Ketamine pretreatment to alleviate the pain of propofol injection: A randomized, double blind study

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Citation

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Abstract

Background: Propofol has the disadvantage of causing pain or discomfort on injection.[1 3] The aim of the study was to assess the efficacy of ketamine pretreatment to alleviate the propofol injection pain.Methods: One hundred ASA I and II adults, scheduled for various elective surgical procedures under GA were included in the study. The patients were randomly divided into two groups to receive 2ml of pretreatment ketamine solution (0.2mg.kg^{1}) or 0.9% saline intravenously. The venous drainage was occluded manually at midarm. One fourth of the total calculated induction dose of propofol was administered over a period of 5 seconds. The patients were asked about the pain on injection. The verbal response and the behavioral signs, such as facial grimacing, arm withdrawal or tears were noted. A score of 0-3 which corresponds to no, mild, moderate and severe pain was recorded.Results: Pain was reduced significantly in the ketamine group ($p<0.001$) with no significant side-effects. Conclusions: We concluded that pretreatment with intravenous 0.2 mg kg^{-1} ketamine was effective in relieving propofol injection pain.

INTRODUCTION

Although pain on injection of intravenous drugs is usually not considered as a serious complication of anaesthesia but it may be distressing to the patients and can reduce the acceptability of an otherwise useful agent. Pain during injection is a limiting factor in the use of some anaesthetic drugs like propofol, etomidate and diazepam.

Propofol is a popular induction agent, especially for short cases, day care surgeries and when a laryngeal mask is to be used. It produces a good quality of anaesthesia and rapid recovery. However, it often has the disadvantage of causing pain or discomfort on injection.$_{1}$ Various methods have been used to alleviate this pain including use of larger veins$_{4567}$, but the site may be inconvenient. A large number of drugs like local anaesthetics$_{8}$, narcotics$_{11121314}$, metoclopramide$_{12131415}$, ondansetron$_{16}$, and nitroglycerin$_{17}$ have been used to modify the pain with varying results. Ketamine is an anaesthetic agent that has analgesic and local anaesthetic properties.$_{18}$It is a phencyclidine derivative that produces dissociative anaesthesia in clinical doses of 1-2 mg kg^{-1} intravenously. In the sub-anaesthetic doses, it reduces the propofol injection pain by virtue of its local anaesthetic property .$_{1920}$

In a randomized, double blind study; we used intravenous ketamine pretreatment to determine whether it decreases the propofol injection pain.

METHODS

One hundred ASA I and II adult patients, scheduled for various elective surgical procedures under general anaesthesia were included in the study. After the approval from ethical committee written informed consent was obtained from all the patients. All patients were made familiar with verbal pain score. Intensity of injection pain was assessed using a four point verbal response scale.

Figure 1

Pain Score	Degree of pain	Response
0	None	Negative response to questioning
1	Mild	Pain reported in response to questioning only ,without any behavioral signs
2	Moderate	Pain reported in response to questioning and accompanied by a behavioral sign or pain reported spontaneously without questioning
3	Severe	Strong vocal response or response accompanied by facial grimacing ,arm withdrawl or tears

All the patients received oral alprazolam 0.25 mg and ranitidine 150 mg approximately 2 hour before induction of anaesthesia. ECG, NIBP and SpO_2 monitoring was established and 18-gauge cannula was inserted on the dorsum of the left hand. The patients were then randomly divided into two groups. Group I (50 patients): received 2 ml of ketamine solution ($0.2mg.kg^{-1}$)

Group II (50 patients) : received 2ml of 0.9% saline intravenously.

The solutions were prepared by an independent anaesthesiologist and the investigator did not know the content of the solution. Injection propofol (2.5 mg kg^{-1}) was loaded in a syringe. After 55 seconds of pretreatment, the venous drainage was occluded manually at midarm by an assistant. One fourth of the total calculated dose of propofol was administered over a period of 5 seconds. The level of pain was assessed at zero, one and two minutes after administration of propofol by a second observer who was unaware of the group to which the patient had been allocated. The patients were asked a standard question about the pain on injection of propofol, the verbal response and the behavioral signs, such as facial grimacing, arm withdrawal or tears were noted.[5] A score of 0-3 which corresponds to no pain, mild, moderate and severe pain was recorded at zero, one and two minutes (Table II-IV). Adverse effects, if any, were noted. Induction of anaesthesia was completed with the remaining calculated dose of propofol. Tracheal intubation was facilitated with injection vecuronium and anaesthesia was maintained as per surgical requirement.

The collected data was compiled and paired t-test was used to assess variance between preoperative and intraoperative values in the respective groups. Unpaired t-test was used to assess the difference between the two groups. A p-value of <0.05 was considered statistically significant.

RESULTS

There was no statistical significance among the age, sex and body weight of patients among both the groups. Age ranged from 18 to 50 years and the body weight ranged from 40 to 85 kgs (Table I).

Figure 2

Table 1

Group	Age Mean ± SD	Weight Mean ± SD	Sex M : F
A (n=50)	36.26 ± 12.040	55.12 ± 13.837	12 : 13
B (n=50)	33.58 ± 12.626	54.72 ± 9.934	27 : 23
p-value	> 0.05	> 0.05	> 0.05

The number of patients who experienced pain or discomfort in either group is shown in Table II, III and IV.

Figure 3

Table 2: Different grades of pain score at 0 minute

Group	PAIN SCORE			
	0	1	2	3
A (n=50)	37 (74)	10 (20)	3 (6)	0 (0)
B (n=50)	3 (6)	5 (10)	16 (32)	26 (52)
p-value	P<0.001	P<0.001	P<0.001	p<0.001

At zero minute the overall incidence of pain in the saline group was 94%, compared with 26% in the ketamine group (p<0.001). No patient in the ketamine group experienced severe pain as compared to 26 patients in the saline group (p<0.001). The number of patients who experienced mild to

moderate pain was 21(42%) and 13(26%) in the saline and ketamine groups respectively. No patient in either group experienced pain or discomfort during the injection of the pretreatment solution.

Figure 4

Table 3: Different grades of pain score at 1 minute

Group	PAIN SCORE			
	0	1	2	3
A (n=50)	40 (80)	6 (12)	2 (4)	2 (4)
B (n=50)	2 (4)	5 (10)	12 (24)	31 (62)
p-value	P<0.001	P>0.05	P<0.001	p<0.001

At one minute the overall incidence of pain in the saline group was 96%, compared with 20% in the ketamine group (p<0.001). 2 (4%) patients in the ketamine group experienced severe pain as compared to 31 (62%) patients in the saline group (p<0.001). The number of patients who experienced mild to moderate pain was 17 (34%) and 8 (16%) in the saline and ketamine groups respectively.

Figure 5

Table 4: Different grades of pain score at 2 minute

Group	PAIN SCORE			
	0	1	2	3
A (n=50)	43 (86)	3 (6)	3 (6)	1 (2)
B (n=50)	2 (4)	5 (10)	22 (44)	21(42)
p-value	P<0.001	P>0.05	P<0.001	p<0.001

The overall incidence of pain in the saline group at two minutes was 96%, compared with 14% in the ketamine group (p<0.001). One patient in the ketamine group experienced severe pain as compared to 21 patients in the saline group (p<0.001). The number of patients who experienced mild to moderate pain was 27 (54%) and 6 (12%) in the saline and ketamine groups respectively.

After propofol, 3 (6%) patients in ketamine group and 13 (26%) patients in the saline group had myoclonic movements. Four patients in each group had skin rashes in the upper limb into which propofol was injected. No active intervention was required, and all rashes disappeared spontaneously. There were no emergence reactions defined as dreams, hallucinations, delayed recovery and looking dissociated from surroundings in either treatment group.

DISCUSSION

Chemically, propofol belongs to the group of sterically hindered phenols. Hence, like other phenols propofol irritates the skin, mucous membrane and venous intima. Pain on injection of propofol has been reported and is an important limitation of its use.[1] Although, it is not a serious side effect, efforts are underway to reduce the severity of pain on discomfort. Various studies have been recommended using larger veins[7], decreasing speed of injection, injecting the drug into a fast running intravenous fluid[721] diluting it with 5% glucose or 10% intralipid[6] , mixing lidocaine in propofol[8], venous occlusion[22], pretreating with alfentanil[1423], meperidine, tramadol, metoclopramide[12], ondansetron[16] , pentothal[24], cooling to 4°C, injecting cold saline 4% before propofol[2526] and preparation of skin with nitroglycerine ointment[17].

The exact mechanism for the production of pain with propofol injection is yet to be established. The free fraction of propofol has been implicated, which explains a slight delay before pain is experienced.[27] The incidence of pain on injection of propofol using dorsal hand veins is reported to be 39% as compared to 3% incidence in forearm veins[28], whereas injecting propofol at 4-5°C results in a decrease in incidence of pain from 46% to 23%[25], lidocaine pretreatment reduces the incidence of pain to 32%.[8] Anaesthetic and subanaesthetic doses of ketamine are 1.5-2.5 mg kg^{-1} and 0.5 mg kg^{-1} respectively. In the present study we used ketamine in a dose 0.20 mg kg^{-1} which is much lower than the dose for producing central analgesic effect. As a non-competitive NMDA receptor agonist, ketamine may activate NMDA receptors either in the vascular endothelium or in the central nervous system. It seems likely that the reduction in injection pain was the result of a peripheral action which attenuated the efferent pain pathway.[2029]

The study was designed to ascertain whether pretreatment with the low dose of ketamine could attenuate the pain produced by propofol and one minute was allowed for its action to begin. We chose one minute interval with the presumption that this period might be sufficient, as most patients feel numbness after the intradermal injection of a local anaesthetic.

Tan and Kua et al in 1998 studied the effect of ketamine pretreatment on propofol injection pain and found that the incidence of pain was reduced from 84% to 26%.[20] Barbi et al in 2003 studied that whether pretreatment with ketamine would reduce infusion line pain in propofol sedation in 122

children undergoing gastroscopy. In their study the incidence of pain of propofol infusion was significantly reduced in patients pretreated with ketamine (8% vs 37%, p = 0.0001). They concluded that pretreatment with ketamine (0.5 mg.kg-1) was very effective in preventing propofol infusion $pain_{30}$. In 2006 Seung WK et al studied small dose 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 $injection_{31}$. The incidence of pain in our study was also comparable with previous studies with the reduction of pain from 94% to 26% and this compares favorably with other methods.

CONCLUSION

Pretreatment with intravenous ketamine provides a simple and safe method of reducing the incidence of pain on injection of propofol. We suggest intravenous 0.2 mg kg^{-1} ketamine pretreatment to alleviate pain on propofol injection.

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