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Original Research Article

Comparative study of two different intubating doses of cisatracurium for hemodynamic changes during coronary artery bypass grafting under general anaesthesia

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ABSTRACT

Background: The aim of the study was to compare hemodynamic response, assessment of intubating condition, time to achieve TOF 0 and any adverse effects associated with two different doses of cisatracurium i.e., 0.15mg/kg (3x ED95) and 0.3mg/kg (6x ED95) for endotracheal intubation during Coronary artery bypass grafting (CABG).

Materials and Methods: It was a prospective single blinded randomized controlled clinical trial, conducted by two investigators in 296 patients aged between 50-70 years of both sexes of ASA III grades. Patients having ejection fraction >45% and undergoing CABG were included in the study. Patients with neuromuscular diseases, anticipated difficult airway, morbid obesity and any associated valvular heart diseases were excluded from the study. Patients were randomly allocated into 2 groups depending on the doses of cisatracurium. Group R (n=148) → received 0.15 mg/kg, Group D (n=148) → received of 0.3 mg/kg. After 60 seconds of injecting cisatracurium, TOF was recorded every 30 seconds until it reaches 0, then laryngoscopy and endotracheal intubation was carried out using Macintosh laryngoscope blade no. 4 by one of the senior investigators who was blinded. The vital parameters such as heart rate (HR), systolic blood pressure (SBP), diastolic blood pressure (DBP), Mean arterial pressure (MAP) were monitored for 10 minutes after the administration of cisatracurium. Patients were monitored clinically for any adverse effects of histamine release.

Results: The mean time required to achieve TOF 0 in Group D (0.3mg/kg) was shorter compared to Group R (0.15mg/kg) which was statistically significant. During intubation Group D showed statistically significant stable heart rate variation than Group R. Mean SBP, DBP and MAP did not differ between groups. No incidence of histamine release was observed in any of the group.

Conclusion: Patients who received 0.3mg/kg of cisatracurium showed stable heart rate fluctuation during laryngoscopy and intubation and lesser time to achieve TOF 0 compared to patients who received 0.15mg/kg of cisatracurium.

1. Introduction

Cardiovascular stability is an important determinant to maintain the delicate balance between myocardial oxygen demand and supply in patients undergoing coronary artery bypass grafting (CABG). Cisatracurium besylate is an intermediate acting nondepolarizing muscle relaxant and it does not release histamine. It is three times more potent than atracurium besylate and has slower onset of action.[1] Increased potency is associated with greater specificity of

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drug action and fewer side effects. ED 95 of cisatracurium in adults is 0.05 mg/kg. The recommended intubating dose is 0.15mg/kg (3 times of ED95).[2] Doses as high as 8 times of ED95 were found to maintain good cardiovascular stability and faster onset of action in non-cardiac surgery.[3] There was a greater increase in median plasma histamine concentrations in patients who received a dose of 2 times the ED^{95} of atracurium than in patients receiving two, four, or eight times the ED95 of cisatracurium.[4]

The aim of the present study was to compare hemodynamic response, assessment of intubating condition, time required to achieve train of four (TOF) 0 and any adverse effects of histamine release associated with two different doses of cisatracurium i.e., 0.15mg/kg (3 times of ED95) and 0.3mg/kg (6 times of ED95) for endotracheal intubation during CABG under general anaesthesia. We have chosen cisatracurium because it can be safely used in patients with liver and kidney disease undergoing CABG as many patients have comorbid conditions like diabetes mellitus, hypertension, peripheral vascular disease affecting end organ function of liver and kidney.

2. Materials and Methods

Institutional Ethics Committee approval was obtained prior to commencement of study. An informed and written consent was taken from every patient selected for the study. Calculated sample size was 296 at 95% confidence level & at 80% power, Sample size formula (n) $\cdot = [(z_{1-\alpha/2} + z_{1-\beta})^2 x\ (\sigma_1^2 + \sigma_2^2)] / (\mu_1 - \mu_2)^2$ was applied; where σ_1, σ_2 = Standard Deviation of hemodynamic parameters (heart rate, systolic BP, Diastolic BP in two different doses) and μ_1, μ_2 = Mean difference of hemodynamic parameters (heart rate, systolic BP, Diastolic BP in two different doses).

It was a prospective single blinded randomized controlled clinical trial, conducted by two investigators in 296 patients of both genders. Patients having ejection fraction>45%, age between 50-70years, ASA III grades undergoing CABG were included in the study. Patients with neuromuscular diseases, anticipated difficult airway (Mallampati score III and more), morbid obesity (BMI over > 30 kg/m2) and any associated valvular heart diseases were excluded from the study. Patients were allocated randomly using a computer-generated randomization chart into 2 groups depending on the doses of cisatracurium.

1. Group R (n=148) → Received 0.15 mg/kg i.e., 3 times of ED95. (Recommended Dose).
2. Group D (n=148) → Received of 0.3 mg/kg i.e., 6 times of ED95. (Double Dose).

All patients were kept nil by mouth for six hours prior to the surgery. On the day of surgery patient was taken to the operating room and routine monitors (ECG, SpO_2, $EtCO_2$, temperature) were applied. Peripheral IV line was secured and right radial artery was cannulated and baseline values were recorded. TOF Watch S (Neuromuscular monitoring device) was attached to left hand of the patient to monitor the adductor pollicis muscle (Figures 1 and 2). All patients were premedicated with inj. midazolam 0.02mg/kg and inj. fentanyl 2mics/kg intravenously. Anaesthesia was induced with inj. etomidate 0.3mg/kg. Inj. cisatracurium was administered in the required dose according to the groups they belong to. Central line was inserted in right internal jugular vein after induction of anesthesia.

The first investigator injected the drug as per randomization schedule and monitored the TOF. After 60 seconds of injection of cisatracurium, TOF was recorded every 30 seconds until it reaches zero. HR, SBP, DBP and MAP were monitored every one minute for 10 minutes after the administration of muscle relaxant. Once the TOF score reached zero, patient was intubated with appropriate size cuffed portex endotracheal tube (males 8, females- 7) by using Macintosh laryngoscope blade no 4 by second investigator who was blinded. After confirming $EtCO_2$, anesthesia was maintained with O_2+ air+ sevoflurane & titrated anesthesia mixture (Inj. midazolam 8mg+ Inj. fentanyl 800mics+ Inj. cisatracurium 50mg diluted in 50 ml NS). Patients were monitored clinically for any adverse effects of histamine release like skin erythema, bronchospasm, hemodynamic changes.

Figure 1: TOF-watch S (TOF monitor)

2.1. Statistical analysis

Intubating condition score was assessed with Fisher's exact test. Time required to achieve TOF 0 was assessed with Man Whitney test. Mean HR, SBP, DBP & MAP between 2 groups were assessed with unpaired t test. The results were considered significant at $P < 0.05$.

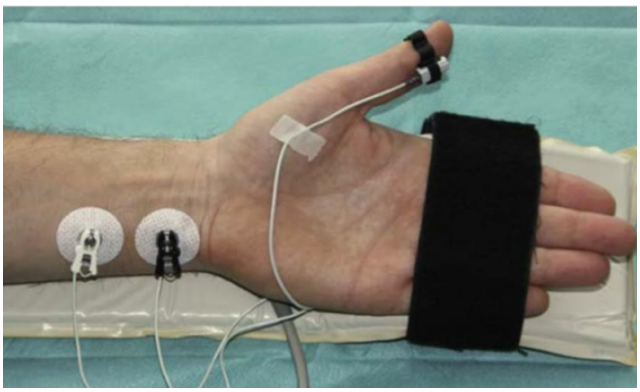
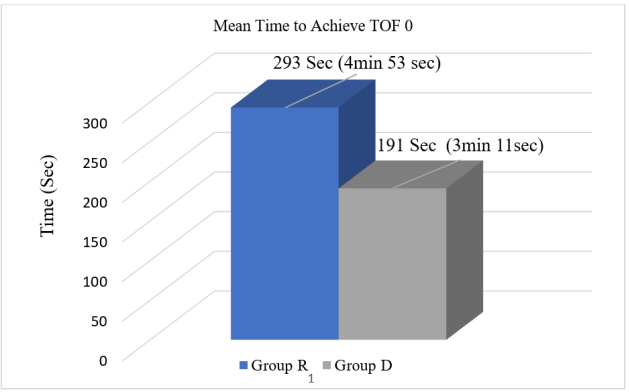
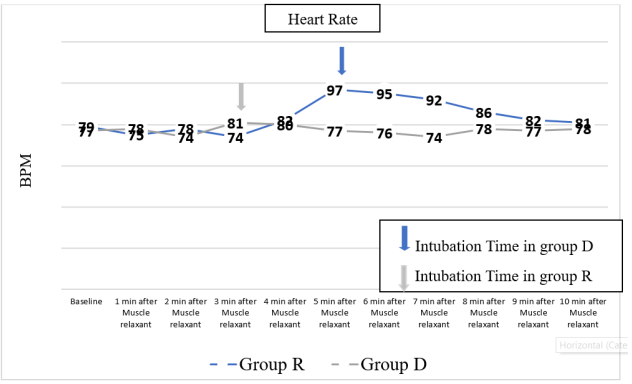


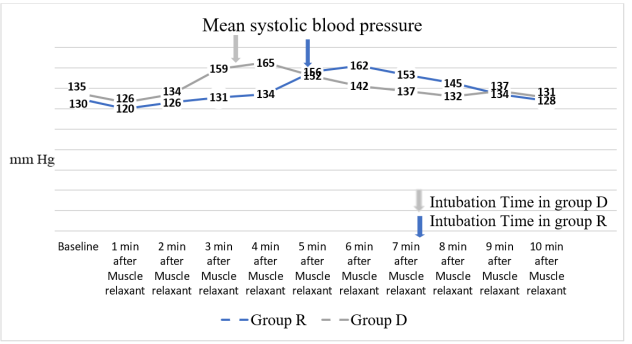
Figure 2: Position of the electrodes. Two surface electrodes (positive and negative terminals) were applied on the skin over the ulnar nerve at the wrist. The TOF sensor attached over the thumb



Graph 1: Comparison of mean time to achieve TOF 0 in both the groups



Graph 2: Comparison of mean heart rate variation in both the groups



Graph 3: Comparison of mean systolic blood pressure variation in both the groups

3. Results

The demographic data of the patients in the two groups were comparable with respect to age, sex, weight, height, ASA grading, Mallampati Classification and Cormack Lehane Grade. (p value >0.05)

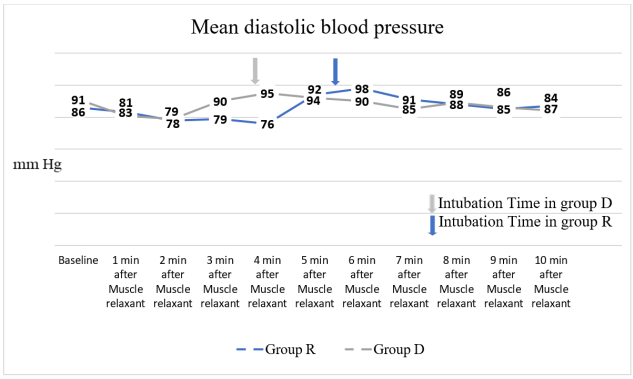
Table 1: Comparison of demographic data in both the groups

Demographic Data	Group R	Group D	P-value
Age (Years)	57 ±7.5	59 ±8	0.18
Sex (M/F)	124/24	133/15	0.12
Weight (Kg)	71 ± 13.2	68 ± 12.5	0.13
Height (cm)	164 ± 8.8	166 ± 10.6	0.15
ASA (II/III)	54/94	45/103	0.26
MPC (I/II)	66/82	77/71	0.20
CL Grading (I/II)	59/89	68/80	0.3

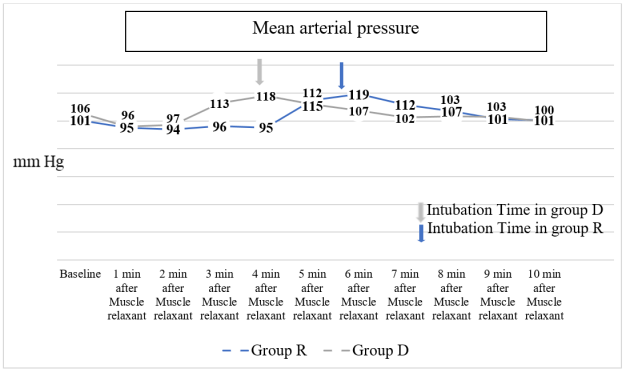
The mean time required to achieve TOF 0 in Group D (0.3mg/kg) was significantly shorter with 191 ± 20.02 seconds compared to Group R (0.15mg/kg) with 293 ± 25.20 seconds which was statistically significant (P=0.001). During intubation Group D showed relatively more stable heart rate variation from baseline than Group R which was statistically significant. (p value<0.05). Mean systolic, diastolic blood pressure and mean arterial pressure at Baseline and every 1 min after giving muscle relaxant till 10 minutes did not differ between groups. (p value >0.05). Excellent to Good intubating condition were noted in both the groups, irrespective of the dose. (p value >0.05). There was no incidence of histamine release recorded in any of the group. (p value >0.05)

4. Discussion

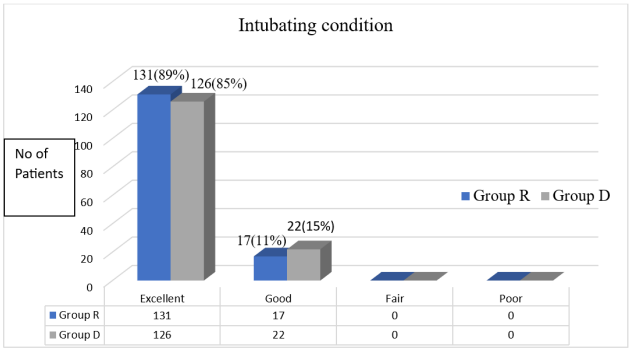
Cisatracurium besylate is a benzyl isoquinoline introduced to clinical use in 1995.[6] Requirement of cisatracurium (0.15mg/kg) is less in order to achieve similar degree of neuromuscular blockade for intubation as compared



Graph 4: Comparison of mean diastolic blood pressure variation in both the groups



Graph 5: Comparison of mean arterial pressure variation in both the groups

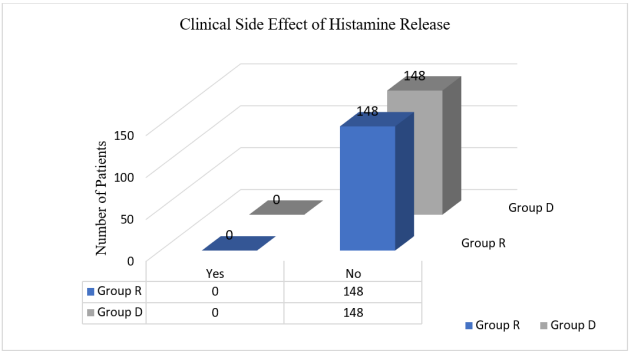


Graph 6: Comparison of intubating condition in both the groups

Table 2: Scoring of intubating condition as per Cooper et al scoring system[5]

Score	Jaw Relaxation	Vocal Cord Position	Response to Intubation
0	Poor (Impossible)	Closed	Severe bucking or coughing
1	Minimal (Difficult)	Closing	Mild coughing
2	Moderate (Fair)	Moving	Slight diaphragmatic movement
3	Good	Open	None

8- 9 was considered excellent intubating condition,
6-7 was considered as good intubating condition,
3-5 was considered as fair intubating condition and
0-2 was considered as poor intubating condition.



Graph 7: Comparison of clinical side effect of histamine release in both the groups

to atracurium (0.5 mg/kg). As a result, less laudanosine is produced. laudanosine crosses the blood-brain barrier and may cause excitement and seizure activity. As it undergoes Hoffman elimination which occurs in plasma and tissue, elimination half-life of cisatracurium is unchanged and is responsible for approximately 77% of the overall elimination. In patients with renal dysfunction, the bolus dose of cisatracurium does not prolong the duration of action. Both clearance and volume of distribution of cisatracurium are increased in patients with hepatic failure but the clinical duration of action remains unchanged.[7]

Cisatracurium 0.15mg/kg had a significantly longer onset time in elderly patients.[8] This makes it not an ideal NMBA in cardiac surgery as incidence of hemodynamic instability increases after induction of anaesthesia in high-risk patients despite its organ independent metabolism. We wanted to compare the onset of action of cisatracurium of 0.3mg/kg with 0.15mg/kg in order to find out whether higher dose of cisatracurium shows faster onset so that it can be used in cardiac surgery more frequently especially when liver and kidney are adversely affected with failing liver and kidney function.

Ouattara et al. used cisatracurium of 0.15-0.3 mg/kg for induction in 18 patients scheduled for cardiac surgery and they found it as a suitable neuromuscular blocking agent for fast-tracking cardiac surgery.[9]

Cammu et al. compared large bolus dose (8x ED95) with continuous infusion of cisatracurium during hypothermic cardiopulmonary bypass surgery and found high bolus dose of cisatracurium appeared to be safe but the consumption was significantly greater than with continuous infusion.[10]

Shaikh et al. in 2022 compared 0.3 mg/kg, 0.2 mg/kg and 0.1 mg/kg of cisatracurium in 90 patients for intubation during non-cardiac surgeries and found 0.3mg/kg of cisatracurium showed faster onset, longer duration with better cardiovascular stability.[11] Our study also showed 0.3mg/kg of cisatracurium had stable heart rate fluctuation during intubation as compared to 0.15mg/kg of cisatracurium.

In 2014, El-Kasaby et al. concluded that 0.3mg/kg of cisatracurium provide faster onset of neuromuscular blocking with stable hemodynamics without any signs of histamine release clinically in 64 patients during elective abdominal surgery.[12]

In 2011, Amini et al compared 0.25 mg/kg, 0.20 mg/kg and 0.15 mg/kg of cisatracurium in 123 patients undergoing non-cardiac surgeries and concluded that doses of 0.25 and 0.20 mg/kg showed shorter time for endotracheal intubation.[13]

Berg et al carried out a clinical trial on 141 patients for CABG where different doses of cisatracurium were administered and found that there was no elevated plasma histamine concentration and no significant hemodynamic changes with different dosages of cisatracurium.[14]

Another clinical trial by Selcuk et al in 2005, conducted on 38 patients undergoing laparotomies to compare the evidence of histamine release between cisatracurium bolus and infusion doses. They concluded that cisatracurium did not cause systemic or cutaneous histamine release in any of the group.[15]

In our study, heart rate remained stable during intubation in Group D compared to Group R which was statistically significant (P value <0.05). Higher dose (6x ED95) of cisatracurium showed reduced heart rate fluctuation during induction of anesthesia. Unlike other neuromuscular blocking drugs like vecuronium and rocuronium, cisatracurium does not alter the heart rate.[16]

Systolic, diastolic and mean arterial pressure were increased in both the groups as a stress response to intubation but it was statistically not significant. (P value <0.05).

Mean time to achieve TOF 0 in Group D and Group R were 3 minutes 11 seconds and 4 minutes 53 seconds, respectively, which were also statistically significant and similar to the above-mentioned findings (P value <0.05).

Both the groups showed excellent intubating condition. There was no clinical evidence of histamine release in any of the group in our study.

5. Limitation

This was a single-centered study. Further, studies should be done in patient with hepatic or renal disease in order to observe the efficacy of drug. Our study was done in ASA III patients without end organ dysfunction.

6. Conclusion

During laryngoscopy and intubation, heart rate remained stable in patients who received 0.3mg/kg of cisatracurium compared to patients who received 0.15mg/kg of cisatracurium. Although intubating conditions were similar in both the groups but time to achieveTOF0 was significantly lower in patients who received 0.3mg/kg of cisatracurium. Blood pressure changes (SBP, DBP and MAP) between the two groups were not statistically significant. No clinical side effect of histamine release observed in any of the group.

7. Sources of Funding

None.

8. Conflict of Interest

None.

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