Original Research Article

Comparison of different doses of Injection Cisatracurium to establish optimal dose for reduction of propofol injection pain

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Abstract

Background and Aims: The aim is to compare different doses of injection Cisatracurium given prior to injection propofol intravenous (IV) with venous occlusion by applying tourniquet for thirty seconds; and to establish the optimal dose of it. It is recommended for prevention of pain associated with propofol injection; and is to be compared with that of lignocaine injection for patients undergoing general anaesthesia. **Methods:** Patients undergoing operations with general anaesthesia are randomized to receiveeither injection 0.9% normal saline (control group) NS, Inj.Lignocaine (0.5 mg/kg) L, Inj. Cisatracurium (0.03 mg/kg) C1, Inj. Cisatracurium (0.1mg/kg) C2 and Inj. Cisatracurium (0.15 mg/kg) C3. All study drugs are administered into largest vein of hand with tourniquet applied for 30 seconds, followed by propofol injection (0.5 mg/kg). Pain is evaluated using four-point scale. **Results:** The propofol injection pain was definitely lower in pre-treatment with venous occlusion for 30 seconds in 0.1 mg/kgInj. Cisatracurium C2,0.15 mg/kg Inj. Cisatracurium C3 group and inInj. Lignocaine L group, than 0.03 mg/kg Inj.Cisatracurium C1 and control group with 0.9% normal saline NS given intravenously. There was no significant in-between difference with 0.1mg/kg Inj. Cisatracurium C2 group and 0.15mg/kg Inj. Cisatracurium C3 group. There was significant difference between injection 0.5mg/kg Inj. Lignocaine L, 0.1 mg/kg Inj. Cisatracurium C2 and 0.15mg/kg Inj. Cisatracurium C3 groups for pain perception with propofol injection given intravenous following tourniquet release after 30 seconds. **Conclusion:** Pre-treatment with venous occlusion for 30 seconds with0.1mg/kg Inj. Cisatracurium C2 decreases the propofol injection pain as effectively as 0.15mg/kg Inj. Cisatracurium C3; and that may be an optimal dose without significant complications.
Key Word: Cisatracurium, general anaesthesia, lignocaine, propofol pain.

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INTRODUCTION

Injection Propofol is a drug used for induction and maintenance during general anaesthesia. Pain is a common side effect associated with propofol injection[3]. The incidence of pain with IV propofol varies between 28% and 90% in adults. Pain is described as extremely sharp (Pain score 3), aching (Pain score 2) or burning (Pain score 1) and no pain (pain score 0). On the top, the hyper dynamic cardiovascular response to the pain can precipitate adverse events in high-risk patients with a history of coronary artery disease (CAD) and/or abnormal heart rhythm (arrhythmias)[30] Various Pharmacological and Non-Pharmacological remedies to reduce propofol pain have been attempted. Co-injection with Lignocaine[4,5] Ketamine[6], Thiopentone[7], Ondansetron[8], Dexamethasone[9], Opioids[10], Paracetamol[12] or Dexmeditomidine[13] (with or without tourniquet) has been tried. Among this Inj. Lignocaine pre-treatment with venous occlusion for thirty seconds is recommended as most effective method to reduce the incidence and severity of propofol injection pain when

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the site of injection is at the back ofhand[1, 14, and 15]. But this procedure has failure rate of 13-48% [14, 15]. So there is need for alternative methods or agents for reducing propofol injection pain[1]. The addition of Inj. Cisatracurium (a non-depolarizing neuromuscular blocking agent) to lignocaine has been shown to improve the quality of analgesia during Intravenous Regional Anaesthesia.[16] We therefore assumed that tourniquet-controlled pre-treatment with Cisatracurium can reduce propofol injection pain.[17,18,19] The aim of the study is to establish the optimal dose of Inj. Cisatracurium as compared to .15mg/kg Inj.Cisatracurium; which is an intubation dose and 0.03 mg/kgof Inj. Cisatracurium, which is maintenance dose; for general anaesthesia with propofol injection. The efficacy of these three different doses (0.03mg/kg, 0.1mg/kg, and 0.15mg/kg) ofInj. Cisatracurium is compared with that of Inj.Lignocaine.

MATERIAL AND METHOD

The present study is carried out in tertiary care teaching hospital, between June 2017 to October 2018. Institutional ethical committee approval is obtained for study and written informed consent is obtained from patients undergoing elective non cardiac surgery under general anaesthesia. This is a double blind, prospective, controlled study. Patients are randomized to receive either normal saline (control group)NS, Inj. Lignocaine(0.5 mg/kg)L, Inj.Cisatracurium (0.03 mg/kg)C1,Inj. Cisatracurium (0.1mg/kg)C2, and Inj. Cisatracurium (0.15 mg/kg)C3 . All study drugs are administered into largest dorsal vein of hand with venous occlusion for 30 seconds, followed by Inj.propofol (0.5 mg/kg) Pain is evaluated using four-point scale. 250 patients are randomized for study.

Inclusion criteria are:

1. American Society of Anesthesiologists physical status I or II
2. Age limit 18 years to 65 years

Exclusion Criteria are:

1. Allergy to propofol or egg
2. Mallampatti class III-IV
3. H/O of difficult intubation
4. H/O Cardiovascular, Respiratory, Neuro or Neuro- muscular and Psychiatric diseases

Conduct of study: 250 Patients of ASA Grade I and II with age limit 18 to 65 years, scheduled for general anesthesia are divided in five groups of 50 each. Patients are randomly assigned to one of five group, using a randomization table: Control Group, [Ns] pre-treatment with normal saline Lignocaine Group,[L] Pre-treatment with 0.5 mg/kg preservative free Inj.Lignocaine. Cisatracurium 0.03 Mg/Kg Group, [C1] Pre-treatment with 0.03 mg/kg inj.Cisatracurium. Cisatracurium 0.1Mg/Kg Group, [C2] Pre-treatment with 0.1mg/kg Inj.Cisatracurium. Cisatracurium 0.15mg/Kg Group, [C3] Pre-treatment with 0.15mg/kg inj. Cisatracurium. All drugs are stored at room temperature and are diluted to identical volume of saline with 10ml. Syringe. Patient in Operation room is connected to lectrocardiogram (ECG), Pulse-oximetry (SpO2); Non-invasive Blood Pressure monitors (NIBP). 20G cannula is inserted to largest visible vein on forearm. Three-way and cannula is flushed with ringer lactate solution. Venous tourniquet is applied just above elbow. Pre-treatment study drug is administered intravenously in double blind manner. Tourniquet is released after 30 seconds. Then 0.5 mg/kg injection propofol is delivered via cannula. To judge pain and muscle paralysis, patients is asked by anesthesiologist, at 10 seconds and 20 seconds interval after initial dose for injection pain until unresponsiveness. Pain score is evaluated by anesthesiologist who is blinded for procedure, using four-point scale. (0=No pain;1= mild pain; 2=moderate pain and3=severe pain.) Induction of anesthesia is conducted with remaining 1.5 mg/kg injection propofol. Tracheal intubation is facilitated by additional injection Cisatracurium to total dose of 0.15 mg/kg. Injection Fentanyl is added as 1 µgm/kg as opioids. Anesthesia is maintained with inhalational agent; Sevoflurane and 50% nitrous oxide -oxygen. Adverse effects at injection site (pain, oedema, inflammation) are assessed by study investigator for 24 hour after surgery.

STATISTICAL ANALYSES

- Few of our references studied earlier[29] along with Confidence Interval (CI) of 95% and p value <0.05, we had conducted a pilot study on 20 patients.
- Using this information, we could get sample strength of 44 in each group with two sided α-error of 5% and power study to be >80%. To compensate for potential dropout, 250 participants (50 per group) were considered necessary.
- Continuous variables are expressed as mean ± SD or median (range). Categorical variables are described as n (%).
- Demographic data is analysed with one way analysis of variance and χ^2-test.
- Between –group variation in the incidence of pain is analysed using χ2-test. Differences in the mean pain intensity score were analysed using linear trend analysis with chi square test.
- Statistical significance is defined as $p < 0.05$. Statistical analysis is performed with Epi info software.

RESULTS

The study included 250 patients (n=50/group). A flow chart is shown in Figure1. Demographic and clinical characteristics of the patients are presented in Table 1. Data regarding pain scores are shown in Table 2.

Figure 1

Table 1: Demographic and clinical characteristic of patients

Characteristic	Control Group (n=50)	Lignocaine Group (n=50)	Cisatracurium 0.03 mg/kg Group (n=50)	Cisatracurium 0.1 mg/kg Group (n=50)	Cisatracurium 0.15 mg/kg Group (n=50)
Age in years	30.58±5.89	32.32 ±10.73	36.46 ±13.48	37.84 ±13.93	34.61 ±10.12
Male/Female	14/36	11/39	15/35	22/28	14/36
ASA grade, I/ II	17/33	11/39	18/32	18/32	15/35
Average Weight in kg	55.77±6.83	54.7±11.65	58.48±9.52	55.96±11.62	54.63±9.42

Data presented as mean± SD or n There is no statistical significant between group differences found in clinical characteristics like Age, Sex, ASA grade, and average Weight in Kg. ($p \geq 0.05$)

Table 2: Propofol Associated pain in patients undergoing operations under general Anasthesia with pre-treatment medication

Pain Score	Control Group(n=50)	Lignocaine Group(n=50)	Cisatracurium 0.03mg/kg Group(n=50)	Cisatracurium 0.1mg/kg group (n=50)	Cisatracurium 0.15 mg/kg Group (n=50)
Median sore	3(0-3)	0.5(0-3)	1(0-3)	0(0-3)	0(0-3)
Any Pain	45(90%)	25(50%)	34(68%)	20(40%)	19(38%)
Pain Grade					
0, none	5(10%)	25(50%)	16(32%)	30(60%)	31(62%)
1, mild	4(8%)	17(34%)	13(26%)	11(22%)	10(20%)
2, moderate	11(22%)	7(14%)	13(26%)	6(12%)	6(12%)
3, severe	36(60%)	1(2%)	8(16%)	3(6%)	3(6%)

Percentage of patients having pain is maximum (90%) in the control group and is significantly higher as compared to those who had 0.1mg/kg(40%) and 0.15mg/kg (38%) of injection Cisatracurium. It is also noted that only half (50%)of patients who are given pretreatment with injection Lignocaine; had pain as compared to 90% of the control group after propofol injection. Percentage of patient having pain is significantly more in patients who are given 0.03 mg/kg [C1] of injection Cisatracurium as compared to those who are given 0.1mg/kg [C2] and 0.15mg/kg [C3] of it. Similarly 60% of control group [NS] has severe pain. The percentage is significantly higher as compared to other groups. Severity of pain is comparable in the patients who are given pretreatment with 0.1mg/kg and 0.15mg/kg of Cisatracurium for propofol injection pain with 30 seconds venous occlusion.

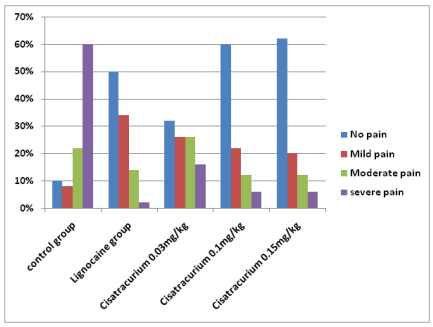

Figure 1: Graphical representation of in-between comparison of all study drugs

Table 3: Comparison of pain in C1, C2, C3, NS and Lignocaine group

	No Pain	Pain	X^2	P value
Lignocaine	25	25	**2.64**	**.1038**
[C1]cisatra.03mg/kg	16	34		**Comparable**
Chi sq. test for linear trend of pain gradation			6.44	**0.01 (significant p<0.05)**
Comparison Group	No Pain	Pain	X^2	P value
Lignocaine	25	25	**. 6465**	**. 4213**
[C2]cisatra.1mg/kg	30	20		**Comparable**
Comparison Group	No Pain	Pain	X^2	P value
Lignocaine	25	25	1.1014	**. 314**
[C3]cisatra.15mg/kg	31	19		**Comparable**
Comparison Group	No Pain	Pain	X^2	P value
Lignocaine	25	25	17.190	**0.0003**
[NS]Normal Saline	5	45		**significant**

Table 3: In-between Comparison of C1, C2 and C3 for severe pain

Comparison Group	No Pain	Pain	X^2	P value
[C1]cisatra.03mg/kg	16	34	6.805	**. 009**
[C2]cisatra.1mg/kg	30	20		**significant**
Comparison Group	No Pain	Pain	X^2	P value
[C1]cisatra.03mg/kg	16	34	7.8683	**. 005**
[C3]cisatra.15mg/kg	31	19		**significant**
Comparison Group	No Pain	Pain	X^2	P value
[C2]cisatra.1mg/kg	30	20	7.820	**. 9957**
[C3]cisatra.15mg/kg	31	19		**Comparable**

OBSERVATIONS

Incidence of pain is definitely lower in Lignocaine and all three doses of Cisatracurium group compared to control group [NS]. So can be used for propofol pain relief. There was no significant between-group difference in the incidence of mild pain for C1,C2 and C3 The incidence of moderate and severe pain was significantly lower in [C2] and[C3] and Lignocaine [L]group compared to [C1] [C1], in the dose of 0.03mg/kg has some analgesia compared with NS but ineffective for moderate and severe pain relief. For severe pain relief, C2 and C3 are comparable Pretreatment with lignocaine or injection Cisatracurium can be used for analgesia for propofol injection pain

DISCUSSION

Propofol is an intravenous (IV) anesthetic drug used for induction and maintenance during anesthesia. The incidence of pain with IV propofol varies between 28% and 90% in adults[3]. Scott *et al.*[26] pointed out that certain factors are responsible for the pain on injection of propofol. Klement and Arndt [27] reported that the dilution ofpropofolwith10%intralipidwasbetter in effect than to be diluted with 5% glucose in reducing propofol injection pain, while Doenicke *et al.* [28] showed that propofol injection pain could be reduced when a higher percentage of fatemulsion was used in the propofol formulation. Intheropofole mulsion preparation, the drug will be distributed differently between the two phases,[26]

with an outer aqueous phase and an inner lipid phase. In a bolus injection, only the outer aqueous phase comes into contact with the intima of the vein. The concentration of this irritating agent in the aqueous phase may be responsible for venous pain. Many other factors appear to affect the incidence of pain, which include site of injection, size of vein, speed of injection, buffering effect of blood, temperature of propofol[26] and concomitant use of drugs such as local anaesthetics and opiates. The aetiology of propofol injection pain is fully not understood. It can be immediate or 10-20 seconds. Propofol being a Phenol compound; the pain receptors of the skin are directly stimulated causing irritation of mucous membrane and venous intimae for immediate pain.[26] In addition it may activate kallikrenin-kinin system with release of kinins causing delayed pain with venous dilatation and hyper-permeability.[26] Ganta and Fee[31] reported that the incidence of pain using lignocaine 10 mg immediately before propofol injectionwassignificantlyreducedfrom49.4%to21.1%.Lignocaine relieves propofol pain by change in pH or reversible blockade of pain pathway. The pre-treatment with isatracurium0.1mg/kg or 0.15 mg/kg was equally effective compared with lignocaine. Cisatracurium is non-depolarizing muscle relaxant affects sensory nerve endings, nerve trunks and muscle spindles. Addition of small doses to IVRA improves quality during and after procedure. It does this by direct diffusion of LA from the vessel into nearby nerves followed by blockade of nerve trunks at proximal site. The present study findings show that Cisatracurium in a dose of 0.1mg/kg is an acceptable alternative to lignocaine, opioids, ketamine, NSAIDs used for propofol injection pain. The major advantages are that it is needed for GA with muscle relaxation; avoiding side effects from other drugs. No sign of muscle weakness or respiratory paralysis is observed as; the onset of Cisatracurium is 1.5-2 minutes and propofol is injected within 30 seconds of tourniquet release. We have studied the wide range of Cisatracurium with pre-treatment to establish optimal dose; for propofol injection pain relief. (n=250) Data from the present study indicate that pre-treatment with 0.1 mg/kg Cisatracurium is as effective as 0.15mg/kg Cisatracurium in attenuating pain during intravenous injection of propofol. Pre-treatment with 0.03 mg/kg Cisatracurium decreased the intensity but not the frequency of pain. These findings indicate that Cisatracurium has a primary analgesic effect. Yun-Hee Kim, JinNamgung and Choon-HakLim[29] concluded that 0.15 mg/kg Cisatracurium retained in tourniquet-occluded veins effectively decreased the incidence and severity of pain induced by propofol injection without any significant complications in general anaesthesia. They studied only the recommended intubation or maintenance dose and further study is therefore required to establish the optimal dose of Cisatracurium for prevention of propofol pain. We have effectively proved the optimal dose of 0.1mg/kg of injection Cisatracurium for this study.

CONCLUSION

In conclusion 0.1mg/kg Cisatracurium retained in tourniquet-occluded vein for 30 seconds effectively decreases the incidence and severity of propofol injection pain as good as 0.15 mg/kg Cisatracurium without significant complication in general anaesthesia.

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Conflict of Interest: None Declared