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Original Research Paper

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COMPARISON OF EFFICACY OF INTRAVENOUS LIGNOCAINE VERSUS BUTORPHANOL AS PRETREATMENT IN REDUCING PAIN DUE TO PROPOFOL INJECTION.

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ABSTRACT **Background And Aims:** Propofol is almost an ideal intravenous anesthetic agent but pain on injection becomes a major side effect. This study compares the efficacy of lignocaine and butorphanol in reducing the pain on propofol injection. **Methods:** After obtaining approval from institutional ethical committee and consent, hundred patients aged between 18 to 60 years, belonging to ASA physical status I and II posted for elective surgeries were randomly allocated into two groups of 50 each, group L received intravenous Lignocaine 40mg and group B received Butorphanol 2mg with manual venous occlusion one minute prior to propofol administration. The grade of the pain was assessed using Mc Crirrick and Hunter scale. Hemodynamic parameters were also monitored. Analysis was done by SPSS software. Chi square test and Fisher exact test was used for incidence of pain and severity of pain respectively. P value <0.05 was considered statistically significant. **Results:** Both the groups were similar with respect to demographic variables. The incidence of pain was 18% in group receiving butorphanol and 38% in group receiving lignocaine with p value of 0.026. The severity of pain, grade I was 18% in group receiving butorphanol and 26% in group receiving lignocaine, the severity of pain, grade II was 12% in group receiving lignocaine and 0% in group receiving butorphanol with p value of 0.014. **Conclusion:** Pretreatment with Butorphanol 2mg is more effective than 2% lidocaine (40 mg) in minimizing the incidence and severity of pain associated with propofol injection.

KEYWORDS : propofol, lignocaine, butorphanol, grade of pain.

INTRODUCTION

In the history of anesthesia, the wide-spread use of intravenous anesthetic induction agents came much later to that of inhalational anesthetic agents [1]. The, much celebrated demonstration of ether by William Morton took place in 1846, while the introduction of the first fast-acting intravenous anesthetic drug, the thiopentone, came nearly a century later in 1934. The primary advantage of this newer route of anesthetic administration was the speed of onset. The use of a fast-acting intravenous anesthetic agent allowed anesthetists to get through stages of anesthesia swiftly to the point that they are nearly imperceptible. In modern anesthetic practice, the use intravenous induction of anesthesia far exceeds that of inhalational induction. This owes to the introduction of newer agents, namely propofol in 1977, but also to advancements in airway management and pharmacological support of the cardiovascular system [2].

Propofol introduced in 1977, is an alkyl phenol. It has attractive properties like titratable level of anesthesia, absence of cumulation, rapid and clear-headed recovery and minimal side effects, is an ideal agent for induction of anesthesia. Kay and Rolly confirmed its potential as an anesthetic agent and is being used for clinical purpose since 1982[3]. Propofol is the most widely used intravenous anesthetic agent for induction and maintenance of anesthesia as well as for sedation inside and outside operation theater [4]. Propofol is almost an ideal intravenous anesthetic agent because of rapid onset and shorter duration of action, easy titration and favourable profile for side effects but pain on injection becomes a major side effect [6]. It is one of the most important problem in current practice of clinical anesthesia by American anesthesiologist [7].

Propofol is known to cause sharp, severe, stinging or burning pain on injection. This can be distressing to the patient. This pain causes agitation and interference with smooth induction of anesthesia and is considered to be clinically unacceptable. Propofol causes immediate pain because of the venous irritation and also can lead to a delayed type of pain after about 15 seconds due to the activation of kallikrein and bradykinin [8]. In some studies, the incidence of propofol injection pain has been estimated about 28 - 90% [9] and about 85% in another study [10].

The various suggested methods to alleviate this pain are injection in larger size veins [5], cooling [6] or warming [7], the propofol solution, pretreatment/pre-injection of various drugs like local anesthetics [8,9,10], opioids[11,12,13,14], thiopentone sodium [15], metoclopramide [16], clonidine [20] and ketamine [21].

Intravenous lignocaine, local anesthetic has been well documented to reduce the incidence and severity of pain on injection of propofol [8,9]. The most effective dose for lignocaine with venous occlusion was 60 mg in one study.[22] But 40 mg is the most commonly used dose when premixed with 200 mg of propofol. Intravenous Lignocaine with Venous occlusion is an effective method in relieving propofol-induced pain. Massad et al. recommended 60 seconds occlusion time in their report [23]. Another study did not find difference when the duration of venous occlusion was 15, 30, or 60 seconds [24].

Opiates were shown to exert peripheral analgesic action in addition to their well-known central effects though a clearcut discrimination between peripheral and central analgesics is debatable [25]. The analgesia produced by both peripheral

and central mechanisms may be additive or even synergistic. Moreover, peripheral opioid receptors have been described and shown to mediate analgesic effect when activated by opioid agonist [26]. Butorphanol is an agonist at receptors. Its activity at receptors is either antagonistic or partially agonistic. It is five to eight times as potent as morphine and is available only in parenteral form [27]. The site of action of butorphanol in reducing the pain of propofol injection is not clear but it could be either through opioid receptors (central and or peripheral), local anesthetic action, or both. The incidence of pain on propofol injection in one study after pretreatment with butorphanol was observed to be approximately 20% [28].

In this study we compared lignocaine and butorphanol in decreasing pain on injection of propofol during intravenous induction of anesthesia. The objectives of our study was to compare the efficacy of intravenous Lignocaine versus Butorphanol in reducing pain on propofol injection and to compare the adverse effects and patient satisfaction.

MATERIALS AND METHODS

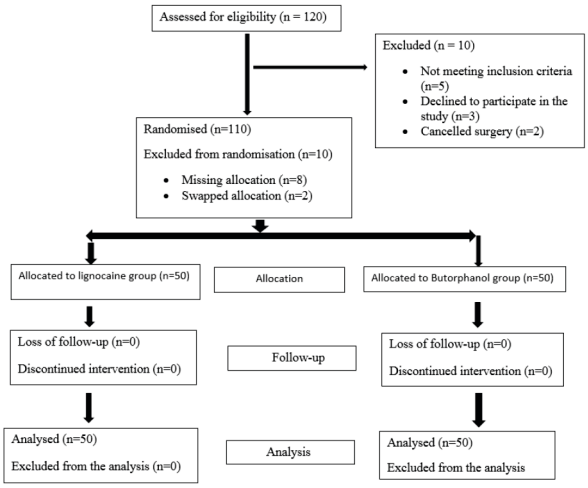
A clinical study comparing lignocaine and butorphanol as pre-treatment to reduce pain on injection of propofol in patients posted for elective surgical procedures under general anaesthesia was undertaken at Mandya Institute of Medical Science during June 2020 to May 2021, a period of 12 months, after approval from institutional ethics committee.

Hundred patients posted for various elective surgical procedures were studied in a randomized prospective manner and the study population was divided into 2 groups B and L of 50 each, group B received 2mg (2ml) of Butorphanol and group L received 40 mg (2ml) of 2% Lignocaine. Patients aged between 16 and 60 years of ASA I and II posted for elective surgeries were included in the study. Patients of ASA grade III and IV, Patients allergic to propofol, lignocaine and butorphanol, Patients who are not able to communicate, Patients who have received any analgesic or sedation 24hrs prior to surgery were excluded from the study. A thorough pre-anesthetic evaluation with general physical and systemic examination was done in the evening before the proposed surgery. All the necessary investigations were done. After explaining the anesthetic procedure to the patients, informed written consent was taken to include them in the study. All patients were prescribed 0.5 mg of alprazolam and ranitidine 150 mg orally the previous night. Patients were advised to be nil oral from 12 am onwards on the previous day of surgery. On arrival of patient to operating room, a 20gauge intravenous cannula secured. All ASA standard monitors were attached and baseline values recorded. No analgesic drugs were given before induction. Patients were already been informed about the scale for propofol injection pain advocated by Mc Crirrick and Hunter (Table-1). The patients received 2 mL of the pretreatment solution prepared at room temperature either Butorphanol 2mg or Lignocaine 40mg for a period of 5 seconds while the venous drainage was occluded manually at midarm by an assistant for one minute. The occlusion was released and after one minute, one fourth of the total calculated dose of propofol 2mg/kg of body weight was administered for a period of 5 seconds. During a 10-second pause before the induction of anesthesia, patients was questioned about the pain intensity on injection which was explained to them during Pre-anesthetic evaluation and before injection of propofol injection. Induction of anesthesia was continued with propofol. Tracheal intubation was facilitated with Inj. Vecuronium and anesthesia was maintained with inhaled anesthetics supplemented with Fentanyl.

Table 1. Mc Crirrick And Hunter Scale Of Evaluation Of Propofol Injection Pain

Degree of Pain	Response
None (Grade-0)	No response to questioning
Mild (Grade-1)	Pain reported in response to questioning only without any behavioural signs.
Mild (Grade-2)	Pain reported in response to questioning and accompanied by behavioural sign or pain reported spontaneously without questioning.
Severe (Grade 3)	Strong vocal response or response accompanied by facial Grimacing, arm withdrawal or tears.

Intraoperative monitoring includes - NIBP, ECG, Pulse-oximeter. The heart rate, blood pressure and SpO_2 were monitored continuously. The following parameters were studied: Pain during induction, PR, BP, SPO2 & ECG recordings before induction, during induction, intra operatively at 5min, 10min, 15min and post operatively.



Flow Chart For Patient Recruitment.

RESULTS

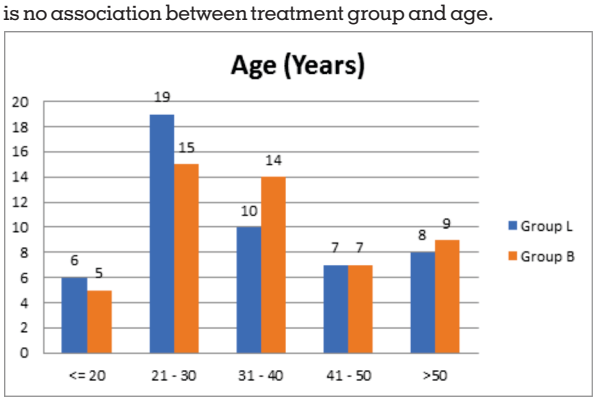
Data was collected and statistical analysis was performed as explained in the methodology of the study. The results and interpretations are as explained below Age (Years)

Table No: 2 Age Distribution Of Cases In Study Group

Age (Years)	Group L	Group B	Total	P-value
<= 20	6 (12%)	5 (10%)	11 (11%)	0.864
21 – 30	19 (38%)	15 (30%)	34 (34%)	
31 – 40	10 (20%)	14 (28%)	24 (24%)	
41 – 50	7 (14%)	7 (14%)	14 (14%)	
>50	8 (16%)	9 (18%)	17 (17%)	
Total	50	50	100	

p value calculated using χ2-test

Majority of the patients observed in the age group of 21-30 years in both the treatment groups: 38% in group L and 30% in Group B. Chi-square p value (0.864) is greater than 0.05. There is no association between treatment group and age.



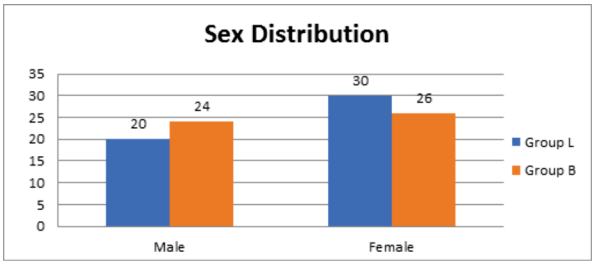
Graph 1: Age Distribution Of Cases In Study Groups

Table 3: Sex Distribution Of Cases In Study Groups

Sex	Group L	Group B	Total	P-value
Male	20 (40%)	24 (48%)	44 (44%)	0.42
Female	30 (60%)	26 (52%)	56 (56%)	
Total	50	50	100	

p value calculated using χ2-test.

Among the patients 20 (40%) were males and 30 (60%) were females in group L, where as in group B, 20 (40%) were males and 30 (60%) were females. Chi-square p value (0.420) is greater than 0.05. There is no association between treatment group and sex.



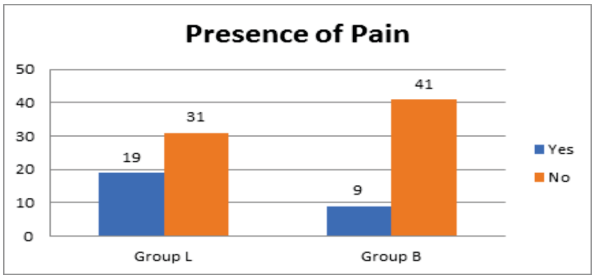
Graph 2: Comparison Of Sex Distribution In Study Groups.

Table No 9 Comparison Of Presence Of Pain In Study Groups

Presence of Pain	Group L	Group B	Total	P-value
Yes	19 (38%)	9 (18%)	28 (28%)	0.026
No	31 (62%)	41 (82%)	72 (72%)	
Total	50	50	100	

p value calculated using χ2-test.

It was observed that, incidence of pain among Group L (38%) was higher than Group B (18%). Chi-square p value (0.026) is less than 0.05 and it is statistically significant.



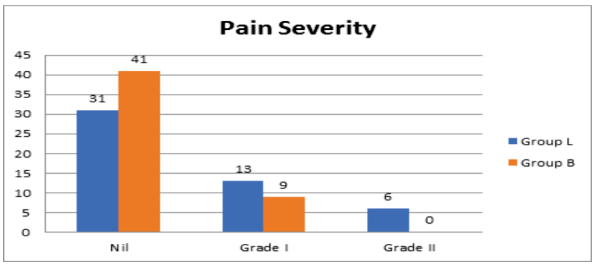
Graph 8 Comparison Of Presence Of Pain In Study Groups

Table No 10 Comparison Of Pain Severity In Study Groups

Pain Severity	Group L	Group B	Total	P-value
Nil	31 (62%)	41 (82%)	72 (72%)	0.014
Grade I	13 (26%)	9 (18%)	22 (22%)	
Grade II	6 (12%)	0 (0%)	6 (6%)	
Total	50	50	100	

p value calculated using Fisher Exact test.

It was observed that, severity of pain was observed more in group L compared to group B. Fisher exact test p value (0.014) is less than 0.05 which is statistically significant.



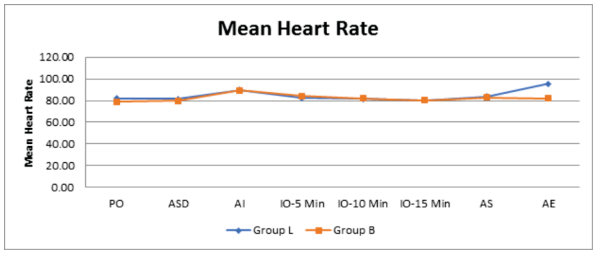
Graph 9 Comparison Of Pain Severity In Study Groups

Table No 11 Comparison Of Heart Rate In Study Groups

	Group L (N=50)		Group B (N=50)		P-Value
	Mean	SD	Mean	SD	
HR – Pre-Operatively	82.06	11.36	79.00	8.42	0.129
HR - After Study Drug	81.56	10.93	79.84	8.29	0.378
HR - After Intubation	89.90	8.25	89.36	7.22	0.728
HR - Intra-Operatively 5 Mins	82.62	8.10	84.04	7.05	0.352
HR - Intra-Operatively 10 Mins	81.66	7.42	81.94	6.61	0.843
HR - Intra-Operatively 15 Mins	80.30	6.65	80.34	6.46	0.976

p values calculated using two independent sample Student's t-test

As p-value is greater than 0.05 at each time point, there is no significant difference in mean values between the two treatment groups (group L and Group B) at each time point



Graph 10 Comparison Of Mean Heart Rate In Study Groups.

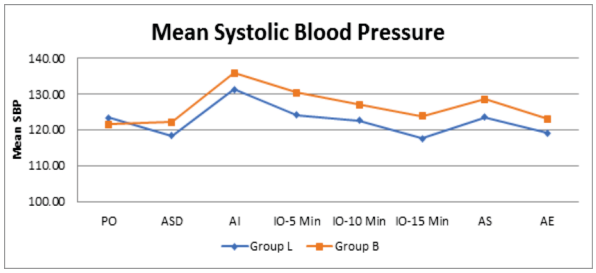
PO = Preoperatively, ASD = After Study Drug, AI = After Intubation, IO-5 Min = Intra-Operatively 5 Mins, IO-10 Min = Intra-Operatively 10 Mins, IO-15 Min = Intra-Operatively 15 Mins, AS = After Surgery, AE = After Extubation

Table No 12 Comparison Of Systolic Blood Pressure Changes In Study Groups.

	Group L (N=50)		Group B (N=50)		P-Value
	Mean	SD	Mean	SD	
SBP – Pre-Operatively	123.34	13.83	121.60	12.41	0.509
SBP - After Study Drug	118.34	11.33	122.16	11.82	0.102
SBP - After Intubation	131.22	10.40	135.76	11.30	0.039
SBP - Intra-Operatively 5 Mins	124.12	9.29	130.36	10.18	0.002
SBP - Intra-Operatively 10 Mins	122.58	8.71	126.94	8.63	0.014
SBP - Intra-Operatively 15 Mins	117.54	18.44	123.86	7.78	0.028

p values calculated using two independent sample Student's t-test

Mean SBP is higher in group B for time points, After Intubation, Intra-Operatively 5 Mins, Intra-Operatively 10 Mins, Intra-Operatively 15 Mins and there is statistically significant difference in mean values between the two treatment groups (group L and Group B) at each of these time points.



Graph 11 Comparison Of Mean Systolic Blood Pressure In Study Groups

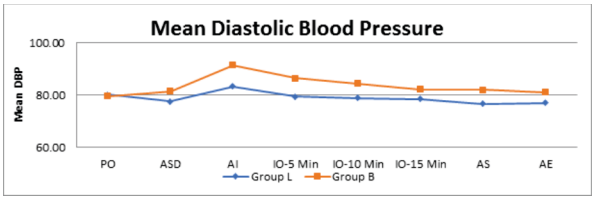
PO = Pre-operatively, ASD = After Study Drug, AI = After Intubation, IO-5 Min = Intra- Operatively 5 Mins, IO-10 Min =Intra-Operatively 10 Mins, IO-15 Min = Intra-Operatively 15 Mins, AS =After Surgery, AE = After Extubation

Table No 13 Comparison Of Diastolic Blood Pressure Changes In Study Groups

	Group L (N=50)		Group B (N=50)		P-Value
	Mean	SD	Mean	SD	
DBP – Pre-operatively	80.14	9.96	79.60	8.11	0.767
DBP - After Study Drug	77.46	7.86	81.30	7.78	0.016
DBP - After Intubation	83.22	8.67	91.30	7.50	<0.001
DBP - Intra-Operatively 5 Mins	79.26	6.35	86.30	7.73	<0.001
DBP - Intra-Operatively 10 Mins	78.84	6.19	84.38	5.41	<0.001
DBP - Intra-Operatively 15 Mins	78.42	5.47	82.20	5.15	0.001

p values calculated using two independent sample Student's t-test

Mean DBP is higher in group B for time points, After Study Drug, After Intubation, Intra-Operatively 5 Mins, Intra-Operatively 10 Mins, Intra-Operatively 15 Mins and there is statistically significant difference in mean values between the two treatment groups (group L and Group B) at each of these time points.



Graph 12 COMPARISON OF MEAN DIASTOLIC BLOOD PRESSURE IN STUDY GROUPS

PO = Pre-operatively, ASD = After Study Drug, AI = After Intubation, IO-5 Min = Intra-Operatively 5 Mins,
IO-10 Min =Intra-Operatively 10 Mins, IO-15 Min = Intra-Operatively 15 Mins, AS =After Surgery, AE = After Extubation

Table No 14 Comparison Of Spo-2 Changes In Study Groups

	Group L (N=50)		Group B (N=50)		P-Value
	Mean	SD	Mean	SD	
SPO2 – Pre-operatively	97.76	1.42	96.74	0.96	<0.001
SPO2 - After Study Drug	99.70	0.61	99.18	4.24	0.392
SPO2 - After Intubation	99.84	0.47	99.72	1.46	0.581
SPO2 - Intra-Operatively 5 Mins	100.00	0.00	100.00	0.00	NA*
SPO2 - Intra-Operatively 10 Mins	100.00	0.00	100.00	0.00	NA*
SPO2 - Intra-Operatively 15 Mins	100.00	0.00	100.00	0.00	NA*

cannot be computed because the standard deviations of both groups are 0.

p values calculated using two independent sample Student's t-test

Mean SPO2 is higher in group L for time points Preoperatively.

DISCUSSION

Propofol is the most widely used intravenous anesthetic agent. Pain on propofol injection is a problem that all anesthesiologist faces every-day. Patients remembers it as one of the unpleasant encounters with anesthetists.[29] Chemical name of propofol is 2,6 diisopropylphenol. All phenols irritate skin and mucous membrane. Thus, propofol is expected to cause pain.[30] Pain on propofol injection has also been described by some, that pain is due to vascular involvement.[31] Pain on propofol injection is classified as immediate and delayed. The immediate pain is due to irritation of vein endothelium whereas delayed pain is due to release of mediators such as kininogen from kinin cascade.[32] Several methods for prevention of pain have been tried with varying degree of success. Various factors affecting pain on propofol injection are cannula gauge, size of vein, volume, speed of injection, the use of local anesthetics, dilution of propofol, temperature and premedication.[33]

When propofol is injected to larger veins, the pain experienced by the patients are less. It is due to minimal contact of propofol with the endothelial wall of vein. The injected propofol can mix with blood freely and can have buffering effect.[34] For our study we preferred a larger vein on the dorsum of hand.

Speed of injection is also an important factor which determines the pain on injection. Scott et al noticed that fast injection causes less pain. Rapid injection may clear the drug quickly from vein and replace it with blood. Slower injection may increase the increase the concentration and duration of exposure of propofol to vein wall.[35] In our study, one fourth induction dose of propofol was given over 5 seconds in both the groups.

Several investigators have demonstrated that increased concentration of propofol in aqueous phase increases pain. Doenicke et al noticed that regular LCT preparation of propofol have more propofol concentration in aqueous phase. They also demonstrated that pain could be reduced by increasing the lipid content of propofol [36]. Another preparation of propofol, a combination of MCT and LCT emulsion will cause less pain due to less concentration of propofol in aqueous phase.[37] In our study we used regular LCT preparation of propofol in both the groups.

Many drugs have been given as pretreatment to reduce pain on propofol injection. Lignocaine is the most commonly used drug. Being a local anesthetic, it can inhibit bradykinin-kallikrein system by reversibly blocking the peripheral pain pathways.[38] In our study we used 40mg of Lignocaine. The dosage of lignocaine was similar to the study conducted by M H Nathanson who compared lignocaine and alfentanyl for reduction of pain on propofol injection.[39]

Picard and Tramer in a systematic literature review involving 6,264 patients of 56 reports on the prevention of propofol (2mg/kg) injection pain, studied about three different techniques/methods of pain alleviation used in the various studies, including lignocaine administered intravenously before injection of propofol, after mixing with propofol and lignocaine given with a tourniquet (intravenous retention for 1-2 minutes before injection of propofol).[40] Consequently, intravenous retention of lignocaine with tourniquet was found to be the most useful model for investigating the peripheral actions of a study drug in the absence of a central effect, which was the model used by Fujii et al.[41]. In our study we used lignocaine with manual compression.

Butorphanol tartrate is a synthetic, strong analgesic with both opioid receptor agonist and antagonistic properties.[42] It is an agonist at kappa receptors and is either antagonistic or partial agonist at mu receptors and 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 could be through opioid receptors (central and or peripheral), local

anesthetic action or both. 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. The dosage of Butorphanol (2mg) was similar to the study conducted by Anil Agarwal comparing butorphanol and lignocaine for reduction of pain on propofol injection.[43]

In our study, we chose four-point verbal categorical scoring system as advocated by Mccrirrick and Hunter because it is simple and readily understood by patients and many previous studies reporting pain on injection of propofol have used either all or none or categorical scoring systems, thus allowing easier comparison with literature. Also, we were concerned that the appropriate hand eye coordination required for a VAS might not be present in all patients during the rapidly changing state of consciousness of anesthesia induction. Hence, we chose four-point verbal categorical scoring for pain assessment in our study.

In our study, distribution of age ranged between 18-60 yrs. Majority of the patients, observed in the age group of 21-30 years in both the groups. Among the patients, 40% were males and 60 % were females in group L, where as in group B, 40% were males and 60% were females. The sex difference between the groups is statistically insignificant. Hence demographic characteristics are similar and comparable in both groups.

Vital parameters like heart rate, systolic blood pressure, diastolic blood pressure, oxygen saturation and ECG were recorded during preinduction, induction, intra operatively at 5min, 10min, 15min. Mean SBP and DBP is higher in group B for time points-After Intubation, Intra-Operatively 5 Mins, 10 Mins, 15 Mins and significant difference present in mean values between the two treatment groups (group L and Group B) at each of these time points. A dose of 0.025 mg/kg intravenous butorphanol increases pulmonary artery pressure, pulmonary wedge pressure, left ventricular end-diastolic pressure, systemic arterial pressure, pulmonary vascular resistance, and cardiac index [44].

Out of 50 patients of each study group, 62% in lignocaine group and 82% in butorphanol group did not have pain. The incidence of pain on propofol injection was found to be more in lignocaine group and it was statistically significant. 26% in lignocaine group and 18% in butorphanol group had grade I pain.12% in lignocaine group and 0% in butorphanol group had grade II pain. The severity of pain on propofol injection was also found to be more in lignocaine group and it was statistically significant. Thus, butorphanol 2mg was found to be more effective than 2%lignocaine 40mg in reducing both incidence and severity of pain on propofol injection.

CONCLUSION

Propofol is almost an ideal IV induction agent which produces a good quality of anesthesia with rapid onset and rapid recovery. However, it often has the disadvantage of causing pain or discomfort on injection. Various methods have been tried to alleviate the pain on propofol injection. In our study we compared the efficacy of pretreatment with lignocaine and butorphanol on reduction of pain on propofol injection.

We conclude that Pretreatment with butorphanol 2 mg is more effective than 2% lidocaine (40 mg) in minimizing both the incidence and severity of pain associated with propofol injection.

SUMMARY

Propofol is the most frequently used IV anesthetic today. Induction of anesthesia with propofol is associated with several side effects with pain during intravenous injection being major among them. In view of the above consideration, this clinical study was performed to compare the efficacy of lignocaine and butorphanol as pretreatment to decrease pain on propofol injection.

A hundred ASA physical status I & II patients, both male and female posted for various elective surgeries under general anesthesia were studied. The patients were divided into two groups of fifty each: Group L: Received 2% lignocaine (40mg) as pretreatment, Group B: Received butorphanol 2mg as pretreatment. The patients in both groups were comparable with respect to demographic and hemodynamic parameters. Pretreatment with butorphanol 2 mg was found to be more effective than 2% lidocaine (40 mg) in minimizing both the incidence and severity of pain associated with propofol injection.

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REFERENCES

1. Checketts MR, Alladi R, Ferguson K, et al. Recommendations for standards of monitoring during anaesthesia and recovery 2015: association of anaesthetists of Great Britain and Ireland. Anaesthesia 2016; 71: 85e93
2. Khan KS, Hayes I, Buggy DJ. Pharmacology of anaesthetic agents I: intravenous anaesthetic agents. Cont Educ Anaesth Crit Care Pain 2014; 14: 100e5.
3. Pandit JJ, Andrade J, Bogod DG, et al. 5th National Audit Project (NAP5) on accidental awareness during general anaesthesia: summary of main findings and risk factors Anaesthesia 2014; 69: 1089e101
4. Kay B, Rolly.G. ICI 35868, A new intravenous induction agent. Acta Anaesthesiol Belg 1977;28: 303-16.
5. Mohsin MU, Ahmad MS, Israr H, Furqan a. role of ketamine in subanesthetic dose to alleviate propofol injection pain in patients undergoing cesarean section surgery. Pakistan Armed Forces Medical Journal. 2018 Dec 31;68(6):1551-55.
6. Wani MA, Wani S, Dogra S, Jitendra M. Comparison of Injection Dexmedetomidine with Injection Ketamine in Alleviation of Propofol Injection Pain. JK Science. 2018;20(1):30.
7. Dutta h, chattopadhyays, pal R. Pain on Injection of MCT/LCT Preparations of Propofol and Etomidate: A Double Blind Randomised Comparative Study. Journal of Clinical & Diagnostic Research. 2019 Feb 1;13(2).
8. Klement W, Arndt JO. Pain on injection of propofol, the effect of concentration and dilution.Br J Anaesth 1991; 67, 281- 4. 5)
9. Wong WH, Cheong KF. Role of tramadol in reducing pain on propofol injection. Singapore Med J. 2001;42(5):193–5. 6)
10. Morton NS, Johnston G, White M, Marsh BJ. Propofol in paediatric anaesthesia. Pediatr Anesth. 1992;2(2):89–97 7)
11. Agarwal A, Raza M, Dhiraj S, Pandey R, Gupta D, Pandy CK, et al. Pain during injection of propofol: the effect of prior adminstration of butorphanol. Anesth Analg 2004; 99: 117-9.
12. D. Memis, A. Turan et al. The prevention of propofol injection pain by tramadol or ondansetron, European Journal of Anaesthesiology (2002), 19:1:47-51 Cambridge University Press.
13. Nathanson MH, Gajraj NM, Russell JA. Prevention of pain on injection of propofol: a comparison of lidocaine with alfentanil. Anesth Analg 1996; 82: 469-71.
14. Kwak, K.; Kim, J et al. Reduction of pain on injection of propofol: combination of pretreatment of remifentanil and premixture of lidocaine with propofol, European Journal of Anaesthesiology: 2007 :24 :746-750.
15. Haugen RD,Vaghdia H et al. Thiopentone pretreatment for propofol injection pain in ambulatory patients. Can J Anaesth; 1995;42: 1108-12.
16. Ganta R, Fee JP. Propofol pain – Comparison of lignocaine with metoclopramide. Br J Anaesth 1992:69: 316-7.
17. Yoshikawa T, Wajima Z Ogura A et al. Orally administered clonidine significantly reduces pain on propofol injection. Br. J. Anaesth.2001; 86; 874-6.
18. Barbi et al. Pretreatment with intravenous ketamine reduce propofol injection pain. Paediatric anaesthesia 2003;13;764-8.
19. Kim DH, Chae YJ, Chang HS, Kim JA, Joe HB. Intravenous lidocaine pretreatment with venous occlusion for reducing microemulsion propofol induced pain: Comparison of three doses of lidocaine. J Int Med Res. 2014;42:368–75. [PubMed] [Google Scholar]
20. Massad IM, Abu-Ali HM, Al-Ghanem SA, Badran IZ, Ammari BA, Daradkeh SS. Duration of venous occlusion with lidocaine for preventing propofol induced pain. Saudi Med J. 2008;29:971–4. [PubMed] [Google Scholar]
21. Massad IM, Abu-Ali HM, Abu-Halaweh SA, Badran IZ. Venous occlusion with lidocaine for preventing propofol induced pain. A prospective double-blind randomized study. Saudi Med J. 2006;27:997–1000. [PubMed] [Google Scholar]
22. Depue K, Christopher NC, Raed M, Forbes ML, Besunder J, Reed MD. Efficacy of intravenous lidocaine to reduce pain and distress associated with propofol infusion in pediatric patients during procedural sedation. Pediatr Emerg Care. 2013;29:13–6. [PubMed] [Google Scholar]
23. Pang WW, Mok MS, Huang S, Hwang MH. The analgesic effect of fentanyl, morphine, meperidine, and lidocaine in the peripheral veins: A comparative study. Anesth Analg 1998;86:382-6
24. Stein C, Schafer M, Cabot PJ, Carter L, Zhang Q, Zhou L, et al. Peripheral opioid analgesia. Pain Rev 1997;4:171-85. 17.
25. Millers Textbook of anaesthesiology 8th edition.
26. Aggarwal A, Raza M, Dhiraaj S, Pandey R, Gupta D, Pandey CK, et al. Pain during injection of propofol: The effect of prior administration of butorphanol.

Anesth Analg 2005;100:903-6.
27. Merskey H, Bogduk N, editors. Classification of Chronic Pain. 2nd ed. Seattle: IASP press; 1994. 2.
31. Barash PG, Cullen BF, Stoelting RK, Cahalan MK, Stock MC, Ortega R, et al. Acute pain management. Clinical anaesthesia. 8th ed. Philadelphia: 2017;1563- 64
32. Morgan & Mikhail's Clinical Anesthesiology. Chronic pain management. 6 th ed. United states.2018;1051-60
33. Serpell M. Anatomy, physiology and pharmacology of pain. Surgery Oxford. 2006 Oct;24(10):350-353.
34. Health PJ, Kennedy DJ, Ogg TW et al. Which intra induction agent for day surgery? A comparision of propofol, thiopentone, methohexitone and etomidate. Anaesthesiology 1998; 53(1): 53-55.
35. Huggins NJ, Target controlled intravenous Anaesthesia using Diprifusor.Anaesthesia. 1998; 53(1): 53-55.
36. Mc Leskey CH et al. Adverse events in multicenter phase IV study of propofol: evaluation by anaesthesiaologists and post anaesthesia care unit nurses. Anaesthesia and Analgesia 1993 oct; 77(4): 3-9.
37. Bryson HM, Fulton BR, Faulds D et al. Propofol. An update of its use anaesthesia and conscious sedation. Acta Anaesthesiol Scand Drugs. 1995;50(3): 513 – 59.
38. Sa Rego MM, Watcha MF, White PF, et al. The Changing Role of Monitored anaesthesia care in the ambulatory setting. Anaesthesia andAnalgesia 1997; 85(5): 1020-1036.
39. Swanson ER, Seaberg DC, Mathias S. The use of propofol for in the emergency department. Acad Emerg Med. 1996; 3(3): 234-38.
40. Masaki Y, Tanaka M, Nishikawa T. Physicochemical compatibility of propofollignocaine mixture.Anesth Analg 2003; 97: 1646-51.
41. Chen TL, Ueng TH, Chen SH, et al. Human cytochrome P450 monooxygenase system is suppressed by propofol. Br J Anaesth 1995; 74: 558-562.
42. Veroli P, O'Kelly B, Bertrand F et al. Extra hepatic metabolism of propofol in man during the anhepatic phase of orthotopic liver transplantation. Br J Anaesth 1992;68:183-86.
43. Kay NH, sear JW, v ping ton J et al. Disposition of propofol in patients undergoing surgery: A comparision in men and women. Br J Anaesth 1986; 58:1075-1079.
44. Kirkpatrick T, cock shott ID, Douglar EJ et al. Pharmacokinetics of propofol (Diprivan) in elderly patients. Br J Anaesth 1988;60:146-150.