ORIGINAL ARTICLE

Comparative Study of Evaluation of Pain on Injection of Propofol Pretreatment with two Different Doses of Butorphanol

Rajesh Mahajan, Mukta Jatindra, Sanam Kassana, Smriti Gulati, Robina Nazir, Anjali Mehta

Abstract

In a prospective, double-blind, placebo-controlled, randomized trial one-hundred-sixty eight ASA I-II adults, undergoing laparoscopic cholecystectomy were randomly assigned into 3 groups of 56 each. Group L received lidocaine 2% (40 mg), Group B-1 received butorphanol 1 mg. and Group B-2 received butorphanol 2 mg. One min after pretreatment patients received one-fourth of the total calculated dose of propofol (2.5 mg/kg) over 5 s. In the lignocaine group 28 (50.00%) patients had pain during propofol injection as compared with 11 (19.64%) and 9 (16.07%) in the butorphanol 1mg and butorphanol 2mg groups, respectively ($P < 0.05$). Intergroup comparison revealed that although the incidence of pain at propofol injection was more in lignocaine group, the severity was primarily mild and comparable among the three groups ($P > 0.05$). Butorphanol decreased the frequency ($P < 0.05$) of propofol pain when compared with lidocaine. However severity of pain on injection of propofol was comparable among both the groups given pretreatment with butorphanol. ($P > 0.05$). No difference in complications, such as pain, edema, wheal, or flare response, were observed at the injection site within the first 24 h after the operation. Duration of analgesia was higher in Group-B-2 compared to other two groups. (142.5±33.96 minutes in Group-B-2, 76.07±23.56 minutes in Group-B-1 and 80.35±21.48 minutes in Group -L). However this was also associated with higher number of patients in deep sedation at 30 minutes. Pretreatment with butorphanol 1 mg or 2mg are equally effective in relieving pain on injection of propofol & more effective than lignocaine.

Key Words

Propofol, Butrophanol, Lidocaine, Pain

Introduction

Propofol is one of the commonest drugs used for induction of anesthesia in millions of patients every year. Its advantages include rapid onset, short duration of action, easy titration and favorable profile for side effects. However its use is associated with pain or discomfort on intravenous injection in 28%-90% of patients and 30% patients have severe pain on injection of propofol. Various non pharmacological and pharmacological means have been tried to relieve pain on injection of propofol. (1, 2)

Among pharmacological means opioids like remifentanil, sufentanil, pethidine and butorphanol have been tried with variable success. In a single study evaluating the use of butorphanol in preventing pain on in injection of propofol, Agarwal and colleagues found pretreatment with butorphanol in doses of 2 mg to be effective in relieving pain on injection of propofol (1,2). We tried to evaluate the effectiveness of lower dose, 1 mg of butorphanol relieving pain on injection of propofol and compare its efficacy with butorphanol 2 mg and lignocaine 2%, 2 ml, a standard regimen used in various studies.

Material and Methods

After receiving permission from our institutional ethical committee and written informed consent, this

From the Department of Anaesthesia Govt. Medical College, Jammu J&K India
Correspondence to : Dr. Rajesh Mahajan , Assistant Professor, Department of Anaesthesia Govt. Medical College, Jammu J&K India

prospective study was conducted in double - blind randomized way. Patients having allergy to any of the study drugs and difficulty in communication were excluded from the study. A total 168 consecutive patients were included with ASA physical status I and II, aged 18-60 years undergoing elective surgical procedures. With the computer generated table of random number patients were assigned into one of the three groups of 56 each. Patients were premedicated with tablet alprozolam 0.25 mg and ranitidine 150 mg PO before surgery and 2 hours before induction of anesthesia. Intravenous access was secured in all the patient s in pre recovery with a 20 G intravenous cannula and lactated ringer lactate solution was started at the rate of 10-12 drops per minute. Once patient was shifted into operation theatre, routine monitoring was instituted which consisted of electrocardiogram, non-invasive arterial blood pressure and pulse oximetry monitoring. After this IV infusion was stopped and pretreatment solutions of 2 ml was administered before induction of anesthesia with propofol depending on the group to which they belonged. Group l; lignocaine 2%; Group B- 1; butorphanol 1mg & Group-B-2; butorphanol 2mg. All pretreatment drugs were made in 2 ml and loaded in a 2 ml syringe that was covered with black tape. The IV infusion was stopped and pretreatment solution was injected. After one minute of dwell over time, one fourth of total calculated dose of propofol was injected over 5 seconds. The induction dose of propofol was 2 mg / kg. All study drugs were at room temperature. A second independent anesthesiologist, who was unaware of the group to which the patient had been allocated, assessed the level of pain after propofol injection. Induction was completed with the remaining dose of propofol and tracheal intubation was facilitated with vecuronium. Anesthesia was maintained with 33% oxygen in nitrous oxide, isoflurane. In group L, additional butorphanol 1 mg was administered to after intubation to achieve adequate analgesia.

During the propofol 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 were questioned every 5-10 seconds during induction for any 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), 3=moderate pain (pain reported in response to questioning and accompanied by a behavioral sign or pain reported spontaneously without questioning) and 3 = severe pain (i.e. strong vocal response or response accompanied by facial grimacing , arm withdrawal , or tears 2. Postoperatively oxygen saturation and Ramsay sedation score was used to assess sedation (4)

1: Anxious or agitated; 2: Co-operative and tranquil; 3: Drowsy but responsive to command; 4: Asleep but responsive to glabellar tap; 5: Asleep with a sluggish response to tactile stimulation; 6: Asleep and no response.

The score was re-evaluated every 10 min in postoperative recovery up to 120 min and every 15 min thereafter. Excessive sedation was defined as a sedation score which was greater than four.

Oxygen saturation was noted in post anesthesia care unit. Any desaturation if any was classified as major or minor. Major oxygen saturation was described as fall in saturation more than 10% from baseline and minor as fall 5-10% from baseline value of oxygen saturation (5) .If saturation was less than 95%, supplemental oxygen was administered. Postsurgical pain was assessed on postoperative period using VAS and time to vas score of 4 was noticed when first rescue dose of analgesia as tramadol 1 mg/kg was administered. Duration of analgesia was described as time when first rescue dose of tramadol was administered. Within 24 h after operation, the injection site was checked for pain, edema, wheal, or flare response by an anesthesiologist who was unaware of which drug was administered.

Statistics Analysis

All raw data of study parameters were entered into a Microsoft excel spread sheet and analyzed using IBM SPSS v17.0. The categorical variables were analyzed using Mantel-Haenszel chi-square test or Fischer exact test as appropriate. Parametrical numerical valuables were analyzed using independent sample -test. All statistical analysis was two tailed, and a value of <0.05 was considered statistically significant.

Results

One hundred sixty eight patients were enrolled in this study . comprising 71 males and 97 females . There were 56 patients in each treatment group. Groups were similar with respect to age, weight, and ASA status (*Table 1*). In the lignocaine group 28 (50.00%) patients had pain during propofol injection as compared with 11 (19.64%) and 9 (16.07%) in the butorphanol 1mg and butorphanol 2mg groups, respectively ($P < 0.05$) (*Table 2*). Intergroup comparison revealed that although the incidence of pain

Table 1 Patient Characteristics

	Group L (Lignocaine)	Group B-1 (Butorphanol 1 mg)	Group B-2 (Butorphanol 2 mg)	Statistical significance
Age (years)	34.6±11.3	35.7±10.3	33.6±14.2	p>0.05 NS
Sex (m/f)	25/31	24/32	22/34	p>0.05 NS
ASA class (I/II)	30/26	32/24	23/33	P>0.05 NS
Weight (kg)	54.4±11.5	52.6±13.7	54.8±14.2	p>0.05 NS
Duration of Surgery	50.84±15.05	48.56±18.24	49.56±16.36	p>0.05 NS

Data represented as mean±SD S=significant, NS=not significant

Table 2 . Assessment of Pain on IV Injection of Propofol

	Group L (Lignocaine)	Group B-1 (Butorphanol 1 mg)	Group B-2 (Butorphanol 2 mg)	Statistical significance
No pain	28*	45	47	p<0.05 S
Pain	28*	11	9	p<0.05 S
Grading of pain				
Mild	21*	10	9	p<0.05 S
Moderate	6*	1	0	p>0.05 S
Severe	2	0	0	p>0.05 NS

**p<0.05(lignocaine 40 mg versus butorphanol 2 mg and butorphanol 1 mg) S=significant ,NS=not significant*

Table 3. Ramsay sedation scores at 30 minutes in Post anesthesia recovery unit

Sedation Scores	Group L (lignocaine)	Group B-1 (butorphanol 1mg)	Group B-2 (butorphanol 2mg)	P Value
1	2	1	1	p>0.05 NS
2	33	32	12*	p<0.05 S
3	19	22	35	P>0.05 NS
4	2	1	8*	P<0.05 S
5	0	0	3	p>0.05 NS

**p<0.05(butorphanol 2 mg versus butorphanol 1 mg and lignocaine 40 mg) S=significant, NS=not significant*

Table 4. Time (in minutes) to requirement of first analgesia in three groups

Time	Group L (lignocaine)	Group B-1 (butorphanol 1mg)	Group B-2 (butorphanol 2 mg)	p Value
30 min	2	3	0	p>0.05 NS
60 min	20	26	2*	p<0.01 S
90 min	28	22	6*	p<0.05 S
120 min	6	4	12	p>0.05 NS
150 min	0	1	22**	p<0.05 S
180 min	0	0	12*	p<0.05 S
210 min	0	0	2	p>0.05 NS

**p<0.05 (butorphanol 2 mg versus butorphanol 1 mg and lignocaine 40 mg) **p<0.01(butorphanol 2 mg versus butorphanol 1 mg and lignocaine 40 mg) S = significant, NS = not significant*

at propofol injection was more in lignocaine group, the severity was primarily mild and comparable among the three groups (P > 0.05) Butorphanol decreased the frequency (P < 0.05) of propofol pain when compared with lidocaine. However severity of pain on injection of propofol was comparable among both the groups given pretreatment with butorphanol. (P > 0.05). No complications, such as pain, edema, wheal, or flare response, were observed at the injection site within the first 24 h after the operation. Duration of analgesia was higher in Group-B-2 compared to other two groups. (142.5±33.96minutes in Group-B-2, 76.07±23.56 minutes

in Group-B-1 and 80.35±21.48 minutes in Group -L). However this was also associated with higher number of patients in deep sedation at 30 minutes. Further, 6 patients had major desaturation and 8 had minor desaturation in PACU in Group-B-2. None of the patients in Gp-L and in Gp B-1 had major desaturation. Four patient in Gp-L and three in Gp B-1 had minor desaturation. The incidence of major desaturation was significantly higher in Group-B-2($p<0.05$). Two patients each in group-L and group-B-2 and one patient in group B-1 had slight reddishness at the site of injection at 24 hours and this was comparable

Discussion

In our study we found that butorphanol 2 mg as equally efficacious as butorphanol 1 mg in reducing incidence and severity of pain associated with iv injection of propofol ($p<0.05$). Use of higher dose of butorphanol did not confer any advantage over dose of 1 mg except prolonged duration of postoperative analgesia, albeit at cost of higher sedation and desaturation episodes in PACU. The use of propofol, most commonly used induction agent with a favorable profile, is associated with pain in 60% of patients, with 30% these patients reporting excruciating pain. Some of these may recall the induction of anesthesia as most painful part of perioperative period (1). Propofol is an excellent IV anesthetic, a phenol which can irritate the skin, mucous membrane, and venous intima. It may activate the kallikrein kinin system and release bradykinin, thereby producing venous dilation and increased permeability, which leads to increased contact between the aqueous phase of propofol and free nerve endings resulting in pain on injection1. Several pharmacological and non-pharmacological interventions have been used to alleviate this pain such as using larger veins, diminishing speed of injection, injecting propofol into a fast running IV fluid, diluting it with 5% glucose or 10% intralipid , prior injection of lidocaine, alfentanil, fentanyl, or pentothal , injecting cold saline at 4°C before propofol, cooling propofol to 4°C (and mixing lidocaine in propofol . Although use of antecubital vein and venous occlusion with pretreatment with lignocaine has been found to be most efficacious interventions, these two have not become standard of care (1-3,7-19). Reasons for this may be additional procedural steps involved in the occluding the vein leading to delay in routine busy operation room schedule. Injection of propofol antecubital vein is highly efficacious in preventing pain when compared with hand vein as injection site, but has not gained much favor due to inherent pitfalls. An IV line in the antecubital vein may be occluded when the elbow is flexed and unintentional extravasation may not be detected as quickly as when the dorsum of hand is used (1).

Pretreatment with a plethora of drugs found to be efficacious in preventing pain on injection of propofol is still popular and even now interventions with low efficacy like premixing of drugs especially lignocaine is still commonly used for their ease. Use of opioids to relieve pain on injection of propofol does make a sense as these are part of balance anesthesia regimen for preventing intubation response and excellent analgesia. Various opioids like remifentanil, alfentanil, sufentanil. Fentanyl, pethidine, tramadol and butorphanol have been evaluated for this purpose in varying doses and been found to be efficacious (1-3, 19). However as per butorphanol, only one study has evaluated its efficacy at a fixed dose of 2 mg (2). Hence we evaluated the efficacy of butorphanol for this purpose at lower doses.

Butorphanol tartrate is a synthetic opioid analgesic with both agonist and antagonistic properties. It is an agonist at kappa receptors, is either antagonistic or partial agonist at opoid receptors, and is 5-8 times more potent than morphine. After IV administration the onset of analgesia occurs 1 minute and peak effect is seen in 4-5 minutes. The site of action of butorphanol in reducing the pain of propofol injection is through the opioids receptors (central and or peripheral), local anesthetic action, or both (2). We administered butorphanol 1 minute before the injection of propofol. Butorphanol could have acted centrally, as the analgesic action of the drug starts within 1 minute. However, one cannot exclude the role of sedative effect of butorphanol when assessing pain associated with propofol injection (2, 20, 21). Our study differs from Agarwal's study as we not only evaluated the lower doses of butorphanol for relieving pain on propofol; we also determined its analgesic efficacy and postoperative side effects if any. Further we used only a single IV cannula to evaluate the pain and this is what we practically do in routine cases where much blood loss and fluids shifts are not expected. Third we allowed intravenous fluids to run after cannulation and this may have cleared any inflammatory mediators released from vein wall due to cannulation and influenced the pain intensity. Fourth we did not administered fentanyl to our patients. Our study can be criticized for not including a placebo group. Although we did not include placebo group

(i.e. no lignocaine group), previous studies report a very high incidence of severe pain up to 30% in placebo group and it would have been unethical to withhold pretreatment for study purposes. Similar use of dwell times with cessation of infusion just prior to administration of pretreatment drug and lack of control group have been reported by Brack and colleagues who evaluated 4 ml lignocaine pretreatment, either mixed or given 3 minutes prior to administration of propofol and found it to be equally effective in relieving pain on propofol injection (22). Although the frequency of pain was higher with lignocaine pretreatment, the pain was mainly mild in intensity. This is in collaboration with other studies where lignocaine pretreatment decreased the frequency and intensity of pain on injection of propofol (2, 7, 9, 16-19). Opioids is one of the highly practical class used to obtund pain on propofol injection as its use does not involves additional drug beyond routine drugs . Further different opioids have been found to be efficacious in relieving pain on propofol injection. In addition to their role in obtundation of stress response and perioperative analgesia cannot be refuted. Butorphanol has been used as a sole analgesic for intraoperative and postoperative analgesia in clinical practice (23-29). Butorphanol has been compared to meperidine and fentanyl in equipotent doses in a dose range of 0.5 to 2 mg and has been found to be better than fentanyl in obtundation of stress response, stable intraoperative analgesia and duration of postoperative analgesia. In the study in outpatient patients undergoing laparoscopic surgery Philips and colleagues compared fentanyl 1mg /kg and butorphanol 20 microgram /kg (23). Butorphanol in these doses was found to be acceptable alternative analgesic in general anesthetic for ambulatory laparoscopy, although time to return to baseline levels of sedation ware longer in patients receiving butorphanol, it did not affect the time to discharge and even contributed to the increased number of positive assessments on the next day. Similar results have been echoed by other studies when butorphanol was used as a component of balance anesthesia with better patient satisfaction when administered in doses of 20 microgram/kg. However in higher doses of 40microgram/kg, butorphanol has been found to result in higher grades and incidence of sedation and respiratory depression and hypoxia with increased time to discharge readiness (23-29). Butorphanol is a kappa -receptor partial agonist as well as weak mu-receptor antagonist whereas fentanyl is predominantly a mu-receptor agonist (20,21,30). Butorphanol is therefore associated with mores sedation than fentanyl, a kappa agonist effect. Although butorphanol 2 mg has been found to be effective in relieving pain on injection of propofol as shown by Agarwal and collegues and our results ,the results of former study were questioned by Lippmann and colleagues who questioned its sedative effects , more so when it was co administered with fentanyl31. Agarwal and collegues rightly justified their interventions as their patients were going major abdominal surgery and not outpatient procedures. It may have been possible that prolong major abdominal surgeries may have masked increased sedation and drowsiness in their patients. However we did a study in patients undergoing laparoscopic cholecystectomy which is a short procedure lasting from forty-five minutes to an hour and found increased incidence and drowsiness and desaturation when butorphanol was administered in doses of 2 mg.

In their study Kaur and colleagues while comparing dose sparring of induction dose of propofol by fentanyl and butorphanol with entropy analysis have found that propofol induction doses with butorphanol 20microgram /kg was 1.05±0.35 mg /kg. There was no further reduction in induction does of butorphanol from 20 microgramg/kg to 40 microg/kg (25) .This could have result from ceiling effect of butorphanol which is a distinct disadvantage of the agonist-antagonist opioids class when compared to the major class of opioids analgesics, the pure mu agonists. Meaning that there is a dose above which higher doses produce no additional pain relief (19,20). Similar observations have been made by Murphy and colleagues, who have reported that there is ceiling to the potency of butorphanol as anesthetic supplements (30). Akin to above effects, lack of increased efficacy of butorphanol in doses more than 1 mg in relieving pain on injection of propofol may be due to ceiling effect of butorphanol (31).

Conclusion

Pretreatment with butorphanol 1 mg or 2mg are equally effective in relieving pain on injection of propofol. In both the doses butorphanol is more effective than lignocaine 40 mg in relieving pain on injection of propofol. There is no need to use higher doses of butorphanol as it leads to higher sedation scores risking hypoxia. Butorphanol 1mg can provide good analgesia when given in addition to other analgesics without risking sedation and desaturation.

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