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Effect of Prior Administration of Butorphanol and Lidocaine on Pain during Propofol Injection

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ABSTRACT

Background: The aim of this study was to investigate the effect of prior administration of butorphanol, lidocaine and normal saline in minimizing Propofol injection pain. **Methods**: The study comprised of 99 patients divided into three groups of 33 each, in the department operation rooms of Anaesthesiology/Surgery, State Referral Hospital of Zoram Medical College, Falkawn, Mizoram during the period of March 2017 to April 2019. Ninety nine patients of ASA grade I and II, aged between 18 and 60 years of both sexes scheduled to undergo major elective surgery under general anaesthesia were included. **Results:** Pain on intravenous injection of propofol was experienced by 9 (27.27%) patients from butorphanol group as compared to 18 (54.55%) and 22 (66.67%) patients in the lidocaine and placebo groups respectively. Data analysis showed a chi-square test value of 15.3 and p-value 0f <0.05. **Conclusion**: The present study shows that prior administration of butorphenol significantly reduced pain on intravenous injection of propofol whereas lidocaine pretreatment too reduces propofol injection pain as compared to a placebo, but failed to show statistically significant results.

Keywords: Propofol, Butorphanol, Lidocaine, Anaesthesia, Normal Saline.

INTRODUCTION

Propofol (2, 6 di-isopropylphenol) is intravenous anaesthetic drug for use in the induction of anaesthesia. Because of its rapid onset of action and rapid recovery time plus less hangover on recovery, it is often the preferred agent for intravenous induction of general anaesthesia. However, its main drawback is pain on injection in 28-90% of patients.[1]

The appropriate use of intravenous analgesics and anaesthetics to decrease the incidence and intensity of pain during Propofol injection for the smooth induction of anaesthesia requires understanding of both the early pharmacokinetics of bolus dose and the pharmacodynamics of the drugs. Various methods have been used for attenuating pain during IV injection of Propofol with varying results, such as using larger veins,[2] injecting into a large antecubital vein,[3] diluting Propofol solution,[4] prior injection of lidocaine,[5] alfentanil,[6] fentanyl,[7] pentothal,[8] metoclopramide,[9] butorphanol,[10] injection cold saline at 4oC before propofol,[11] cooling Propofol to 4oC,[12] or mixing Lidocaine in propofol.[13]

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The analgesic effect of lidocaine may occur because of a local anaesthetic effect or an inhibitory effect on the enzymatic cascade which leads to release of kinin.[14] It has been found that 0.5% lidocaine has the same effective action as 2% lidocaine to reduce Propofol injection pain when different concentration and dosage of lidocaine, like 1ml and 2ml of 1%lidocaine, 1ml and 2ml of 0.5%lidocaine and 2ml of 2% lidocaine were compared to prevent Propofol injection pain.[15]

Butorphanol tartrate is a synthetic, strong analgesic with both narcotic agonist and antagonistic properties. It is an agonist at kappa receptors and is 5-8 times more potent than morphine. After intravenous administration the onset of analgesia occurs rapidly (within 1 minute) with peak effect occurring in about 4-5 minutes. The site of action of butorphanol in reducing the pain of propofol injection is not clear, but it could be through opioid receptors (central and/or peripheral), local anaesthetic, or both10.

MATERIALS AND METHODS

The study was conducted in the department of Anaesthesiology/General Surgery, State Referral Hospital of Zoram Medical College, Falkawn, Mizoram, India, during the period of March 2017 to April 2019. Before taking up the study, approval for carrying out the research work was obtained from

the Hospital Ethical Committee. Informed Consent was taken for each case. Ninety nine patients of ASA grade I and II, aged between 18 and 60 years of both sexes scheduled to undergo major elective surgery under general anaesthesia were included. Patients with a history of adverse response to propofol, lidocaine and butorphanol and patients with hepatic, renal, cardiac, hematological, metabolic and thrombophlebitic diseases and patients who had received an analgesic medication within 24hrs before surgery were excluded from the study. Patients were randomly allocated to one of the three groups, each group comprised of 33 patients. Group I received 0.9% saline (2ml) intravenously [Saline group]. Group II received lidocaine 40mg of 2% solution (2ml) intravenously [Lidocaine group]. Group III received butorphanol 2mg (2ml) intravenously [Butorphanol group].

Pre-anaesthetic evaluation was done in all the patients. Age, sex, weight, height, pre-anaesthetic medications, arterial blood pressure, heart rate and respiratory rate were collected. All patients had received oral pretreatment with ranitidine 150mg and lorazepam 2mg the night before surgery and 2 hours before induction of anaesthesia. On the day of operation, patients were cannulated with 18 gauge intravenous catheter on the dorsum of non-dominant hand for administration of study drug. Another cannula was placed on the other hand for infusion of IV fluids. All were premedicated with injection glycopyrrolate 0.2mg intramuscularly 1hour before induction of anaesthesia. After instituting electrocardiogram, pulse oximeter and non-invasive arterial blood pressure monitoring, the test drugs which were made in 2ml with normal saline was administered over 10 seconds. After 1 min patients were then given one fourth of the total calculated dose of Propofol over 5s. The induction dose of propofol was 2mg per kilogram. All study drugs were maintained at room temperature and used within 30 min of preparation. During the propofol injection, patients were continuously observed for vocal response, facial grimacing, arm withdrawal or tears suggesting severe pain. If the signs and symptoms were absent, then patients were questioned every 5-10secs during induction regarding the presence of pain or discomfort. Pain was graded using a four point scale: 0= no pain, 1 = mild pain (pain reported only in response to questioning without any behavioral signs), 2 = moderate pain (pain reported in response to questioning and accompanied by a behavioral signs or pain reported spontaneously without questioning), 3 = severe pain (strong vocal response or response accompanied by facial grimacing, arm withdrawal or tears)

Within 24 h after the operation, the injection sites were checked for pain and the absence or presence of erythema, wheal or flare. Once the assessment of injection pain had been made, induction of anaesthesia was then completed with remaining dose of Propofol and tracheal intubation was facilitated with injection succinylcholine. Anaesthesia was maintained with halothane, vecuronium and nitrous oxide 66% in oxygen with controlled ventilation.

RESULTS

Table 1: showing age distribution in the three groups

Class interval (in years)	Group I Normal Saline	Group II Lidocaine	Group III Butor phanol
11-20	5	4	2
21-30	10	4	9
31-40	7	12	8
41-50	9	8	8
51-60	2	5	6
Total	33	33	33

Table 2: showing body weight distribution in the three groups

Class interval (in kg)	Group I Normal Saline	Group II Lidocaine	Group III Butor phanol
31-40	1	3	1
41-50	12	10	12
51-60	15	12	13
61-70	3	7	6
71-80	2	0	0
81-90	0	1	1
Total	33	33	33

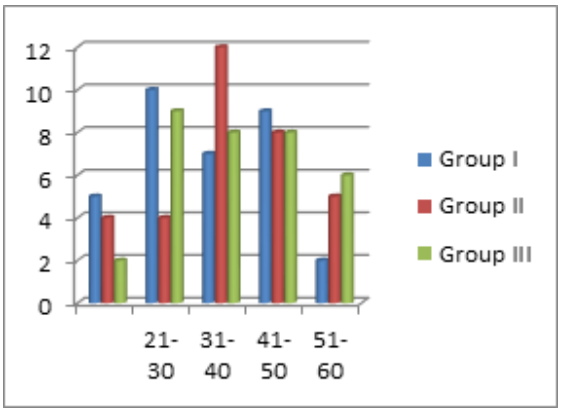


Figure 1: showing distribution of patients in relation to their age in the three groups

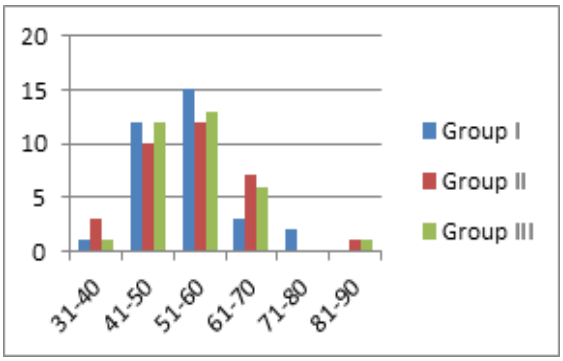


Figure 2: showing distribution of patients in relation to their body weight in the three groups

Over the study period, a total of 99 patients with 33 in each group were studied. Their age ranged from 19-59 years, 18-56 years and 19-59 years in group I, II and III respectively. The overall sex distribution of the three groups was 38 male and 61 female. Their bodyweight ranged from 40-74kgs in group I; 40-84kgs in group II and 40-82kgs in group III. Most of the patients, except 3 patients in group III and 1 each in Group I and II were ASA grade I.

Table 3: showing Sex-wise distribution of patients in the three groups

Sex	Group I Normal saline (n=33)	Group II Lidocaine (n=33)	Group III Butorphanol (n=33)	Chi-square Test (x2) value	P value
Male	13	10	15	0.162	P>0.05
Female	20	23	18		
Total	33	33	33		

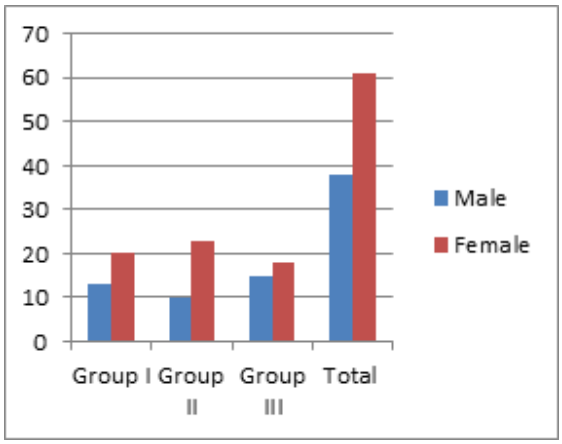
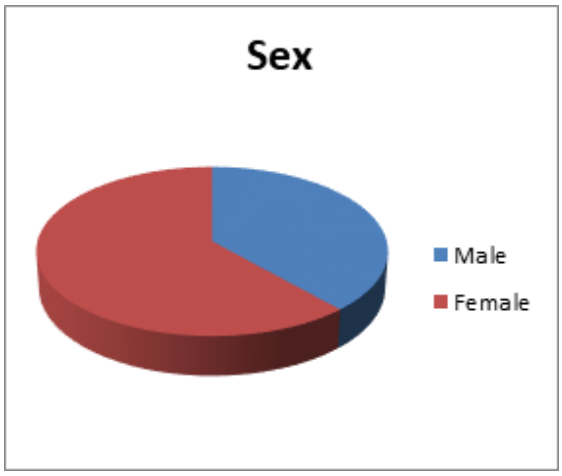
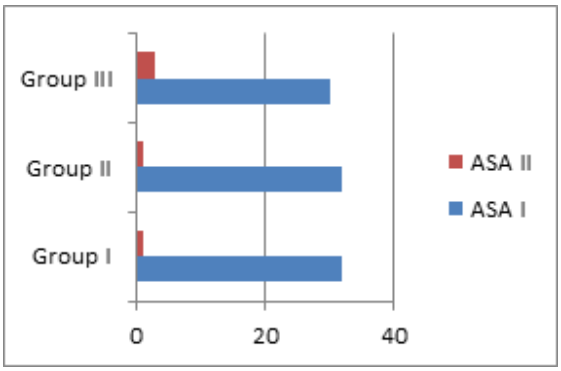


Figure 3: showing sex-wise distribution of patients in three groups



Pie diagram showing overall sex distribution



Bar chart showing ASA distribution in the three groups

[Table 4 & Figure 4] shows the distribution of pain during propofol injection amongst the patients in the three groups. The number of patients with no pain were 11 (33.33%) in group I, 15 (45.45%) in group II and 24 (72.72%) patients in group III. Mild pain was experienced by 16 (48.48%), 10 (30.30%) and 9 (27.27%) of the patients in group I, group II and group III respectively. Number of patients with moderate pain in group I, group II and group III was 6 (18.18%), 7 (21.21%) and 0 (0%) respectively. Severe pain was experienced by 0 (0%), 1 (3.93%) and 0 (0%) of the patients in group I, group II and group III respectively. Chi-square test value was 15.3 and statistically significant (P<0.05). Data analysis showed that prior administration of butorphanol significantly reduced the incidence of pain on propofol injection when compared to placebo and lidocaine.

Table 4: showing the distribution of pain during propofol injection amongst the patients in the three groups

	Group I Normal Saline (n=33)	Group II Lidocaine (n=33)	Group III Butorphanol (n=33)	Statistical test value	P value & remarks
Pain	22 (66.67%)	18 (54.55%)	9 (27.27%)		
Grading of pain					
No pain	11(33.33%)	15(45.45%)	24(72.72%)	Chi-square test	P<0.05
Mild pain	16(48.48%)	10(30.30%)	9 (27.27%)	Value of 15.3	(significant)
Moderate pain	6 (18.18%)	7 (21.21%)	0 (0%)		
Severe pain	0 (0%)	1 (3.03%)	0 (0%)		
Total	33	33	33		

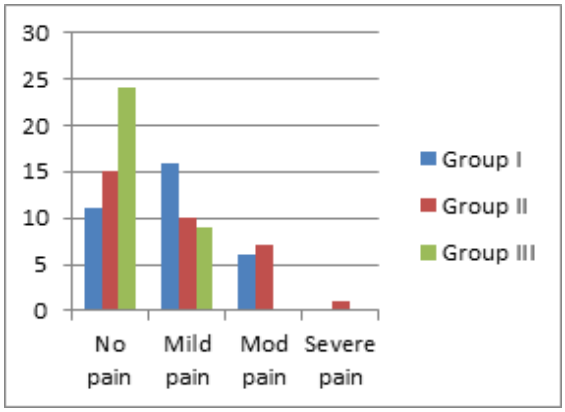


Figure 4: shows the distribution of pain on propofol injection amongst the patients in the three groups

Group I= Normal saline, II=Lignocaine & III=Butorphanol

Table 5: showing the intergroup comparison of pain grades in the three groups.

Intergroup	Chi-square value	P value	Remarks
Group I & II	2.29	P>0.05	Not significant
Group I & III	6.00	P<0.05	Significant
Group II & III	10.14	P<0.001	Highly significant

Group I= Normal saline, II=Lignocaine & III=Butorphanol

In comparing group I and group II, 11 patients in group I had no pain whereas 15 of the patients in group II had no pain on injection of propofol; the number of patients with mild pain in group I was 16 and 10 in group II; group I has 6 patients with moderate pain whereas in group II there were 7 patients with moderate pain; none of the patients in group I experiences severe pain whereas group II had 1 patient with severe pain. Overall, the number of patients with no pain on propofol injection is more (45.45% vs. 33.33%) and lesser number of patients experience mild pain (30.30% vs. 48.48%) in group II when compared to group I. However, the Chi-square test value was 2.29 and found to be statistically not significant (P<0.05). Comparison of groups I and III shows that the number of patients with no pain was 11 in group I and 24 in group III; the number of patients with mild pain in group I was 16 and 9 in group III; Group I has 6 patients with moderate pain whereas group III has no patient with moderate pain; none of the patients in the two groups had severe pain i.e 0. The chi-square value was 6.00 and statistically significant (P<0.05). In comparing group II and III, the number of patients with no pain was 15 in group II and 24 in group III; the number of patients with mild pain was 10 in group II and 9 in group III; 7 patients in group II experiences moderate pain whereas no patients in group III experience moderate pain; severe pain was experienced by 1 patient from group II whereas no patients in group III experiences severe pain (0%). The chi-square test was 10.14 and found to be statistically highly significant (P<0.001).

Data analysis showed that prior administration of butorphanol significantly reduces propofol injection pain whereas in this study lidocaine reduces propofol injection pain on the basis of number of patients, but failed to show any significant reduction of pain on propofol injection statistically when compared to a placebo.

DISCUSSION

Propofol is one of the most commonly used intravenous anaesthetic agents because of its high quality of anaesthesia and rapid recovery. It is an excellent intravenous anaesthetic that belongs to the group of phenols, which can irritate the skin, mucous membrane, and venous intima.[16] It may activate the kallikrein-kinin system and release bradykinin, thereby producing venous dilation and hyperpermeability, which increases the contact between the aqueous phase of propofol and free nerve endings resulting in pain on injection. Pain on injection of propofol, which has been reported to occur in 28-90% of patients, is a major drawback to its use.[17]

Several authors have found that lidocaine reduces pain on propofol injection. Gehan G et al found that a dose of lignocaine 0.1mg/kg significantly reduced the incidence of pain and that there was no improvement when the dose was increased.[18] While investigating the effect of concentration and dosage of lidocaine in reducing propofol injection pain, Adachi H et al found that 0.5% lidocaine has the same effective action as 2% lidocaine for reducing propofol injection pain. A similar study conducted by Huseyin S et al comparing the concentration effect on propofol injection pain had comparable findings.[19] They found that pain was lesser with 10mg/ml concentration as compared to 10mg/ml and concluded that propofol injection pain depends on the amount of free propofol in the aqueous phase. Different concentrations of lidocaine were used in different studies like 4ml of 1% (40mg) and 2ml of 2% (40mg) lidocaine were used to find out satisfactory results.[20] Simultaneous bolus injection of lidocaine with propofol showed a similar clinical efficacy as compared with both pre-administration and pre-mixing of lidocaine in preventing propofol injection pain.[21]

In our study, we used lidocaine in a concentration of 2% in a dose of 40mg administered 1 minute prior to propofol injection (2mg/kg). we observed that lidocaine reduced pain on the basis of number of patients as compared to placebo (54.55% vs. 66.67%) but data analysis showed no statistically significant reduction of pain (P>0.05).

Butorphanol tartrate is a synthetic, strong analgesic with both narcotic agonist and antagonistic properties. It is an agonist at kappa receptors and is 5-8 time more potent than morphine. After IV administration the onset of analgesia occurs rapidly (within a minute) with peak effect occurring in about 4-5 minutes. The site of action of butorphanol in reducing the pain of propofol injection is not clear, but it could be through opioid receptors (central and/or peripheral), local anesthetic action or both. We administered butorphanol 1 minute before injection of propofol. Butorphanol could have acted centrally, as the analgesic action of the drug starts within 1 minute. However, one cannot exclude the influence, if any, of the sedative effect of butorphanol when assessing pain associated with propofol injection.

In our study, we found that 22(66.67%) patients in the control group experienced pain on propofol injection as compared to 18 (54.55%) and 9 (27.27%) patients in lidocaine and butorphanol groups respectively. Out of these, 16 (48.48%) patients in the control group experience mild pain as compared to 10(30.30%) and 9(27.27%) patients in the lidocaine and butorphanol groups respectively. Moderate pain was experienced by 6 (18.18% and 7 (21.21%) patients in the control group and lidocaine group respectively whereas none of the patients in butorphanol group experienced moderate pain. One patient (3.03%) in the lidocaine group experienced severe pain as compared to none of the patients in both the control and butorphanol groups. Statistical analysis showed the chi-squire test value as 15.3 and $p<0.05$. Our study showed that butorphanol was the most effective amongst the studied drugs in attenuation pain on propofol injection. Our datas were comparable with that of Anil Agarwal et al.[10] They reported that 39 (78%) patients in the control group had pain during propofol injection as compared to 21 (42%) and 10 (20%) in the lidocaine and butorphanol groups respectively ($p<0.05$). Mild pain was experienced by 5 (10%) patients in the control group as compared to 15 (30%) and 10 (20%) of the patients in their lidocaine and butorphanol groups respectively. 18 (36%) patients in their control group experienced moderate pains compared to 5 (10%) and 0 (0%) patients in the lidocaine and butorphanol groups respectively. Their control group had 16 (32%) patients with severe pain whereas only 1 (2%) patient in lidocaine group and none in the butorphanol group complained of severe pain. Their results also showed that butorphanol was the most effective amongst their studied drugs.

In the present study, we used butorphanol and lidocaine to minimize pain during propofol injection and these were compared to placebo. We found that butorphanol was the most effective amongst the studied drugs in attenuating pain on propofol injection. Patients' distribution in groups regarding age, sex, weight and ASA status were comparable amongst the groups. The greater number of female patients in this study (male: female ratio being 38:61) signifies that most of the cases were cholecystectomy and cholelithiasis is common in female population.

CONCLUSION

It can be concluded that administration of butorphanol one minute before the injection of propofol was the most effective amongst the studied drugs in attenuating pain on propofol injection. Lidocaine pretreatment too decreased the incidence of propofol injection pain as compared to placebo, even though data analysis failed to show statistically significant results.

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