Cisatracurium Pretreatment with Tourniquet - Role in Propofol Injection Pain: A Prospective, Randomized, Double Blind and Control Study

Chandrakant Uraiya[1], Rashmi Pal[2], K.K. Arora[3]

ABSTRACT

Introduction: Propofol is an anaesthetic drug which is given to induce and maintain anaesthesia in adults undergoing surgery. This prospective, randomized, controlled study was designed to evaluate the efficacy of cisatracurium as a pretreatment drug in reducing incidence and severity of propofol injection pain.

Material and methods: Patient undergoing general anaesthesia were randomized in four groups of 25 patients each. Group A received normal saline (control group), Group B received Cisatracurium 0.05mg/kg IV, Group C received Cisatracurium 0.1mg/kg IV, Group D received Cisatracurium 0.15mg/kg IV. All drugs were administered into the largest dorsal vein of the hand with venous occlusion for 30 sec, followed by propofol (0.5mg/kg). Pain was evaluated using a four point scale.

Result: Cisatracurium 0.15mg/kg significantly lowers both incidence and severity of propofol induced pain. Cisatracurium 0.1mg/kg and cisatracurium 0.05mg/kg both significantly lower the severity of pain but not the incidence as compared to control group.

Conclusion: Cisatracurium is an effective drug in reducing propofol induced pain. It reduces the incidence and severity both of pain in 0.15mg/kg dose. Whereas only severity is decreased with 0.10 mg/kg and 0.05 mg/kg dose of cisatracurium without any significant complications.

Keywords: ASA - American Society of Anaesthesiologist, VRS - Verbal Rating Scale, PR - Pulse Rate, HR - Heart Rate, SBP - Systolic Blood Pressure, DBP - Diastolic Blood Pressure, RR - Respiratory Rate

INTRODUCTION

Propofol is a popular induction agent because it provides a smooth induction and faster recovery than other drugs such as thiopentone. The main disadvantage of propofol is that it often causes severe pain. This is because propofol is usually injected into a hand vein and can cause skin irritation. This can make the anaesthesia experience unpleasant. Pharmacological and non-pharmacological interventions to reduce propofol injection pain have been attempted with varying success. These include co-injection with lidocaine[1,2,] injection of propofol into a large vein[3,] and pretreatment with lidocaine[4,5], ketamine[6], thiopental[7], ondansetron[8], dexamethasone[9], opioids[10,11], paracetamol[12] or dexmedetomidine.[13]

One method for preventing propofol induced pain is to give lidocaine either before the propofol injection or mixed in with the propofol. This procedure has a failure rate of 13-48%[14], however indicating the need for alternative methods for reducing propofol – associated pain. So we use cisatracurium, it is a neuromuscular- blocking drug or skeletal muscle relaxant in the category of non-depolarizing neuromuscular-blocking drugs, used adjunctively in anaesthesia to facilitate endotracheal intubation and to provide skeletal muscle relaxation during surgery or mechanical ventilation. It shows intermediate duration of action.

So this prospective double – blind, randomized and controlled study is being undertaken to compare (investigate) the efficacy of 3 different doses of cis-atracurium as a pretreatment drug, simultaneously using tourniquet and to determine the optimum dose of cisatracurium in reducing pain associated with propofol injection.

MATERIAL AND METHODS

This study was conducted in Department of Anaesthesiology M.G.M.Medical college indore after getting permission from the college ethics committee. The procedure was explained in detail to all patients. An informed and written consent were taken. Inclusion and exclusion criteria was applied.

The study was conducted on 100 patients after written informed consent. The calculated sample is 25 per group with total sample size of 100 for the four groups of the study. 100 patients equally and randomly divided into four groups 25 patients each. Group A received normal saline, Group B received Cisatracurium 0.05mg/kg IV, Group C received cisatracurium 0.1mg/kg IV and Group D received cisatracurium 0.15mg/kg IV.

Baseline hemodynamic parameters (systolic blood pressure, diastolic blood pressure, heart rate, RR, SPO2) were recorded.

A 20 G cannula was inserted into the largest visible vein

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on the radial side of forearm, attached to a three way tap, and flushed with Ringer's lactate solution, with no local anaesthetic intervention. No analgesic drug was given to the patient. A venous tourniquet was applied just above the elbow to increase the local concentration of the pretreatment drug administered in a double blind manner. The tourniquet was inflated and pretreatment drug (10ml) was administered through the selected vein.

The tourniquet was released after 30 sec. then, 0.5 mg/kg propofol was delivered via the intravenous cannula.

In order to evaluate pain and determine the possibility of muscle paralysis, patients were asked "does it hurt?" by the anaesthetist at 10 sec. after the initial propofol dose, and at 20 sec intervals thereafter until unresponsive.

Any spontaneous movement of the wrist, elbow or shoulder were noted.

Pain was evaluated using a four point verbal rating scale (VRS): 0, no pain; 1, mild pain (pain reported only in response to questioning and without behavioural signs); 2 moderate pain (pain reported in response to questioning and with behavioural signs, or pain reported without questioning); 3 severe pain (strong vocal or behavioural response).

Each patient's highest pain score were documented. Adverse effects (including airway obstruction and diplopia) also were noted.

Induction of anaesthesia was completed with the remaining 1.5mg/kg propofol.

Tracheal intubation facilitated with additional cisatracurium to a total dose of 0.15 mg/kg per patient. Anaesthesia maintained with 50% nitrous oxide and 50% oxygen and isoflurane in titrated manner.

Adverse effects at the injection site (pain, oedema, wheal, inflammation) assessed by the study investigator for 24 hr after surgery, using spontaneous reporting and patient interview.

Inclusion criteria

1. Age – 18 to 60 years, of both sexes.
2. American Society of Anaesthesiologist Grade I and II.

Exclusion criteria

1. Study refusal.
2. Allergy to propofol or egg lecithin.
3. Mallampati class III-IV.
4. Limited neck mobility.
5. Patients with airway problems suggesting difficult intubation.
6. Patients with disorder of cardiovascular, respiratory, hepatic, renal or neuromuscular systems

Experimental protocol

Check Flow chart 1

STATISTICAL ANALYSIS

Statistical analysis was performed using SPSS. Data was analysed for normality of distribution using Shapiro-Wilk test, p value=0.156 indicated that data was normally distributed, thus parametric test of significance were applied. The comparison of continuous data variables between the groups was done using ANOVA. To compare the groups on the basis of categorical data, chi square test

saline tourniquet off

Control group (Saline)	30 sec	Propofol 0.5mg/kg	Assessed pain intensity using a 4 point scale	Propofol 1.5 mg/kg	Check loss of conscious ness	Cisatracurium 0.15mg/kg	4 min.	intubation

Cisatracurium 0.05 mg/kg

Cisatracurium 0.05mg/kg group	30 sec	Propofol 0.5mg/kg	Assessed pain intensity using a 4 point scale	Propofol 1.5 mg/kg	Check loss of conscious ness	Cisatracurium 0.1mg/kg	4 min.	intubation

Cisatracurium 0.1mg/kg

Cisatracurium 0.1mg/kg group	30 sec	Propofol 0.5mg/kg	Assessed pain intensity using a 4 point scale	Propofol 1.5 mg/kg	Check loss of conscious sness	Cisatracurium 0.05mg/kg	4 min.	intubation

Cisatracurium 0.15mg/kg

Cisatracurium 0.15mg/kg group	30 s	Propofol 0.5mg/kg	Assessed pain intensity using a 4 point scale	Propofol 1.5 mg/kg	Check loss of conscious sness	saline	4 min.	intubation

Flowchart-1: Experimental protocol

Propofol Induced Pain	Group A		Group B		Group C		Group D	
	No.	%	No.	%	No.	%	No.	%
Absent	2	8.0	6	24.0	8	32.0	14	56.0
Present	23	92.0	19	76.0	17	68.0	11	44.0
Total	25	100.0	25	100.0	25	100.0	25	100.0
Mean Rank	61.50		53.50		49.50		37.50	

Table-1: Comparison of incidence of propofol induced pain among the groups

Groups	Immediate pain				Delayed pain											
	Upto 10 sec				10- 30 sec				30-50 sec				50-70 sec			
	Pain Score				Pain Score				Pain Score				Pain Score			
	0	1	2	3	0	1	2	3	0	1	2	3	0	1	2	3
Group A	2	5	10	8	2	12	11	0	5	20	0	0	25	0	0	0
Group B	6	12	5	2	7	16	2	0	11	14	0	0	25	0	0	0
Group C	8	13	3	1	8	16	1	0	21	4	0	0	25	0	0	0
Group D	14	7	3	1	21	3	1	0	25	0	0	0	25	0	0	0
Chi square value	32.409				49.199				42.165				-			

Table-2: Distribution of pain score amongst study participants in various groups.

was employed. P value < 0.05 was considered statistically significant.

RESULTS

The average rank in the Group D is lower than Group A which is statistically significant, p value is 0.001 (p<0.05). While the mean rank in all the other pairs were comparable, which was statistically not significant (p>0.05) (Table 1).

The difference in mean pain scores upto 10 seconds in all the drug groups was statistically significant from that of the control group, (p<0.05). While the difference in mean pain scores between the groups were not found to be statistically significant (p>0.05) (Table 2).

In 10 -30 sec the mean pain scores were significantly higher in Group A in comparison to the Group B (p=0.004), Group C (p=0.001) and Group D (p=0.000). On inter group comparison, the differences in mean pain scores between Group B and Group C was not found to be significantly, whereas it was found to be significant for Group C versus Group D (p=0.009) and Group B versus Group D (p=0.002).

In 30-50 sec the mean pain score in the control group and Group B were not significantly different (p=0.115) whereas the difference was statistically significant between Group A and Group C (P =0.000) and between Group A and Group D (P =0.000).On inter-group comparison, the mean pain score was found to be significantly lower in Group C in comparison to Group B (p<0.05) and Group D in comparison to Group B

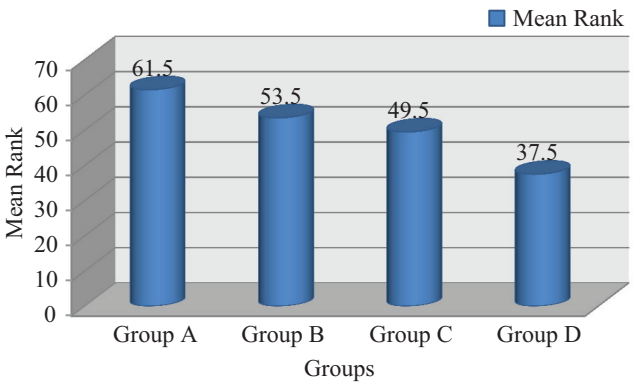

Figure-1:

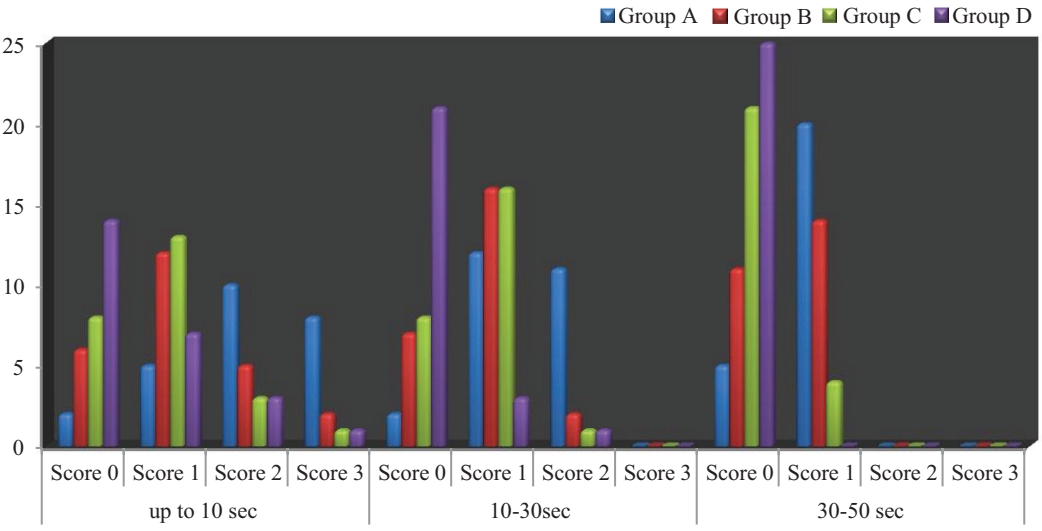

Figure-2: Distribution of pain scores amongst study participants in various groups

(p<0.05).The difference in mean pain score in Group C and Group D were found to be statistically insignificant. (Figure 1,2)

DISCUSSION

Propofol is an intravenous sedative and hypnotic agent commonly used for induction of anesthesia. Propofol induced pain has been reported since the initial studies and is still a limitation of this, otherwise excellent intravenous anesthetic agent.

All phenols irritate skin and mucous membrane. Thus, propofol being an alkylphenol is expected to cause pain in spite of the fact that it is almost isotonic. Propofol induced pain has also been described as angialgia by some meaning that the pain is due to vascular involvement. Propofol induced pain is immediate upto 10 sec as well as delayed after 10–20 sec. The immediate pain is due to irritation of vein endothelium whereas delayed pain is due to the release of mediators such a kininogen from kinin cascade[15] leading to vasodilation and hyperpermeability.

various studies have been conducted to prevent it, with different levels of success obtained. Cisatracurium, an upcoming non- depolarizer can prove to be a rewarding drug in this respect.

Cisatracurium besilate trade name Nimbex is a bisbenzyltetrahydroisoquinolinium. Cisatracurium is a neuromuscular- blocking drug or skeletal muscle relaxant in the category of non-depolarizing neuromuscular-blocking drugs. Cisatracurium is a nondepolarizing skeletal muscle relaxant, and it is known that neuromuscular blocking agents affect sensory nerve endings, nerve trunks and muscle spindles.[16,17] Cisatracurium may reduce propofol injection pain via blockade of peripheral nerve endings followed by blockade of nerve trunks at a proximal site.[18]

This study shows that cisatracurium is an acceptable alternative to lidocaine, opioids, ketamine, NSAIDs or other drugs used for propofol induced pain. A major advantage of cisatracurium over other drugs is that cisatracurium is required for muscle relaxation in general anaesthesia, thus avoiding side-effects from additional drugs used for reducing propofol-associated pain.

In our study we used Cisatracurium pretreatment with tourniquet.

This is a prospective, double – blind, randomized and controlled study conducted on 100 patients. We used cisatracurium in three different doses 0.05mg/kg IV, 0.1mg/kg IV and 0.15mg/kg IV along with control group. All drugs were administered into the largest dorsal vein of the hand with venous occlusion for 30 sec., followed by propofol bolus of 0.5mg/kg over 30 sec. All the groups were comparable in their mean age, sex, weight of the patients along with ASA grade (I and II).

The incidence of propofol induced pain in our study groups are as follows:- 92%, 76%, 68% and 44% in control group, cisatracurium (0.05mg/kg), cisatracurium (0.10mg/kg), cisatracurium (0.15mg/kg) respectively.

We found that the incidence of pain in cisatracurium -0.15mg/kg group is significantly lower than the control group (p=0.001*) and no other group differed significantly from the control group in terms of incidence of propofol induced pain in patients undergoing general anaesthesia.

We found that immediate (upto 10 sec) pain score was statistically significantly decreased in all the drug groups from the control group (p< 0.05). As mentioned earlier that immediate type of propofol induced pain is due to irritation of vein endothelium and on analyzing the observations of our study it can be inferred that cisatracurium 0.05mg/kg is as effective as cisatracurium 0.15mg/kg in reducing the severity of propofol induced pain in immediate phase. It probably exerts this action simply because of its primary analgesic effect. i.e, by decreasing the irritation of vein endothelium. There is only one study which goes in favour of our study in the context of propofol induced pain in immediate phase on cisatracurium reported so far.

Delayed pain (10-30sec) the pain scores were significantly higher in control group in comparison to cisatracurium 0.05mg/kg (p=0.004), cisatracurium 0.10mg/kg (p=0.001) and cisatracurium 0.15mg/kg (p=0.000). Pain score in this phase also significantly decreased in cisatracurium 0.15mg/kg from cisatracurium 0.05mg/kg (p=0.002) and cisatracurium 0.1mg/kg (p=0.009), but the groups B and C did not differ significantly in this regard. So it can be inferred that for delayed pain at 10-30 seconds, cisatracurium 0.05mg/kg is equally effective to cisatracurium 0.1mg/kg for propofol induced pain, the later two doses being equally effective for this phase (p=0.959). This action of the study drug is explained by the fact that it may have a role in decreasing kininogen factors and permeability of blood vessels, at higher doses.

The pain score at 30-50 seconds differed significantly between control group and cisatracurium 0.10mg/kg (p=0.000) and between control group and cisatracurium 0.15mg/kg (p=0.000). They also found pain score in cisatracurium 0.10mg/kg and cisatracurium 0.15mg/kg was significantly lower from cisatracurium 0.05mg/kg (p<0.05) with a P values of 0.002 and 0.000 respectively. So we can infer that for delayed pain at 30-50 seconds cisatracurium 0.15mg /kg and cisatracurium 0.10mg/kg both are more effective to the same extent for propofol induced pain as compared to cisatracurium 0.05mg/kg.

At 50 – 70sec in all the groups pain score was recorded to be zero (0) patients became unresponsive after 50 seconds and pain assessment could not be done.

As mentioned above delayed pain is due to the release of mediators such as kininogen from kinin cascade, leading to vasodilation and hyperpermeability. The analgesic effect of cisatracurium in delayed pain may be because of its effect in decreasing release of pain mediators from kinin cascade.

Regarding effect of cisatracurium on haemodynamic profile of the patients, there was no significant difference found in heart rate, blood pressure, respiratory rate and arterial oxygen saturation of study participants in any of the drug groups as compared to control group.

There was no patient noticed with any adverse effect, airway

obstruction and diplopia in any patient belonging to any group.

The findings of the present study indicate a possible pharmacological method to prevent pain from propofol injection, and importantly, no signs of muscular weakness or evidence of respiratory difficulty were noted by the observer or reported by the patients in the present study. This is supported by study done by kim et al in 2014.[19] Cisatracurium-associated muscle weakness was not a concern in the design of the present study, since the onset of cisatracurium is 3–5 min after administration and propofol was injected within 30 s following tourniquet release.

CONCLUSION

This prospective, randomized, double blind and controlled study may conclude that cisatracurium, an intermediate acting non depolarizer is a safe and effective drug for propofol- induced pain, without significant haemodynamic and adverse effects. It reduces both the incidence and severity of propofol induced pain.

Cisatracurium 0.15mg/kg significantly lowers incidence of propofol induced pain, where as only 0.10mg/kg dose is sufficient to reduce severity of propofol induced pain. Further more, 0.05mg/kg dose of cisatracurium is efficient in reducing the severity of pain upto 30 seconds and higher dose 0.10mg/kg dose is required for pain experienced after 30 seconds. No previous studies have been reported in this context and future studies are too required to support it.

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