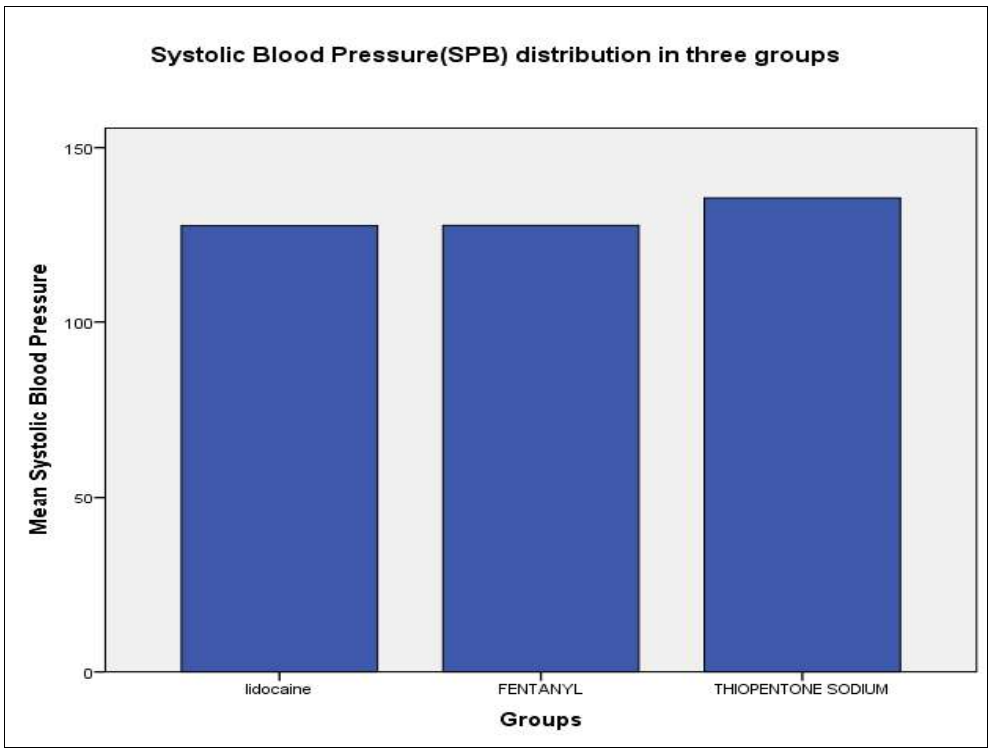

Fig 7: Distribution of cases in three groups based on Systolic Blood Pressure.

Diastolic blood pressure

Table 7: Comparison of cases in three groups based on diastolic blood pressure

Group	Diastolic blood pressure		P value(ANOVA)
	Mean	Std. Deviation	
Lidocaine	80.00	4.648	0.003
Fentanyl	82.10	3.961	
Thiopentone sodium	77.29	4.314	

There is significant difference in Diastolic Blood Pressure between the three groups (p-value=0.003).

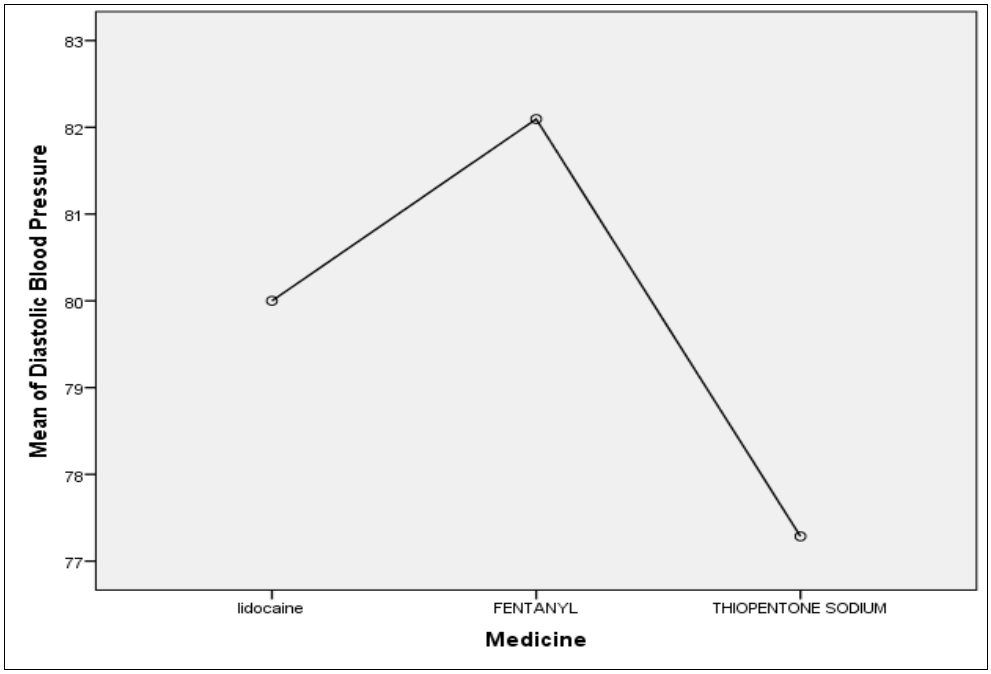

Fig 8: Mean plot- Diastolic Blood Pressure

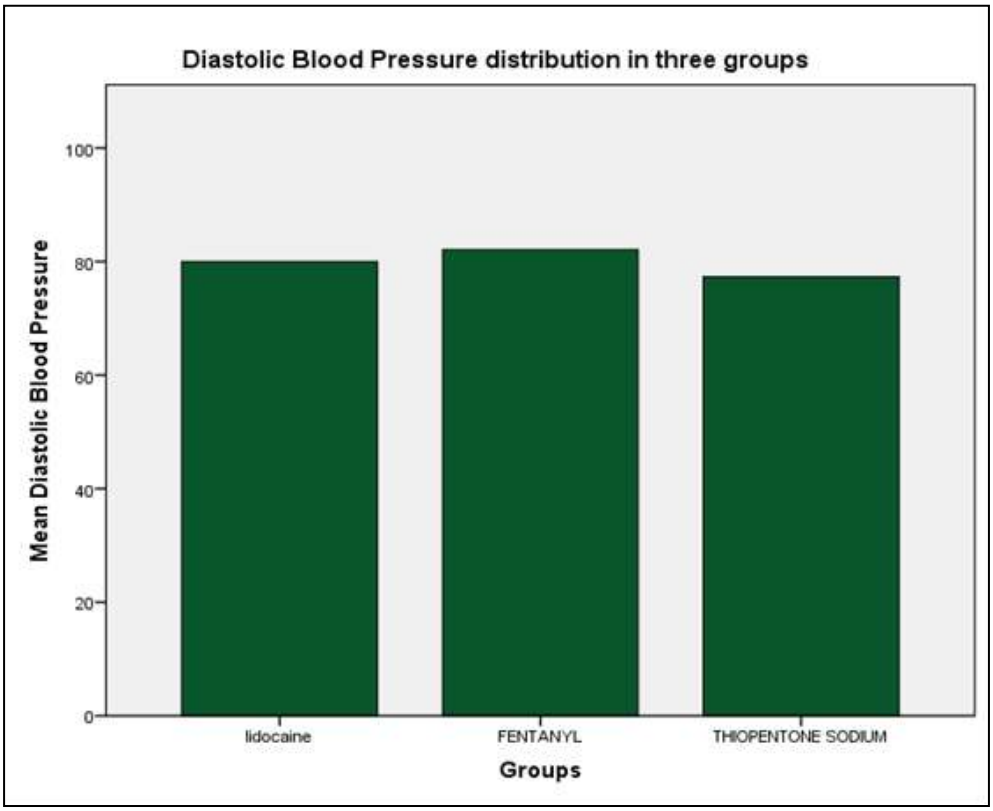

Fig 9: Distribution of cases in three groups based on Diastolic Blood Pressure.

Oxygen Saturation

Table 8: Comparison of cases in three groups based onoxygen saturation

Group	SPO2		P value (ANOVA)
	Mean	Std. Deviation	
Lidocaine	99.33	0.730	0.199
Fentanyl	98.86	0.854	
Thiopentone Sodium	98.95	1.071	

There is no significant difference in Oxygen Saturation (SPO2) between the three groups

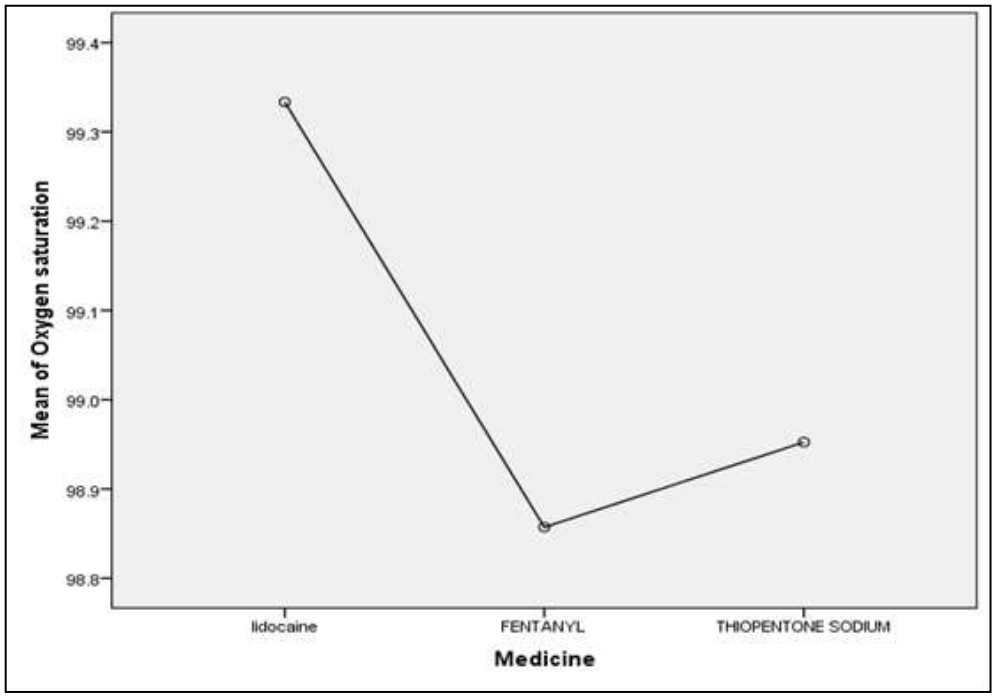

Fig 10: Mean plot- Oxygen Saturation

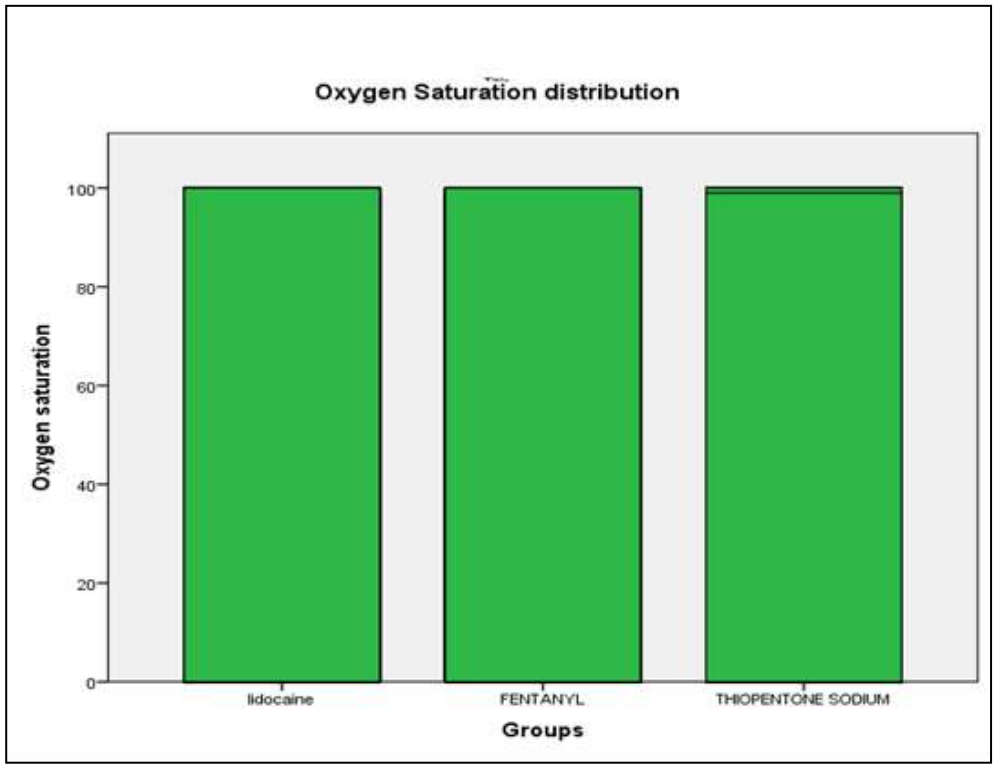

Fig 11: Distribution of cases in three groups based on Oxygen Saturation

Pain

Table 9: Comparison of cases in three groups based on incidences of pain

Pain Scale	Group			Total
	Lidocaine	Fentanyl	Thiopentone Sodium	
Not perceived	11(52.4%)	11(52.4%)	14(66.7%)	36(57.1%)
Pain reported only when asked	9(42.9%)	9(42.9%)	7(33.3%)	25(39.7%)
Moderate pain	1(4.8%)	1(4.8%)	0	2(3.2%)
Severe Pain	0	0	0	0
Total	21	21	21	63

Fisher's exact test, p-value=0.170.

The incidence of pain on propofol injection were same in both groups, i.e. Group L (Lignocaine) and Group F(Fentanyl) the percentage value is equal to 47.7% (10 out of 21). In Group T (Thiopentone Sodium) the percentage value is 33.3%(7 out of 21). Severe pain were not reported in any of the cases. Applying Fisher's exact test for the incidence of pain on propofol injection in the three groups, the difference between the groups (Group L vs. Group F, Group F vs. Group T, Group L vs. Group T) were statistically not significant(P=0.170). Among the cases in three groups, the lowest incidences of pain on propofol injection were observed in Group T, whereas Group L and Group F shown the same incidences of pain on propofol injection.

Severity of Pain

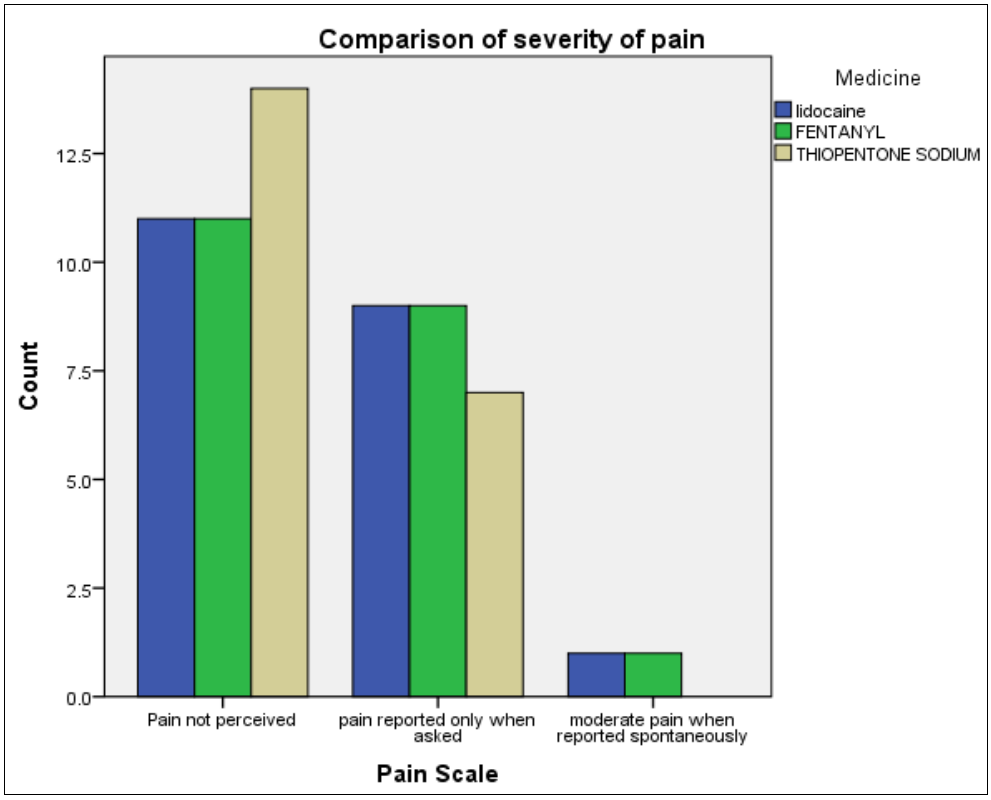

Fig 12: Distribution of cases in three groups based on severity of pain

The incidence and severity of pain were not significantly different between the Lignocaine, Fentanyl and Thiopentone sodium groups.

Discussion

The study should be elaborately discussed with the significance of the results with the help of earlier work and reports.

Propofol is commonly used for induction of anaesthesia, although the pain during its injection remains a major concern. Several methods have been used to lessen the pain of propofol injection. The goal of the current study was to examine the effectiveness of pretreatment with 2% lignocaine, fentanyl, and thiopentone sodium on alleviating discomfort caused by propofol.

Propofol is a member of the class of phenols that can irritate mucous membranes, the skin, and the intima of veins.31 Propofol causes pain on injection by acting indirectly on the endothelium to activate the kallikrein-kinin system and releases bradykinin, thereby producing venous dilatation and hyperpermeability. These events increase the interaction between the aqueous phase of propofol and free nerve endings [6, 35]. Propofol injection pain has been reduced using a variety of techniques, including using larger veins, [40] slowing down the injection process, injecting propofol into a fast-moving intravenous fluid, diluting it with 5% glucose or 10% intralipid, injecting lidocaine, alfentanil, fentanyl, or thiopental beforehand, injecting cold saline at 4 degrees Celsius before propofol, and mixing lidocaine and cooling propofol to 4 degree Celsius.

The mechanism by which thiopentone reduces pain on propofol injection is unknown but could involve several mechanisms. First, thiopental physical characteristics, such as its alkalinity or lipid solubility may reduce pain sensitivity [24]. Second, thiopental and propofol administered concurrently at subanaesthetic dosages may reduce the sense of pain [46]. Finally, thiopental may work by inhibiting bradykinin from being released.

According to our study, thiopental had a lower incidence of discomfort after receiving a propofol injection than the groups receiving lignocaine and fentanyl. According to a study by Akbari *et al*. on the effectiveness of ketamine, magnesium sulphate, and sodium thiopental for treating the pain associated with propofol injections, they reported that pain was significantly less in sodium thiopental (16%) and ketamine (4%), compared to magnesium sulphate (36%) [52]. Thiopental 0.5mg/kg shown noticeably reduced pain compared to lignocaine, according to Kumar *et al*. The effects of normal saline, lignocaine 2%, and sodium thiopental at doses of 0.5 mg/kg and 0.25 mg/kg on pain brought on by propofol injection were compared by Agarwal *et al*. 77% of patients in the saline group, 39% in the lidocaine group, 32% in the 0.25% sodium thiopental group, and 3% in the 0.5mg/kg sodium thiopental group

reported having pain. Therefore, it was advised to administer 0.5mg/kg thiopental sodium 1 minute prior to the injection of propofol.

A derivative of phenyl piperidine, fentanyl is a synthetic opioid that primarily functions as an agonist at opioid receptors. Despite the fact that its primary therapeutic impact is linked to its interaction with opioid receptors in the brain, fentanyl may have local anaesthetic effects on nerves. In a preliminary study by Pang and Huang, fentanyl did have a small analgesic advantage as compared to placebo in lessening the pain associated with propofol injections [13]. In addition, fentanyl provides postoperative analgesia and haemodynamic stability, making it a possible treatment for pain brought on by medicines like propofol.

Kobayashi *et al*. [54] evaluated the effects of 100 mcg fentanyl pretreatment and premixing 40 mg lidocaine with propofol. There was no noticeable difference in pain incidence between the fentanyl and lidocaine groups, however there was a substantial drop in pain incidence in both the fentanyl (40%) and lidocaine (35%), compared to the placebo (80%, p=0.01).54 Although Kobayashi *et al*. supplied fentanyl 3 minutes before propofol injection, we gave it 1 minute before propofol, but it didn't seem to have much impact on how well fentanyl worked to reduce the discomfort of the propofol injection. This finding is consistent with a study (2007) by Imanaga *et al*. [38] in which propofol 1 mg/kg was given as a bolus 1 and 3 minutes after 100 mcg of fentanyl. The 1 minute and 3 minute groups exhibited no noticeable difference, and both had significantly lower pain scores (p=0.001) than the control group. This study backs up our findings that fentanyl given 1 minute before propofol considerably reduced the discomfort induced by propofol.

In the current study, 4.8% of subjects reported significant pain, 42.9% reported mild pain, and none reported severe pain after receiving a propofol injection together with lidocaine and fentanyl. The thiopental group comprised 33.3% of patients with mild pain and none with severe pain. There were no noticeable variations in the frequency or intensity of pain between the three groups.

Conclusion

Results of this study suggest that thiopentone sodium and fentanyl were equally effective as lignocaine in reducing the pain during injection of propofol. All treatments were well tolerated by the patients without significant adverse effects. It can be concluded that pretreatment with thiopentone sodium 0.5 mg/kg and preservative free fentanyl 2 mcg/kg reduced the incidence of propofol induced pain similar to preservative free 2% lignocaine 1 mg/kg.

Conflict of Interest

Not available

Financial Support

Not available

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