www.jmscr.igmpublication.org
Index Copernicus Value: 79.54
ISSN (e)-2347-176x ISSN (p) 2455-0450
crossref DOI: https://dx.doi.org/10.18535/jmscr/v7i6.88

IGM Publication
Journal Of Medical Science And Clinical Research
An Official Publication Of IGM Publication

A Prospective Evaluative Study between Low Dose Ketamine and Fentanyl as Pre Medication for Alleviation of Propofol Injection Pain

Authors
Mohamad Ommid[1*], Saba Ahad[2], Shazada Gani[3], Faisal Rasool Dar[4], Mushtaq Rather[5], Humera Manzoor[6]
[1]Associate professor, Department of Anesthesiology & Critical Care, Govt. Medical College, Srinagar, India
[2,3,5]Lecturer, Department of Anesthesiology & Critical Care, Govt. Medical College, Srinagar, India
[4]Post Graduate scholar, Department of Anesthesiology & Critical Care, Govt. Medical College, Srinagar, India
[6]Assistant Professor, Department of Anesthesiology & Critical Care, Govt. Medical College, Srinagar, India
Corresponding Author
Dr Mohamad Ommid
Associate professor, Department of Anesthesiology & Critical Care, Govt. Medical College, Srinagar, India

Abstract
Purpose: *To evaluate the pain on injection of propofol via pretreatment with low dose of ketamine and low dose of Fentanyl in patients undergoing elective surgery under general anaesthesia.*
Methods: *Total 60 patients were randomly allocated into two groups 6 groups. Group K (Ketamine Group): Received ketamine 0.15 mg/kg iv, 1 minute before injection of propofol and Group F (Fentanyl Group): Received Fentanyl 1.5mcg/kg iv, 1 minute before injection of propofol. All patients were monitored for the blood pressure (MAP), heart rate (HR), and oxygen saturation (SpO2). Additionally, the pain intensity was assessed using a 4-point verbal rating scale (VRS) by professional doctors.*
Results: *The incidence of pain due to propofol injection in Group K 22 (62.85%) of the patients did not represent any pain and in Group F 24 (68.27%) of the patients does not show any pain during propofol injection. However, the difference between the two groups was statistically insignificant with p value of 0.782.*
Conclusion: *From the findings of our study, it may be concluded that pre-treatment with low dose intravenous ketamine 0.15mg/kg and intravenous Fentanyl 1.5mcg/kg with a tourniquet just before propofol injection, significantly reduced the incidence and degree of propofol induced pain without significant adverse hemodynamic effects.*
Keywords: *General surgery, Propofol. Fentanyl. Ketamine, pain.*

Introduction

Propofol is the drug of choice for induction of anesthesia in millions of patients every year because of its rapid onset and short duration of action, easy titration, and favorable profile for side effects.[1] Despite these positive attributes, about three out of five patients experience pain on injection of propofol, with one of these patients reporting severe or excruciating pain. Some patients recall the induction of anaesthesia as the

most painful part of the perioperative period. The quality of pain was described as extremely sharp, aching, or burning. It has been arranged as the seventh most important problem in current practice of clinical anesthesia by American anesthesiologists.[2]

The incidence of pain induced by propofol varies between 28% and 90% in adults and may be severe.[3] Many drugs such as alfentanyl, Fentanyl, lidocaine, thiopental, metoclopramide, aspirin, pethidine, ketamine, have been used to alleviate pain after iv injection of propofol with variable efficacy.[4,5] Among them, lidocaine pretreatment is the most popular method for reducing this pain. However, the failure rate is between 32% and 48% and thus lidocaine can not entirely control propofol induced pain.[6] Ketamine has potent analgesic and local anaesthetic properties, but very few studies have evaluated the efficacy of ketamine in reducing propofol induced pain and the optimal dose required to reduce the pain on injection with propofol.[7]Likewise, Fentanyl which is a commonly used short-acting opioid agonist for intraoperative and postoperative systemic analgesia has some peripherally mediated analgesic action within the clinical dosage range. However, till date, there are very few studies comparing the efficacy of intravenous ketamine and Fentanyl in alleviating pain on propofol injection. Hence, the present was undertaken to evaluate the pretreatment effectiveness of the two readily available drugs in the operating theatre i.e, intravenous ketamine and Fentanyl in attenuating pain due to propofol injection.

Methods

The present study was conducted in the department of anesthesiology in Govt; medical collage Srinagar from 2017 to 2019 for seventy patients of (ASA) physical status I-II of both sexes, aged between 18 to 60 years, equally divided in to two groups, Group K (n=35), and Group F (n=35) undergoing elective surgery under general anaesthesia were included in this observational clinical trial. Patient who were allergic to study drugs, Pregnancy, Emergency surgery, History of muscular disease, History of malignant hyperthermia, Patients taking calcium channel blockers or beta blockers, Hypotension, hypo parathyroid and hypocalcaemia were excluded from the study.

Written informed consent was obtained from all the patients before surgery.

All patients were transported to the operating room without premedication. On arrival to operating room, an 18‑gauge intravenous (IV) catheter was inserted, connected to multichannel monitor, monitoring of electrocardiography, non-invasive blood pressure, oxygen saturation (SpO_2) was started and baseline values were recorded.

The intervention groups receive ketamine 0.15 mg/kg and Fentanyl 1.5mcg/kg, over a period of 5 seconds, 5 minutes after IV cannulation.

Patients and groups

Patients were randomly allocated to one of the groups using table of randomization. Each group consists of 35 patients. Groups were as follows:

Group K (Ketamine Group): Received ketamine 0.15 mg/kg iv, 1 minute before injection of propofol.

Group F (Fentanyl Group): Received Fentanyl 1.5mcg/kg iv, 1 minute before injection of propofol.

Patients in GROUP K received ketamine 0.15 mg/kg and GROUP F Fentanyl 1.5mcg/kg, over a period of 5 seconds, 5 minutes after iv cannulation (time taken for applying monitors) while the venous drainage was occluded using a tourniquet. One minute after pretreatment drug injection, the occlusion was released, and patient was induced with propofol 2mg/kg. Initially 2ml bolus of propofol was injected over 4 seconds, 15 seconds later, patients were asked to grade the pain experienced immediately on propofol injection.

The grading of pain was done using McCrirrick and Hunter scale of evaluation of propofol injection pain. An anaesthesiologist blinded to the study protocol evaluated pain during propofol

injection using the above mentioned scale (McCrirrick and Hunter scale):

McCrirrick and Hunter scale of evaluation of propofol injection pain

Grades	Score	Signs
G0	No pain	negative response to questioning
G1	Mild pain	pain reported only in response to questioning without any behavioral signs
G2	Moderate pain	pain reported in response to questioning and accompanied by a behavioral sign or pain reported spontaneously without questioning
G3	Severe pain	strong vocal response or response accompanied by facial grimacing, arm withdrawal or tears

General anesthesia was induced with IV propofol 2.0–2.5 mg/kg followed by succinylcholine 2 mg/kg to facilitate orotracheal intubation. The trachea was intubated with a cuffed orotracheal tube of appropriate size. Anesthesia was maintained with 60% N_2O in oxygen with 0.5–1% isoflurane. Intermittent boluses of atracurium bromide were used to achieve muscle relaxation. Minute ventilation was adjusted to maintain normocapnia (end tidal carbon-dioxide [$EtCO_2$] between 34 and 38 mm Hg) and $EtCO_2$ was monitored. Each patient received intraoperative analgesia as injection Paracetamal infusion 1gm and injection tramadol 100mg intravenously. The neuro-muscular blockade was antagonized with neostigmine 0.05 mg/kg and glycopyrrolate 0.01 mg/kg and trachea was extubated. All patients stayed in PACU for 24 h after the end of surgery.

The following parameters were studied: Pain during induction, PR, BP, SpO2 & RR recordings before induction and at 1 & 3 minutes after induction .The results were presented as mean+/- standard deviation. For all the tests $P \leq 0.05$ was considered as statistically significant.

Results

Table 1: Comparison of demographic profiles between the two groups

Parameters	Group K n=35	Group F n=35	P value
Age (yrs)	35.55±13.56	32.80±13.37	0.71
Height (cm)	166.3±4.61	168.4±5.54	0.264
Weight (kg)	61.50±8.87	62.50±10.99	0.82
Sex Male/Female	19/16	20/15	0.80
ASAI/II	22/13	24/11	0.314
Duration of surgery	65.1±11.92	68.6±10.93	0.462

Table 2: Degree of pain scores between the two groups

Sensation of pain	Group K n=35	Group F n=35	P value
0: No pain	22 (62.85%)	24 (68.27%)	0.782
1: Mild pain	09 (25.71%)	07 (20.0%)	0.857
2: Moderate pain	02 (5.71%)	03 (8.57%)	0.64
3: Severe pain	02 (5.71%)	01(2.85)	0.87

As shown in Table-1, it is observed that average age of patients in group K was 35.55 years while it was 32.80 years in the group F. The average weight of Ketamine group was 61.50 Kg as against 62.50 Kg for the Fentanyl group. The demographic profile in the two groups were comparable ($p>0.05$). There was no gender variation as well as ASA physical status between the groups ($p>0.05$).

It is evident from table 2 that 62.85% of patients in Group K and 68.27% in Group F experienced no pain while mild pain was felt by 25.71% in Group K and 20.0% in Group F. In Group K, a relatively fewer patients (5.71%) had moderate pain compared to8.57% in Group F. Severe pain was observed in 5.71% of group K and in group F, it was 2.85% showed no statistically significant difference between the groups ($p>0.05$).

In group k 6 (25%) of males represents pain and in group F 3(12.5%) of patients shows pain during injection of propofol while as 8 (33.30%) of female patients shows pain in group K and 7 (29.10%) of female patients shows pain in group F during injection of propofol. Fig 1.

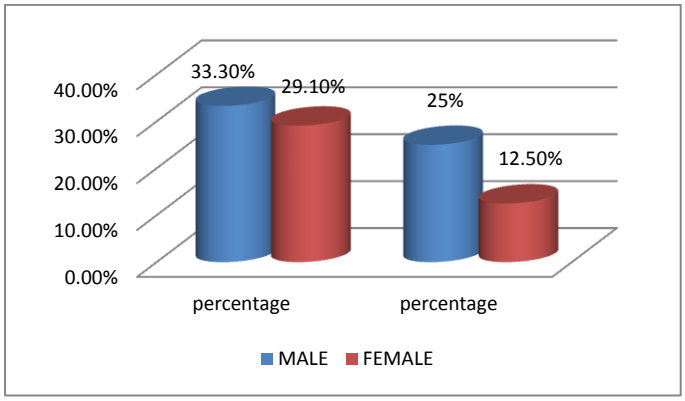

Fig 1

The post operative adverse effects observed among the two study groups. When compared statistically, the results were found not significant with a p value of >0.05.Fig 2

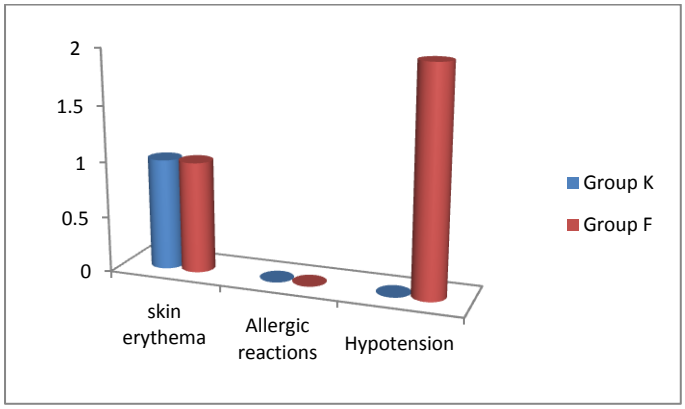

Fig 2

Discussion

Pain on injection of propofol has been ranked 7 propofol induced pain has a failure rate of 32% to 48%. Ketamine and opioids like Fentanyl, both have a local peripheral action.

In the present study, age ranged from 18 to 60 years with the mean age of ketamine group was 35.55±13.56 years and in Fentanyl Group, it was 32.80±13.37 years. The difference in age between both groups were not statistically significant as suggested by the analysis of p value (p= 0.71). In terms of gender, ketamine group had 54.28% males and 45.71% females, whereas fentanyl group comprised of 57.14% males and 42.85% females and was statically insignificant with p value of 0.80. Mean weight in ketamine group were 61.50+8.87 kgs and the mean weight in Fentanyl group were 62.50+10.99kgs. The difference between two groups with regards to distribution of weight was not significant with a p value (p=0.82). (Shivakumar KP et al, 2016)[8], conducted a study on 60 adult patients of ASA class I and II compromising of two groups as ketamine and Fentanyl group, the age distribution ranged from 18-60 yrs with a mean age for ketamine group being 27.7 + 9.24 years and for Fentanyl group 32.23 + 11.83 years. Ketamine group had 43.33% males and 56.67% females, whereas Fentanyl group comprised of 63.33% males and 36.67% females. Mean weight in ketamine group were 60.87+10.98 kgs and the mean weight in Fentanyl group were 58.8 +12.02kgs.The difference between two groups with regards to demographic characteristics were not significant. The results of this study as per the demographic characteristics are concerned are accordance with our present study.

Propofol is the most commonly used IV anesthetic[9]. Although it has an excellent recovery profile (i.e., fast and smooth emergence, infrequent incidence of post operative nausea and vomiting), its use is associated with pain on injection, increased triglyceride levels, and the potential for microbial contamination[10,11]. Pain on injection of propofol occurs in 30%-90% of patients.

In the present study, ketamine in a dose of 0.15mg/kg alleviated propofol induced pain in 62.85% of the patients under Grade 0, 25.71% of patients under Grade 1, 5.71% of patients under Grade 2 and 5.71% of patients represented Grade 3 pain scores among the study population. Iman *et al* concluded that pretreatment with ketamine 0.4 mg/kg was the most effective in attenuating pain associated with propofol injection (92% patients had no pain).[12] However,the ketamine dose used in their study was higher compared to the dose of 0.15mg/kg used in the present study. In 2006 Seung WK *et al* studied the effect of a small dose of ketamine as pretreatment to reduce the pain of propofol injection and concluded that administration of ketamine 100 µg/kg immediately before propofol injection provided

the optimal dose and timing to reduce propofol induced pain on injection.[13] In a similar study conducted by Tan *et al*, ketamine was as effective as lidocaine in attenuating pain during propofol injection with a pain reduction from 84% to 26%. In their study they used 10 mg of ketamine prior to propofol administration without application of tourniquet [14] i.e approximately 0.2mg/kg. The dose used in the present study is low, and it is definitely lower than a dose of ketamine which produces central analgesic effects. Hence the pain attenuation on pretreatment with ketamine can be attributed to a peripheral local anaesthetic like action. This may be due to the non-competitive NMDA receptor antagonism brought about by ketamine in the vascular endothelium.

In the present study, pretreatment with intravenous Fentanyl reduced pain in 68.27% subjects (Grade 0), 20% of the patients (Grade 1), 8.57% of patients (Grade 2) and only 2.85% of patients shows (Grade 3) pain scores among the study population. In a systematic review and meta-analysis conducted by Jalota *et al*, they recommended the routine use of a small dose of opioids before induction of anaesthesia using propofol injection in all patients.[15] In a study conducted by Pang *et al*, they concluded that meperidine was a better drug in alleviating propofol pain compared to Fentanyl. However, the study used the VAS scale for pain assessment, which though a very good scale to assess pain in clinical setting, the appropriate hand eye co ordination required for VAS score might not be present in all patients during the rapidly changing state of consciousness of anaesthesia post induction.

In the present study on comparing pain during propofol injection, 62.85% in ketamine Group and 68.27% in Fentanyl group did not have pain, 25.71% in ketamine Group and 20% in Fentanyl group had mild pain, and 5.71% in ketamine group and 8.57% in Fentanyl group had moderate pain. Severe pain was seen in 5.71% in ketamine Group and 2.85 % in the Fentanyl group. However, the difference between the two groups was statistically insignificant as p value of 0.678. The results of our study are accordance the study conducted by (Shivakumar KP et al, 2016)[16], on 60 adult patients of ASA class I and II allocated to two groups A and B and were administered i.v ketamine 0.15 mg/kg and i.v Fentanyl 1.5 mcg/kg respectively, 1 minute before propofol injection. They found intravenous injection Fentanyl (70%) caused greater alleviation of pain compared to intravenous injection ketamine (63.3%). And also in their study the difference between the drugs were statistically not significant. They concluded that both ketamine and Fentanyl are equally effective in alleviating propofol pain.

Study of the effectiveness of pretreatment drugs are through various methods like, direct intravenous injection, pre mixing with propofol or by brief venous retention with tourniquet which is used prior to propofol injection, that isolates the forearm veins from the rest of the circulation. It is a useful method for studying the peripheral actions of a drug by excluding its central effects. In the present study, a tourniquet was applied briefly before injection of pretreatment drug, which was released during propofol induction. However, further studies are needed to establish the feasibility of this technique in children and in emergency for induction of anesthesia.

Usually females experience greater pain intensity, with or without related distress, compared to that of males. This may be due to the mechanical effect of larger sized veins in males compared to females, and also owing to the difference in the pain sensitivity between either gender.[17] In the present study, out of the 24 subjects who experienced from mild to severe pain majority were females (62.5%) compared to males (37.5%). This was accordance the study done by (Shivakumar KP et al, 2016)[16]. Also females experienced pain of higher intensities compared to males. Hence further studies are required to establish relationship between pain and gender variables.

Propofol induces a decrease in the arterial blood pressure after Induction of anesthesia. This is due

to the decrease in the peripheral vascular resistance, inhibition of both the sympathetic activity and myocardial contractility. Administration of ketamine before propofol has the advantage of producing a non-significant decrease in the arterial pressure compared to preoperative level. This could be explained by the positive effect of ketamine on sympathetic stimulation leading to increase in myocardial contractility and vascular resistance, which in turn leads to increase arterial pressure[18].

In the study by Tan C H et al,[14] hypotension was observed in 58% of the ketamine group and 60% in the control group, and no incidence of heart rate of less than 50 beat/min was observed. In the present study, with the dose of ketamine and Fentanyl used, there was no hypotension with insignificant effect on mean arterial blood pressure and heart rate up to 5mins after intubation which may be due to the fact that the cardio-stimulant effects of ketamine and Fentanyl balanced the cardio-depressant effects of propofol.[18]

Only 5.71% of patients in Group k and 2.85% patients in Group F had severe pain. There were no significant differences in hemodynamic parameters between groups and no adverse events such as arrhythmias and allergic reactions during induction or intubation were seen. None of the patients had post anesthesia emergence reactions during recovery.

References

1. Marik PE; Propofol: therapeutic indications and side-effects. Curr Pharm Des2004;10:3639-49
2. Jalota L, Kalira V, George E, Shi YY, Hornuss C, Radke O, Apfel CC; Prevention of pain on injection of propofol: systematic review and metaanalysis. Bmj, 2011; 342.
3. Tan CH, Onsiong MK. Pain on injection of propofol. Anaesthesia. 1998 May; 53(5):468-76.
4. Koo SW, Cho SJ, Kim YK, Ham KD, Hwang JH. Smalldose ketamine reduces the pain of propofol injection. AnesthAnalg. 2006 Dec;103(6):1444-7
5. Ray S, Pal R, Pal S,Kirtania J, Sarbapalli D, Sarkar U *et al*. Preclusion of pain on injection with propofol: Evaluating the effects of lignocaine or Fentanyl pretreatment. Anesthesia, Essays and Researches.2011;5(1):33-38.
6. Euliano TY, Gravenstein JS (2004). A brief pharmacology related to anesthesia". Essential anesthesia: from science to practice. Cambridge, UK: Cambridge University Press. p. 173. ISBN 0-521-53600-6. Retrieved 2009-06-02.
7. "Drugs@FDA: FDA Approved Drug Products". Accessdata.fda.gov. Retrieved 2013-06-08.
8. RAU J, ROIZEN MF, DOENICKE AW, ET AL: Propofol in an emulsion of long- and medium-chain triglycerides: the effect on pain. Anesth Analg; 93:382-4, 2001.
9. SKLAR GE: Propofol and postoperative infections. Ann Pharmacother; 31:1521-3, 1997.
10. FLETHCHER JE, SEAVELL CR, BOWEN DJ: Pre-treatment with alfentanil reduces pain caused by propofol. Br J Anaesth; 72:342-4, 1994. Saadawy I, Ertok E, Boker A. Painless injection of propofol: pretreatment with ketamine vs thiopental, meperidine, and lidocaine. Middle East J Anaesthesiol. 2007 Oct;19(3):631-44
11. Koo SW, Cho SJ, Kim YK, Ham KD, Hwang JH. Smalldose ketamine reduces the pain of propofol injection. Anesth Analg. 2006 Dec;103(6):1444-7.
12. Tan CH, Onsiong MK, Kua SW. The effect of ketamine pretreatment on propofol injection pain in 100 women. Anaesthesia. 1998 Mar;53(3):302-5.

13. Jalota L , Kalira V, George E, Shi YY, Hornuss C, Radke O et al. Prevention of pain on injection of propofol: systematic review and meta-analysis. BMJ. 2011 Mar 15;342.
14. Kang H-J, Kwon M-Y, Choi B-M, Koo M-S, Jang Y-J, Lee M-A. Clinical factors affecting the pain on injection of propofol. Korean J Anesthesiol 2010 Mar; 58(3): 239-243.
15. Tan CH, Onsiong MK, Kua SW. The effect of ketamine pretreatment on propofol injection pain in 100 women.
16. Koo SW, Cho SJ, Kim YK, Ham KD, Hwang JH. Small-dose ketamine reduces the pain of propofol injection. Anesth Analg. 2006 Dec;103(6):1444-7.
17. Anaesthesia. 1998 Mar;53(3):302-5 Pang WW, Mok MS, Huang S, Hwang MH. The analgesic effect of fentanyl, morphine, meperidine, and lidocaine in the peripheral veins: A comparative study.AnesthAnalg. 1998;86:382–6
18. Kang H-J, Kwon M-Y, Choi B-M, Koo M-S, Jang Y-J, Lee M-A. Clinical factors affecting the pain on injection of propofol. Korean J Anesthesiol 2010 Mar; 58(3): 239-243.