Original Article

A comparative study of efficacy of pre-anaesthetic medication intravenous ketamine versus fentanyl for pain alleviation during general anaesthesia induced by propofol

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Abstract

Pain on injection of propofol has been ranked 7th among 33 clinical problems. Lidocaine pre treatment for reducing propofol induced pain has a failure rate of 32% to 48% . Ketamine and opioids like fentanyl, both have a local peripheral action. The main aim of this study, is to compare the efficacy of i.v ketamine with i.v fentanyl in alleviating propofolpain. After ethical committee permission, 60 adult patients of ASA class I and II after written informed consent were randomly 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. The patients in both groups were comparable with respect to demographic and hemodynamic parameters. Pain was graded as per McCrirrick and Hunter Scale and statistically analysed using chi square test. Fentanyl(70%) caused greater alleviation of pain compared toketamine(63.3%).However the difference between the drugs was statistically not significant. Both ketamine 0.15mg/kg and fentanyl 1.5mcg/kg were equally effective in alleviating propofol pain.

Keywords: Propofol Injection, Ketamine, Fentanyl, Pain, Induction.

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INTRODUCTION

The international association for the study of pain (IASP) defines pain as an "an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage"[1] Pain on injection of an anaesthetic agent leads to patient dissatisfaction and is a recognised adverse effect of the most commonly used i.v inducing agent, propofol. Propofolis a popular drug of choice for induction of anaesthesia in millions of patients owing to its rapid onset, short duration of action, easy titration, and favourable profile for side effects. However, 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.[2] The incidence of this pain 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.[3,4]Among them, lidocaine pretreatment is the most popular method for reducing this pain. However, the failure rate is between 32% and 48% and thus lidocainecan not entirely control propofol induced pain.[3] Ketamine has potent analgesic and local anaesthetic properties, but very few studies have evaluated the efficacy of ketamine in

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reducing propofolinduced pain and the optimal dose required to reduce the pain on injection with propofol.[5]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.[6] However , till date, there are very few studies comparing the efficacy of intravenous ketamine and fentanyl in alleviating pain on propofolinjection. Hence, the present study compares 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.

MATERIALS AND METHODS

A clinical study comparing ketamine and fentanylpre-treatment to reduce pain on injection of protocol in patients posted for elective surgical procedures under general anaesthesia was undertaken at SSIMS&RC, Davangere over a period of six months after obtaining the ethical committee permission.

Sixty patients of ASA grades I and II, aged between 18 to 60 years, posted for various elective surgical procedures were randomly allocated to two different groups of 30 each as described below:

GROUP A: received ketamine 0.15 mg/kg iv, 1 minute before injection of propofol.

GROUP B: received fentanyl 1.5mcg/kgiv, 1 minute before injection of propofol.

Patients belonging to ASA III,IV,V and emergencies, with history of allergic response to propofol, epileptics, pregnant women, patients with difficulty in communication and those who had received analgesics, sedatives and prokinetics within 48 hours prior to the surgery were excluded from the study. All the patients were explained about the procedure and an informed/written consent was obtained. Routine preanaesthetic evaluation was performed. On arrival in the operation room, a 20G cannula was inserted into a vein on the dorsum of the patient's non dominant hand and lactated ringers solution was started. Vital parameters like heart rate, non invasive blood pressure, peripheral oxygensaturation (SpO_2) and respiratory rate were recorded before injecting propofol and at 1 and 3 minutes after propofol injection. Patients in GROUP A received ketamine 0.15 mg/kg and GROUP B 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[7]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):

Table 1: McCrirrick and Hunter scale of evaluation of propofol injection pain

0	None (negative response to questioning),
1	Mild pain(pain reported only in response to questioning without any behavioural signs),
2	Moderate pain (pain reported in response to questioning and accompanied by a behavioural sign or pain reported spontaneously without questioning),
3	Severe pain (strong vocal response or response accompanied by facial grimacing, arm withdrawal or tears).

Tracheal intubation was facilitated with i.v. vecuronium 0.1 mg/kg and anaesthesia was maintained with nitrous oxide, oxygen, i.v vecuronium, i.v fentanyl 2mcg/kg, isoflurane and intermittent positive pressure ventilation. At the end of surgery, patient was extubated after reversal with i.v. neostigmine 0.05mg/kg & i.v glyopyrrrolate 10 mcg/kg. 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

Data was collected and statistical analysis was performed as explained in the methodology of the study. In both ketamine and fentanyl groups, 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.The difference in age between both groups is not statistically significant as suggested by p value of 0.103. In terms of gender, ketamine group had 43.33% males and 56.67% females, whereas fentanyl group comprised of 63.33% males and 36.67% females. The sex difference between the groups is statistically insignificant as suggested by p value of 0.120.Mean weight in ketamine group is 60.87+10.98 kgs and the mean weight in fentanyl group is 58.8 +12.02kgs.The difference between two groups with regards to distribution of weight is not significant. The heart rate, blood pressure and SpO_2 in both groups were compared before induction andat 1 & 3 minutes after induction and is not statistically significant.

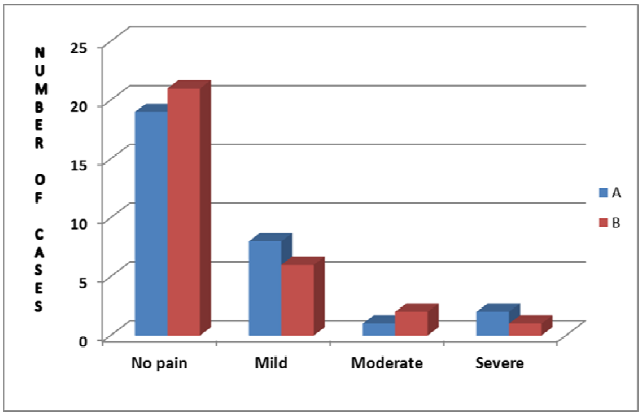
On comparing pain during propofol injection, 63.33% in ketamine group and 70% in fentanyl group did not have pain, 26.67% in ketamine group and 20% in fentanyl group had mild pain,3.33% in ketamine group and 6.67% in fentanyl group had moderate pain. Severe pain was

seen in 6.67% in ketamine group and 3.33% in the fentanyl group. However, the difference between the two groups is statistically insignificant as suggested by p value of 0.789.

Table 2: Comparison of pain during induction in study groups

GRADES OF PAIN	DRUG A		DRUG B		χ^2 Value
	N	%	N	%	
0	19	63.3	21	70.0	
1	8	26.7	6	20.0	
2	1	3.3	2	6.7	1.052^{NS}
3	2	6.7	1	3.3	
Total	**30**	**100%**	**30**	**100%**	

Non Significant at 5 % level



Graph 1: Comparison of pain during induction with propofol

DISCUSSION

Pain due to propofol injection is a major limiting factor in the otherwise useful clinical profile of propofol. Propofol induced pain on injection mainly depends on the amount of free propofolpresent in the aqueous phase.The contact of propofol with free nerve endings of vessels leads to activation of the plasmakinin-kallikrein system, which locally liberates pain mediators .Pain on injection of propofol can be immediate or delayed; immediate pain results from a direct irritant effect whereas delayed pain is the result of an indirect effect via the kinin cascade.[3] Various studies and interventions have been conducted for decreasing propofolinjection pain.The initial preparation of 2% emulsion with castor oil, ethanol, soya oil was later replaced by reformulating it in 10% w/v soya bean oil, egg phosphtide and glycerol owing to pain on injection.[8] Scott *et al* suggested that vein size is an important factor in the etiology of pain on injection of propofol and concluded that there was no pain when propofol was injected in the antecubital veins.[9] Presuming that propofolis injected mid-stream into the lumen of the vein, the larger diameter and faster flow rate through the antecubital vein will minimise the extent to which a high concentration of propofol comes into contact with the sensitive endothelial wall and also the composition of nociceptors along the endothelial wall might differ between the smaller veins of the hand and the larger antecubitalveins.[2]However, it is not feasible to choose the antecubital fossa vein routinely as the i.vsite in antecubital fossa is relatively uncomfortable to patients and may be occluded when the elbow is flexed and unintentional extravasations may not be detected as quickly as when the dorsum of the hand is used. In the present study, a large vein on the dorsum of the hand was chosen for comparing the pretreatment effects of the study drugs. 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 propofolinjection, 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 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.[10] In the present study, out of the 20 subjects who experienced pain majority were females (60%) compared to males (40%).Also females experienced pain of higher intensities compared to males. Hence further studies are required to establish relationship between pain and gender variables. Ketamine, is a non-competitive blocker of glutamate NMDA receptors. In the sub-anaesthetic doses, ketamine possesses analgesic properties. Ketamine analgesia may be mediated by μ or delta opioid receptors. In addition, it was suggested that ketamine analgesia might result from local anaesthetic action.[11] In the present study, ketamine in a dose of 0.15mg/kg alleviated propofol induced pain in 63.33% of the patients. 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 the above 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.Also another added advantage of ketamine is that, propofol induced decrease in the arterial blood pressure after induction of anesthesia is prevented due to its positive effect on sympathetic stimulation leading to increase in myocardial contractility and vascular resistance, which in turn leads to increase in arterial pressure.[15] In the present study, there were no significant haemodynamic changes noted post induction.

In the present study, pretreatment with intravenous fentanyl reduced pain in 70% subjects. 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.[2]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. Also they reported a high incidence of skin erythema/whealdistal to the tourniquet owing to histamine release .[16]In the present study, no side effects were noted with ketamine or fentanyl pretreatment.

CONCLUSION

We conclude that i.v fentanyl(70%) caused greater alleviation of pain compared to i.vketamine(63.3%).However the difference between the drugs was statistically not significant.Both ketamine 0.15mg/kg and fentanyl 1.5mcg/kg were equally effective in alleviating propofol pain and there was no significant hemodynamic changes caused by both drugs.

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