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Research Article

EFFECTS OF FENTANYL AND LIGNOCAINE ON PROPOFOL INJECTION PAIN: A RANDOMIZED, PLACEBO-CONTROLLED DOUBLE-BLIND STUDY

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A B S T R A C T

Background: Pain on intravenous injection of propofol (PIP) is a well-known drawback and is still a limitation of this otherwise excellent IV anaesthetic agent. Efforts are underway to reduce the incidence and severity of this pain.

Aims and objectives: To compare the efficacy of fentanyl with lignocaine in reducing the incidence and severity of PIP.

Materials and Methods: Ninety patients of ASA grade I and II, aged 18-60 yrs, weight 40-80 kg, scheduled for elective surgery under general anaesthesia were randomly allocated to one of the three groups (n=30). Each patient received 2 ml of pretreatment solution over a period of 5 seconds followed one minute later by injection of propofol mixture at a rate of 2.5 ml every 5 seconds until loss of consciousness. Group L (Lignocaine): Pretreatment with 2 ml NS; propofol mixture:10 ml of 1% propofol and 2 ml of 2% lignocaine (40mg). Group F (Fentanyl): Pretreatment with 2 ml fentanyl (100μg); propofol mixture: 10 ml of 1%propofol and 2 ml NS. Group P(Placebo): Pretreatment with2 ml NS; propofol mixture: 10 ml of 1% propofol and 2 ml NS. Pain during injection of propofol mixture and pretreatment solution were assessed and graded as mild, moderate or severe. Heart rate and BP were monitored before laryngoscopy and 1, 2 and 5 minutes after laryngoscopy and every 15 minutes thereafter. The data were represented as frequencies and mean±SD and statistical analysis was done using SPSS Version 15.0. Confidence level of the study was kept at 95%; hence a "p" value <0.05 was considered as statistically significant.

Results: The incidence of pain was 33.33% in Group L, 36.67% in Group F and 80%in Group P. Pain score was significantly lower in Group L and Group F as compared with Group P ($p<0.001$). However, there was no statistically significant difference in pain scores between Group L and Group F ($p=0.713$). Incidence of recall of pain was significantly higher in Group P when compared with Group L ($p=0.024$) and Group F ($p=0.002$). However, no significant difference was seen between Group L and Group F ($p=0.407$). There were no significant haemodynamic changes warranting any medical or surgical intervention in any of the groups.

Conclusion: We conclude that fentanyl can prove to be a better alternative than lignocaine for the prevention of PIP because it has an added advantage of providing intra and post operative analgesia and a stable haemodynamics.

INTRODUCTION

Propofol possesses many characteristics of an ideal anaesthetic agent and is used widely for induction and maintenance of anaesthesia. However, pain on I.V. injection is a well-known drawback reported since the initial studies and is still a limitation of this otherwise excellent IV anaesthetic.[1]The sensation produced is usually described as tingling, cold, or numbing or, at its worst, a severe burning pain proximal to the site of injection. This sensation tends to occur within 10-20 s of injection and lasts only for the duration of the injection.

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The various methods that have been tried to reduce this pain (with variable results) are: injection into larger veins[2], premedication [3], slowing the speed of carrier i.v. fluid infusion or discontinuing fluid during injection [4], dilution of propofol with 5% glucose or 10% intralipid[5], cooling of propofol to 4°C [6], injecting cold saline (4°C) before propofol [7], aspiration of blood in propofol filled syringe prior to injection [8], pretreatment with or concurrent administration of agents like local anesthetics [9-11], opioids [12], NSAIDs [13], Ketamine [14]*etc.*

Lignocaine is the most commonly used agent for the reduction of this pain with additional advantage of blunting the haemodynamic response to laryngoscopy and intubation.

However, lignocaine has a failure rate of 13% to 32% when used for this purpose [15,16]. Also, the lignocaine-propofol mixture which has better efficacy than lignocaine pretreatment is unstable and needs to be prepared immediately before administration. All these have prompted investigators to try other methods for alleviation of propofol injection pain (PIP) in an anticipation of evolving a more effective method. Fentanyl seemed a logical choice to us because of its already proven efficacy in reducing PIP and because of the fact that addition of an opioid satisfies the requirement for balanced anaesthesia technique providing intra & post operative analgesia as well as haemodynamic stability for short procedures.

Aims and objectives

This study was done to compare the efficacy of fentanyl with that of lignocaine in reducing the incidence and severity of PIP. Secondary objectives studied were haemodynamic changes at laryngoscopy and the incidence of recall of pain in the postoperative period.

MATERIALS AND METHODS

The study was conducted over a period of one year after taking institutional ethical committee approval and consent of patients. Ninety patients of ASA grade I and II, aged 18-60 yrs, weight 40-80 kg, scheduled for elective surgery under general anaesthesia were enrolled for study. Patients with deranged physiological parameters; history of chronic pain syndromes, thrombophlebitis, neurological disease; history of adverse reaction to anaesthesia or propofol; undergoing major vascular or cardiac surgery; hysterical patients or patients with difficulty in communication were excluded from the study.

After a thorough preanaesthetic checkup and proper counselling, written/informed consent was taken from all the patients. All patients were premedicated with oral alprazolam 0.25 mg administered on the night prior to surgery and were instructed to keep fasting for 8 hrs pre-operatively.

On the day of surgery, patients' vitals were noted and investigation reports re-examined. Standard anaesthesia monitors (pulse oximeter, NIBP, EtCO2 and ECG) were connected and baseline readings were noted. A 20 gauge cannula was inserted in the largest vein on the dorsum of non-dominant hand. Each patient received 2 ml of pretreatment solution over a period of 5 seconds while the venous drainage was occluded manually at mid forearm. Patients were asked whether they felt any pain during administration of pretreatment solution. Occlusion was released after one minute and induction was done with propofol mixture which was injected at a rate of 2.5 ml every 5 seconds and continued until loss of consciousness as assessed by standard clinical criteria (loss of verbal response and eyelash reflex). Again during injection of propofol mixture, the patients were asked if they had any pain or discomfort in their arm and they were asked to grade it as mild, moderate or severe. Presence of features such as tears, grimacing and limb withdrawal were also noted. Patients were randomly allocated to one of the following three groups using a computer generated random number tables.

Group L (Lignocaine): The pretreatment solution was 2 ml of normal saline and the propofol mixture consisted of propofol 100mg(10 ml of 1% propofol) and lignocaine 40mg (2 ml of 2% lignocaine).

Group F (Fentanyl): The pretreatment solution consisted of 2 ml (100μg) of fentanyl, which was followed 1 minute later by propofol mixture (propofol 100 mg(10 ml of 1%) mixed with 2 ml normal saline).

Group P (Placebo): The pretreatment solution given was 2 ml of normal saline. This was followed 1 minute later by propofol and normal saline mixture (propofol 100 mg (10 ml of 1%) mixed with 2 ml normal saline).

The pretreatment solutions as well as the propofol mixtures were prepared by an independent anaesthesiologist and investigator was unaware of content of solutions. The level of pain was assessed by another independent anaesthesiologist who was unaware of group allocation. The severity of pain was defined according to pain scores advocated by McCrirrick and Hunter [6].[Table 1] The same scoring system was used to assess pain following injection of both propofol mixture and pretreatment solution.

After induction of anaesthesia with propofol, vecuronium bromide 0.1 mg/Kg IV was used to facilitate tracheal intubation. Heart rate and BP were monitored before laryngoscopy and 1, 2 and 5 minutes after laryngoscopy and every 15 minutes thereafter. After assessment of the pain and cardiorespiratory depression after propofol injection, fentany 100μg IV was given to all patients except those in Group F. Anaesthesia was maintained with inhaled technique supplemented with intermittent doses of vecuronium. At the end of surgery, inhalational agents were discontinued and neuromuscular blockade was reversed with inj Neostigmine 0.05 mg/Kg I.V. and Glycopyrrolate 0.01 mg/Kg IV. After tracheal extubation and recovery from anaesthesia, patients were asked if they had any recollection of discomfort or pain during the induction period. Presence of erythema or wheal in arm were recorded. Anyother adverse reactions during intra & postoperative period were also noted.

Statistical tools used

Statistical analysis was done using Statistical Package for Social Sciences (SPSS Inc., Chicago, IL) for Windows Version 15.0. The data were represented as frequencies and mean±SD. Intergroup differences were compared using chi-square test for proportions, analysis of variance (F-statistic) for comparing mean values of parametric data in more than two groups and student's "t" test for two groups. The mean values in a group at different time intervals were compared using paired "t" test. For non-parametric data, such as pain score, Mann-Whitney U test was used. Confidence level of the study was kept at 95%; hence a "p" value <0.05 was considered as statistically significant.

Sample size calculation

Sample size calculation was based on the results of previous study by Tan *et al* [17] and assuming an α-error of 5% and power of 80% so as to detect a difference of 20% in the incidence of pain between the study and control groups which showed that 26 patients were needed in each group. However, we included 30 patients in each group considering possible dropouts.

RESULTS

A total of 90 patients were enrolled in this study (30 in each group). The groups were similar with respect to age, weight,

gender distribution and ASA grade of patients. [Table 2] A total of 14 patients (15.55%) belonged to ASA Grade II. Hypertension, diabetes mellitus and hypothyroidism were present in 9, 3 and 2 patients respectively. Statistically there was no significant difference among the groups with respect to associated problem (p=0.520). [Table 3]

Table 1 *McCrirrick and Hunter* scoring for assessment of pain

Pain score	*Degree of pain*	*Response*
0	None	Negative response to questioning
1	Mild	Pain reported in response to questioning only without any behavioral sign
2	Moderate	Pain reported in response to questioning and accompanied by behavioral sign. Pain reported spontaneously without questioning.
3	Severe	Strong vocal response or, response accompanied by facial grimacing, or withdrawal or tear.

Table 2 Demographic details

	Group L (n=30)	Group F (n=30)	Group P (n=30)	χ^2	p-Value
Age (years)	38.77±13.13	42.70±12.36	36.03±12.23	8.063	0.13
Gender Female/Male	9 (30%)/ 21(70%)	11 (36.67%)/ 19(63.33%)	9 (30%)/ 21 (70%)	0.407	0.82
Weight (kg)	60.13±10.90	59.15±9.42	58.37±9.65	3.087	0.79
ASA Grade I/II	25 (83.33%)/ 5 (16.67%)	24 (80%)/ 6 (20%)	27 (90%)/ 3 (10%)	1.184	0.55

Table 3 Distribution of cases according to associated problems

Associated Problem	Group L (n=30) (lidocaine)	Group F (n=30) (fentanyl)	Group P (n=30) (placebo)
	No.(%)	No.(%)	No.(%)
None	25(83.33)	24(80.00)	27(90)
Diabetes mellitus	0(0)	2(6.67)	1(3.33)
Hypertension	4(13.33)	4(13.33)	1(3.33)
Hypothyroidism	1(3.33)	0(0)	1(3.33)

χ^2=5.184 (df=6); p=0.520

Majority of cases (>90%) reported no pain during injection of pretreatment solution and there was no statistically significant difference among the three groups (p=0.285). [Table 4]

Table 4 Pain during injection of pretreatment solution

Preoperative Pain	Group L (n=30)	Group F (n=30)	Group P (n=30)
	No.(%)	No.(%)	No.(%)
No pain (PS=0)	28(93.33)	27(90.00)	27(90.00)
Mild (PS=1)	2(6.67)	3(10.00)	1(3.33)
Moderate (PS=2)	0(0)	0(0)	2(6.67)

χ^2=5.024 (df=4); p=0.285

Pain was reported in 45(50%) patients (10(33.33%) in Group L, 11 (36.67%) in Group F and 24(80%) in Group P). [Table 5] There were 7 patients(23.33%) in Group L, 6(20.00%) in Group F and 5(16.67%) in Group P who reported mild pain. Moderate pain was reported in 10 (33.33%) patients of Group P, 5(16.67%) patients of Group F and 2(6.67%) patients of Group L. Severe pain was reported in none of the patients of Group F, 1(3.33%) patient of Group L and 9(30%) patients of Group P. Statistically, there was a significant difference in degree of pain in the three groups (p<0.001).

Table 5 Pain during injection of propofol mixture

Pain	Group L (n=30)	Group F (n=30)	Group P (n=30)
	No.(%)	No.(%)	No.(%)
No pain (PS=0)	20(66.67)	19(63.33)	6(20.00)
Mild (PS=1)	7(23.33)	6(20.00)	5(16.67)
Moderate (PS=2)	2(6.67)	5(16.67)	10(33.33)
Severe (PS=3)	1(3.33)	0(0)	9(30.00)

χ^2=28.831 (df=6); p<0.001

Pain score was significantly higher in Group P as compared with Group F (p<0.001) and Group L (p<0.001). However, no statistically significant difference in pain scores was seen when Group L was compared with Group F (p=0.713). [Table 6]

Table 6 Intergroup comparison of pain during injection of propofol mixture

S.No.	Comparison	Z	"p"
1.	Group L vs Group F	0.367	0.713
2.	Group L vs Group P	4.259	<0.001
3.	Group F vs Group P	4.077	<0.001

Mean time to onset of pain was maximum in Group L (11.25±4.89 seconds) followed by Group F (10.00±3.16 seconds) and then Group P (7.71±2.71 seconds) and the difference was statistically significant (p=0.018). [Table 7] Intergroup comparison revealed a significant difference when Group P was compared with Group L and Group F (p=0.011 and 0.035 respectively). However, comparison between Group L and Group F did not reveal a statistically significant difference. [Table 8]

Table 7 Time to onset of pain

S.No.	Group	Time interval (sec) (Mean±SD)	F	"p"
1.	Group L	11.25±4.89		
2.	Group F	10.00±3.16	4.40	0.018
3.	Group P	7.71±2.71		

Table 8 Intergroup comparison of time to onset of pain

S.No.	Comparison	t	"p"
1.	Group L vs Group F	0.702	0.491
2.	Group L vs Group P	2.714	0.011
3.	Group F vs Group P	2.205	0.035

Incidence of recall of pain after recovery from anaesthesia was maximum in Group P (n=24; 100%) followed by Group L (80%) and Group F (63.64%) and a significant difference was seen among groups (p=0.01). [Table 9] Incidence of recall of pain was significantly higher in Group P when compared with Group L (p=0.024) and Group F (p=0.002). However, no significant difference was seen between Group L and Group F (p=0.407). [Table 10]

Table 9 Incidence of recall of pain

Recall	Group L (n=10)		Group F (n=11)		Group P (n=24)	
	No.	%	No.	%	No.	%
Absent	2	20.00	4	36.36	0	0
Present	8	80.00	7	63.64	24	100.00

χ^2=9.12 (df=2); p=0.01

Table 10 Intergroup comparison of recall of pain

S.No.	Comparison	χ^2	"p"
1.	Group L vs Group F	0.687	0.407
2.	Group L vs Group P	5.100	0.024
3.	Group F vs Group P	9.853	0.002

No significant difference in mean heart rate was seen among three groups at baseline and at different time intervals [Figure 1]. No significant difference in baseline MAP values was seen amongst the three groups. A significant difference in mean MAP was seen at 1 minute, 2 minutes, 5 minutes and 30 minutes after laryngoscopy but thereafter there was no significant difference among the groups[Figure 2].

DISCUSSION

PIP is a known entity and can cause agitation, discomfort and hinder the smooth induction of anaesthesia. Thus an effective

method of prevention will be beneficial. Efforts are underway to reduce the incidence and severity of this pain.

Until now, the mechanism of PIP is unclear. Scott *et al* had speculated that pain is caused by activation of the kallikrein–kinin system in plasma by contact with propofol, consequently generating kinins, probably bradykinin [18]**.** Iwama *et al* further supported this hypothesis [19]. In their study conducted in 1998, concentration of Nafamostatmesilate in blood was 100 nmol/L, one min after its IV administration in a dose of 0.02 mg/kg and at this time, PIP was significantly reduced. As this concentration is sufficient to inhibit plasma kallikrein activity, these results are consistent with the hypothesis that propofol activates the plasma kallikrein–kinin system. Doenicke *et al* hypothesized that propofol concentration in the aqueous phase may be the most important variable for pain associated with propofol injection [20]**. Klement andArndlt** also suggested that pain on propofol injection is related to the concentration of propofol in aqueous phase and can be reduced by reducing the concentration of propofol in aqueous phase by diluting it with intralipid [5].

Lignocaine has commonly been used for attenuating PIP. It is an amide local anaesthetic consisting of lipophilic aromatic ring and hydrophilic tertiary amine separated by intermediate amide linkage. Rather than injecting lignocaine prior to propofol, we chose to premix lignocaine with propofol, as this has been shown to be more effective in early studies by Brooker *et al* [21] and Scott *et al*[18]. Later studies by Overbaugh *et al* in 2003 and by Lee and Russell in 2004 further proved the fact [22,23]. So, the propofol–lignocaine mixture must be used quickly after preparation if the lignocaine is to have an anaesthetic effect in the vein and if the risk of pulmonary fat embolism is to be avoided. Also we chose 40 mg as the dose of lignocaine in our study as this was the appropriate dose as suggested by **Johnson *et al*** who had compared 20 and 40 mg lidocaine doses both as pretreatment and mixed with propofol [24].

Fentanyl is a synthetic opioid, primarily an μ opioid receptor agonist and a phenyl piperidine derivative. Though the primary clinical effect of fentanyl is related to its interaction with opioid receptors centrally, it could have local anesthetic effects on nerves. In a preliminary study by ***Pang and Huang*** in 1997, fentanyl did show some analgesic effect in ameliorating propofol injection pain compared with placebo [25]. Besides this, fentanyl also provides haemodynamic stability and analgesia which extends into the postoperative period, making it a potentially useful drug to alleviate pain produced by drug like propofol.

In our study, 80% of patients experienced PIP after pretreatment with normal saline and most of them were of moderate (33.3%) or severe (30%) degree. This is consistent with the findings of Johnson *et al*[24], Mangar *et al*[26] and Gajraj and Nathanson[11] who found the incidence to be 80%, 90% and 85% respectively**.** However, there is wide variability in incidence of pain reported by various authors (from 32.5%to 90%) which may be due to difference in methods of assessment of pain and in sample sizes in the various studies.

In a study conducted by Helmers *et al* [27], 100μg of fentanyl given before propofol injection reduced the incidence of pain significantly from 35.7% to 15% which is in agreement with our study in which pretreatment with fentanyl reduced the pain significantly from 80% to 36.67%.

In a study by Bahar*et al*[28]**,** pretreatment with fentanyl 100μg produced a statistically significant reduction in the incidence of severe pain from 70% to 20% but no reduction in the overall incidence of pain (80%) unlike our study in which both severity and incidence were reduced.

Kobayashi *et al* had compared the effect of pretreatment with 100 μg fentanyl 3 min prior to propofol and premixing of 40 mg lidocaine to propofol [29]. The incidence of pain was significantly less in both fentanyl group (40%) and lidocaine group (35%) compared to placebo (80%, $p<0.01$) but there was no significant difference in incidence of pain between fentanyl and lidocaine group. Their findings are consistent with the findings of our study, even the incidence of pain found by them in different groups is almost same as in ours. Though we gave fentanyl 1 min before propofol injection unlike Kobayashi *et al* who had given it 3 min before propofol, it didn't seem to have much influence on the efficacy of fentanyl in reducing propofol injection pain. This finding is in concordance with a recent study by Imanaga *et al* in 2007 [30] in which propofol 1 mg/kg was injected as a bolus 1 min and 3 min after administration of 100 μg of fentanyl. Both the 1 min group and the 3 min group had significantly lower pain scores ($p<0.001$) than the control group without any significant difference between the two groups. This study supports our study in which 100 μg of fentanyl given 1 min before propofol was very much effective in reducing PIP.

There are other investigators who did not find fentanyl to be as effective as lignocaine in reducing propofol injection pain. One such study was conducted by Pang *et al*[25] to evaluate the efficacy of IV retention of fentanyl 150 μg and lidocaine 60 mg for 1 min using tourniquet in reducing the pain on IV injection of propofol 100 mg given over 20 seconds. Both fentanyl and lignocaine pretreatments were effective as compared to placebo ($p<0.005$), lignocaine 60 mg being more effective than fentanyl 150 μg ($p<0.001$). This difference could be due to use of higher doses of both the drugs in their study.

Alyafi *et al* conducted a study to compare the local efficacy of lignocaine and fentanyl in reducing PIP [31]. They concluded that lignocaine, acting locally, reduces PIP while fentanyl does not. Their result is not consistent with our study or with most of other studies done to evaluate the efficacy of fentanyl in reducing PIP. The smaller sample size in their study (25 in each group) could be the reason for this inconsistency. The complete ineffectiveness of fentanyl to reduce PIP could be due to a smaller time interval (20 sec) before propofol injection. However, this smaller time interval did not deter lignocaine from exerting its effect which is in agreement with the results of study done by Ewart and Whitman who concluded that lidocaine is most effective at reducing pain when given immediately before propofol [32]. In their study, lidocaine 20 mg was injected into dorsal hand vein with a tourniquet in place which was released after varying time intervals and propofol was then injected. Pain was significantly reduced in the groups given lidocaine 10 or 30 sec before propofol.

In our study, 86.7% of the patients who experienced pain at the time of induction recalled it in the post operative period. This is similar to an incidence of 73.3% reported by Johnson *et al* [24]. We confirm their finding that administration of propofol

does not ensure amnesia of noxious events that occur during induction of anesthesia. However the reason for a higher incidence of recall of pain in the control group as compared to lignocaine and fentanyl group could not be explained. Interestingly, there were 3 patients (1 in lignocaine group and 2 in placebo group) who recalled the event of pain after recovery from anaesthesia though they were unable to report it at the time of induction. Had we been slower at giving propofol injection prolonging the time to loss of consciousness, these patients could probably have reported the pain at the time of induction itself.

Only two patient in each group experienced nausea post-operatively in our study. Although hypersensitivity reactions have been reported after propofol injection, we observed no local or systemic reaction following its injection. We did not observe any adverse effects attributable to lignocaine during anaesthesia or any gross effect on the quality of recovery.

Limitations

It was a single-centre study with relatively less number of patients. Another limitation was the use of a subjective test for assessment of pain which is subject to bias.

CONCLUSION

Our study showed that fentanyl has almost equal efficacy as lignocaine in reducing the incidence and severity of PIP as well as in attenuating the haemodynamic response to laryngoscopy and intubation. It also decreased the incidence of recall of pain in the postoperative period. We conclude that fentanyl can prove to be a better alternative than lignocaine for the prevention of PIP because it has an added advantage of providing intra and post-operative analgesia with stable haemodynamics and also avoids the need for an extra manouevre of preparing the lignocaine-propofol mixture immediately before induction.

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