

Comparison of Atracurium versus Cisatracurium Regarding Onset Time, Intubating Conditions and Hemodynamic Parameters during General Anaesthesia: A Randomised Control - Single Blinded Study

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Abstract: ***Introduction:** Ideal neuromuscular blocking agent for intubation should have a rapid onset, brief duration of action, free from hemodynamic changes, and provide excellent intubating conditions which reduces the time for intubation and thereby reduces the hemodynamic stress response. Cisatracurium unlike atracurium is devoid of histamine - induced cardiovascular effects and this would be the greatest advantage in replacing atracurium for the facilitation of endotracheal intubation. So study is designated to compare the effectiveness and potency of atracurium and cisatracurium **Aim of the Study:** to compare the atracurium versus two doses of cisatracurium for intubation conditions with regard to Onset time for intubation, Duration of action, Hemodynamic effects, Complications. **Methodology:** Study conducted on 60 patients scheduled for GA were randomly divided in three groups with 20 patients in each group: Group 1 ATRACURIUM 0.5MG/KG LD. Group 2 CISATRACURIUM 0.15MG/KG LD. Group 3 CISATRACURIUM 0.2MG/KG LD. Intubating conditions and Hemodynamic parameters with any complication were measured. **Results:** Optimal intubating conditions were better in cisatracurium group 3 and this difference was statistically significant. P value -0.041. **Conclusion:** higher doses of cisatracurium provide more rapid onset, longer duration of action, excellent intubating conditions with hemodynamically stable and no signs of histamine release.*

Keywords: Atracurium, Cisatracurium, Neuromuscular Monitoring, Intubation

1. Introduction

Neuromuscular blockers (NMB) have become essential parts of the anaesthetist armamentarium. They aid in endotracheal intubation, mechanical ventilation, reduce anaesthetic requirements, facilitate surgery for long hours and decrease oxygen consumption⁽¹⁾.

The ideal neuromuscular blocking agent for intubation should have a rapid onset, brief duration of action, free from hemodynamic changes, devoid of residual paralysis and provide excellent intubating conditions like fully relaxed jaw, widely open vocal cord and negligible response to intubation which reduces the time for intubation and thereby reduces the toward hemodynamic stress response⁽²⁾.

Cisatracurium unlike atracurium is devoid of histamine - induced cardiovascular effects and this would be the greatest advantage in replacing atracurium for the facilitation of endotracheal intubation. Like atracurium, cisatracurium is metabolized by Hofmann elimination to laudanosine and a monoquaternary alcohol metabolite⁽³⁾. There is no ester hydrolysis of the parent molecule. Hofmann elimination accounts for 77% of the total clearance of 5 to 6 mL/kg per minute. So present study is designated to compare the effectiveness and potency of atracurium and cisatracurium⁽⁴⁾.

Aim of the study

The aim of the study is to compare the effectiveness of atracurium 0.5 (2 ED95) mg/kg IV versus two different doses of cisatracurium, i. e., 0.15 (2 ED95) and 0.20 (3 ED95) mg/kg IV for intubation following induction with regard to

- 1) Onset time for intubation
- 2) Intubating conditions
- 3) Duration of action
- 4) Hemodynamic effects
- 5) Complications and side effects.

2. Review of Literature

Athaluri V V et al 2019 ⁽⁵⁾ Compared the effectiveness of atracurium 0.5 (2 ED95) mg/kg IV versus two different doses of cisatracurium, i. e., 0.1 (2 ED95) and 0.15 (3 ED95) mg/kg IV for intubation with regard to onset time for intubation, intubating conditions, duration of blockade, and hemodynamic parameters. In this study, 150 patients of the American Society of Anesthesiologists Grades 1 and 2 undergoing elective surgeries under general anesthesia were taken up and divided into three groups of 50 each by computer - generated randomization. Group A received Inj. atracurium besylate 0.5 mg/kg IV, Group B received Inj. cisatracurium besylate 0.1 mg/kg IV, and Group C received Inj. cisatracurium besylate 0.15 mg/kg IV.

Results: The three groups were compared regarding the onset of blockade, duration of blockade, condition of intubation, hemodynamic effects, and results analyzed. Cisatracurium 0.15 mg/kg provides excellent intubating conditions with rapid onset of action, with a longer duration of action and no significant hemodynamic changes when compared with cisatracurium 0.1 mg/kg and atracurium 0.5 mg/kg and hence cisatracurium 0.15 mg/kg can be used as an ideal non - depolarizing muscle relaxant for intubation.

Aswani B et al 2020 ⁽⁶⁾ Studied of atracurium and cisatracurium to compare the onset time, duration of action, hemodynamic changes like heart rate, systolic blood pressure, diastolic blood pressure, condition on intubation and signs of histamine release. 60 patients assessed under ASA Grade I and II of both sex between 18 - 70 years of age, scheduled for both elective and emergency surgeries under general anesthesia of duration more than one hour were included in the study. Patients were divided into two groups of 30 each. Group A – 30 Patients received Inj. Atracurium (2xED95) / 0.5mg/kg IV and Group B - 30 Patients received Inj. Cisatracurium (2xED95) / 0.1mg kg iv after induction of the patient. Both the groups were comparable with respect to age, sex, weight, height and duration of surgery. 2 x ED95 dose of Atracurium had better onset of action compared to 2 x ED95 dose of Cisatracurium which was statistically significant. (P < 0.001) There was no statistically significant difference between the two groups regarding haemodynamic parameters (systolic blood pressure, diastolic blood pressure, mean arterial pressure and heart rate), duration of action and signs of histamine release clinically.

Badole U et al 2021 ⁽⁷⁾ Compared the effects of cisatracurium and atracurium during general anaesthesia for abdominal surgery. 60 patients, ASA I&II, 20 - 60 years old underwent elective abdominal surgical procedure under general anesthesia (GA) were randomly assigned into 2 equal groups. Group A where 0.5mg/kg atracurium was given and Group C, where 0.3mg/kg cisatracurium was given. Neuromuscular monitoring was done by stimulating ulnar nerve and recording the action potential of adductor pollicis using TOF count. Standardized GA was given to all patients as follows, fentanyl 2mcg/kg, propofol 2mg/kg, followed by NMB agent of corresponding group at designated dose, patient will be ventilated till TOF count reaches 0, intubation was tried by the anaesthesiologist who was blind to the given NMB, intubation was done if the intubating condition was acceptable (excellent or good), and it was re - attempted every 30 sec if it was poor or inadequate. Anesthesia was maintained by N2O, O2 and sevoflurane to a total MAC 1, controlled ventilation was adjusted to normocarbida. Mean arterial blood pressure (MAP), heart rate, and intubating conditions were recorded. Interpretation of TOF count for the onset of action, clinical duration, recovery index was done.

Results: Clinically acceptable intubating conditions were achieved after 120 sec more frequently after cisatracurium (85%) than after atracurium (0%) and after 180 sec cisatracurium (100%) and atracurium (80%). Cisatracurium had a significant shorter onset time than atracurium (120±30 versus 180±30sec), Atracurium had a significant shorter

duration of action than cisatracurium (30±5 versus 60±5min). There were no evidences of any significant clinical cardiovascular changes in both groups. They concluded that cisatracurium has a rapid onset of action with good intubating conditions, atracurium has an intermediate duration of action, both are potent and safe with excellent cardiovascular stability.

3. Materials and Methods

Study Setting: This prospective, randomized, single blinded study was conducted in Department of Anaesthesia, Jhalawar Medical College, Jhalawar after getting approval from ethical committee of the institution and informed written consent from the patients. In this study 60 patients scheduled for elective surgery under General anaesthesia were randomly divided in 3 groups with 20 patients in each group: Sample size is 60 and patients were randomly divided into 3 groups of 20 in each group

Group 1 - Atracurium 0.5 mg/kg, Group 2 - Cisatracurium 0.15 mg/kg, Group 3 - Cisatracurium 0.20 mg/kg

Inclusion criteria: Age: 18 - 60 years, Eithersex, ASA: I & II, Elective surgery undergoing general anaesthesia, Mallampattiscore: I & II, Who have given valid informed consent.

Exclusion criteria: Not satisfying inclusion criteria, Patients posted for emergency surgery, Patients with difficult airway, Severe cardiovascular, central nervous system, hepatic and renal disease. History of drug allergy to the study drugs.

Material Required

Anaesthesia workstation, Bain's circuit/ closed circuit with circle absorber, Macintosh curved blade laryngoscope of different sizes, Endotracheal tube of different sizes (cuffed), Guedel'sorophayngeal airway, Stylet.

DRUGS - Fentanyl, Glycopyroate, lignocaine, Propofol, sevoflurane, normal saline, mephentamine, atropine, succinylcholine, neostigmine Inj. Atracurium 25 mg ampoule (1ml - 10mg) Inj. Cisatracurium 10 mg vial. (1ml - 2mg). Emergency drugs - Adrenaline, Nor adrenaline, Dopamine, Dobutamine, Hydrocortisone, Dexamethasone, Deriphylline, esmolol, chlorpheniramine. Multiparameter monitor - ECG, NIBP, SPO2, ETCO2, Gasanalyser, neuromuscular monitoring. IV Drip set, IV Fluids. 18 Gauge intravenous canula. 2cc, 5cc, 10cc sterile syringes, spirit swabs. Adhesive plaster.

4. Methodology

Pre - Anaesthetic Evaluation

All patients were examined on the day before surgery that included: - Complete history of patients including any known allergy.

General physical and systemic examination, airway examination, ASA grading and local examination of vertebral column area.

Baseline pulse rate, blood pressure, respiratory rate, height and weight of patient.

Investigations – Hb, TLC, DLC, BT, CT, RBS, Blood urea, Serum creatinine, LFT, Chest X ray (PA view) and ECG.

Special investigations like 2D echo pulmonary function test etc. are advised in special cases.

Examination for adequate mouth opening and neck extension was done. Airway assessment was done using modified Mallampatti grading. Patients were kept nil orally for at least 6 hours preoperatively and 4 hours post operatively. Prior to operation informed and written consent will be taken from patients and relatives. The patient's vital parameters was monitored using electrocardiogram, non-invasive blood pressure measurements and pulse oximetry. The baseline vital parameters was noted and an intravenous line was secured with 18 - gauge. cannula in the dorsum of hand and IV Fluids was started. Patient were premedicated with inj. ondansetron 4 mg IV, inj. glycopyroate 0.2 mg IV. The facemask was connected to a semiclosed anaesthetic circuit and preoxygenation with 100 % oxygen was done in all patients for 5 min through a face mask which is tight fitting. All patients were given fentanyl intravenously at a dose of 2 µg/kg 5 minutes before induction and lignocaine 1.5 mg/kg intravenously 90 seconds before tracheal intubation. Patients was received propofol intravenously at a dose of 1.5 mg/kg over 10 seconds. and patient was given inj. Atracurium/cisatracurium according to group using TOF before intubation.

Laryngoscopy was performed using macintosh curved blade laryngoscope of appropriate size and the anesthesiologist who was performing the laryngoscopy and intubation would score the intubating conditions as optimal, good, poor, inadequate according to the degree of jaw relaxation, vocal cord position and intubating response.

The patients was intubated with appropriately sized Cuffed endotracheal tubes in both males and females. After tracheal intubation, the tracheal cuff was gently inflated, Cough after intubation and after cuff inflation will be graded by the anesthesiologist as none, mild, moderate and severe. Cormack lehanne grading and the occurrence of apnea any time during induction was also be specified by the anesthesiologist.

Hemodynamic parameters such as heart rate, systolic, diastolic and mean arterial pressure were measured after induction, immediately, 1 minute and 5 minutes after intubation.

Maintenance of anaesthesia was done with oxygen 40% + nitrous oxide 60% + 1 - 2% sevoflurane/halothane/isoflurane and with non-depolarising muscle relaxant (Atracurium besylate/ cis-atracurium). At the end of surgery, all anaesthetic agents were stopped and 100% oxygen was given. Respiratory efforts was allowed to return and the residual neuromuscular blockage were reversed with slow inj. neostigmine 0.05mg/kg and inj. glycopyroate 0.008mg/kg. Patients was extubated after complete recovery from neuromuscular blockage. 100% oxygen was

administered through facemask and then patients were shifted to recovery room.

When patient couldn't be intubated due to unacceptable intubating conditions or severe coughing or airway obstruction, we gave succinylcholine at a dose of 1.5 mg/kg intravenously and will perform tracheal intubation and such patients are excluded from the study.

5. Observation

Primary Outcome Measures: The mean onset of neuromuscular blockade and duration of action were calculated for all the three groups. Intubating conditions with limb movement. Intubation score, Coughing after intubation and cuff inflation.

Secondary Outcome Measured: Haemodynamic monitoring - Heart rate, Systolic and Diastolic blood pressure, Mean arterial pressure.

Side Effects

Apnea, Hypotension, Tachycardia, Bradycardia, Bronchospasm, Allergic reaction, Seizure/Myoclonus, Nausea, vomiting. *Assessment of Intubating conditions was done using 3 variables:* 1. Jaw relaxation 2. Vocal cord position 3. Coughing after intubation and cuff inflation was graded using MODIFIED MINOGUE SCALE. *Cormack and lehanne grading was graded as for intubation score.*

Statistical Analysis

All patients data were recorded in proforma of study. Data was expressed in terms of mean and standard deviation. All statistical analyses was carried out using SPSS 15. Statistical analysis was carried out using student's t - test for parametric data and chi square test, fisher's exact test for non parametric data. Heart rate, systolic and diastolic blood pressure and mean arterial pressure were compared using student's t - test. Intubation scores, Cough after intubation and cuff inflation were compared using fisher's exact test. P value < 0.05 was considered as statistically significant. P value < 0.001 was considered as statistically highly significant. P value > 0.05 was considered as statistically non significant.

6. Results

Table 1: Demographic Profiles

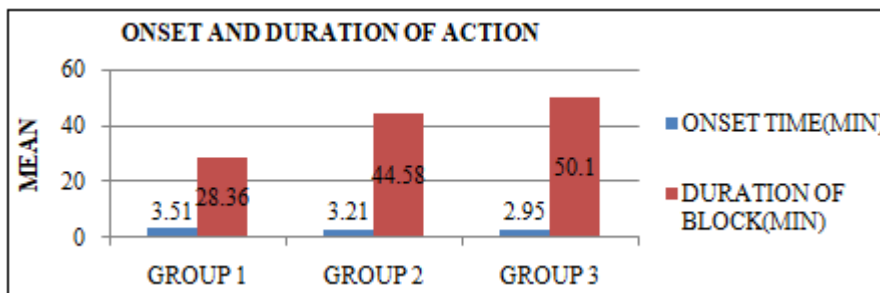
Variable	Group 1	Group 2	Group 3	P Value
Gender (M/F)	8/12	11/9	9/11	>0.05
Age (Years)	35.65±11.59	34.89±12.16	34.75±10.68	>0.05
Weight (Kg)	61.80±8.10	62.74±7.12	62.50±10.03	>0.05

Table 1 shows demographic data (age, weight, sex) of patients in three groups. There was no significant difference between the all three groups with respect to demographic details.

Table 2: Onset time and duration of action

Variable	Group 1	Group 2	Group 3	P Value
Onset (Min)	3.51±0.33	3.21±0.16	2.95±0.27	<0.0001*
Duration (Min)	28.36±3.99	44.58±4.85	50.10±4.36	<0.0001*

There is significant difference among the three groups on mean onset time ($p < 0.001$). There is statistical difference among the three groups on mean duration of blockade time ($p < 0.001$).

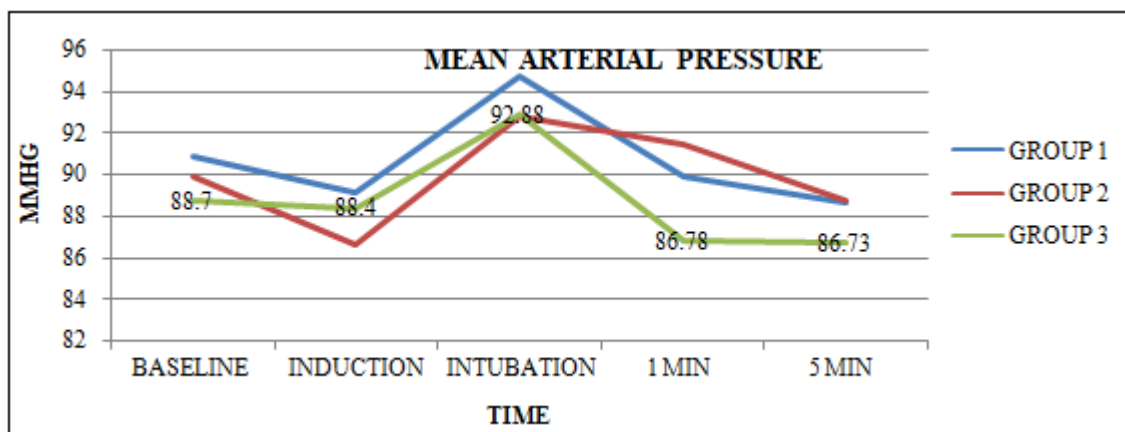


Graph 1

Table 3: Intubation Score

Variable	Optimal	Satisfactory	Poor	Inadquate	Chi - square	P - value
Group 1	11	6	3	0	13.125	0.041
Group 2	17	2	1	0		
Group 3	20	0	0	0		

Table no 3 shows that there is statistical difference between all 3 groups ($p < 0.041$) on intubation score using by RSJ Scale. Group 3 is better then other 2 group.



Graph 2

Above graph shows that there was an increase in mean arterial pressure compared to baseline in all 3 groups after intubation. It gradually returned to baseline at 5 minutes and may be due to stress response and was not statistically significant.

There was side effect of apnea in one patient in group 1, 3 and two patient in group 2 during giving inductin drug. Other complications are negligible and were no statically significant.

Table 4: Cormack Lehane Grading

Cormack Lehane Grading	Group 1	Group 2	Group 3	P Value by Yates Chi - Square
1	16	17	18	0.294
2	4	3	2	
3	0	0	0	

Table no 4 shows about the C. L. grading in all three groups which are not significant.

Table 5: Complications

Side Effect	Group1	Group 2	Group 3	P Value
Apnea	1	2	1	0.965
Hypotansion	1	1	0	0.674
Tachycardia	0	0	0	--
Bradycardia	0	0	0	--
Seizures	0	0	0	--
Bronchospasm	0	0	0	--
Aalergic Reaction	0	0	0	--
Nausea And Vomitting	0	0	0	--

7. Discussion

Muscle relaxants have made anaesthesia much safer and provide good operating conditions. They are used for endotracheal intubation and for surgical relaxation. Neuromuscular blockers (NMB) are very important adjuvant to general anaesthesia. During general anaesthesia, after induction endotracheal intubation is facilitated by either depolarizing or non - depolarizing neuromuscular blocking agent. Succinylcholine is undoubtedly the ultrashort acting muscle relaxant with rapid onset but it has many side effects such as increase in IOP, intragastric pressure, myalgia, bradycardia and cardiac arrest. Hence globally there was search for an alternative for succinylcholine which has rapid onset and less side effects. In 1983 atracurium was introduced in clinical practice having advantage that this new drug is extensively metabolized in such a way that its pharmacokinetics are independent of renal and hepatic function, although less than 10% excreted unchanged by renal and biliary routes. Cisatracurium is a new benzyl isoquinoline neuromuscular blocker which has intermediate

action. It is one of the 10 stereoisomers of atracurium and has a potency approximately three to four times at higher doses than atracurium. It is used in different doses 0.1 mg/kg, 0.2mg/kg, 0.3 mg/kg. It has longer onset of action which makes it less suitable for rapid sequence intubation. In the current study we decided to compare Atracurium and Cisatracurium for onset of action, intubating condition and hemodynamic changes in patients posted for elective abdominal surgeries under general anaesthesia.

Aswani B et al 2020 ⁽⁶⁾ Studied of atracurium and cisatracurium to compare the onset time, duration of action, hemodynamic changes like heart rate, systolic blood pressure, diastolic blood pressure, condition on intubation and signs of histamine release. 60 patients assessed under ASA Grade I and II of both sex between 18 - 70 years of age, scheduled for both elective and emergency surgeries under general anesthesia of duration more than one hour were included in the study. Patients were divided into two groups of 30 each. Group A – 30 Patients received Inj. Atracurium (2xED95) / 0.5mg/kg IV and Group B - 30 Patients received Inj. Cisatracurium (2xED95) / 0.1mg kg iv after induction of the patient. Both the groups were comparable with respect to age, sex, weight, height and duration of surgery. 2 x ED95 dose of Atracurium had better onset of action compared to 2 x ED95 dose of Cisatracurium which was statistically significant. (P < 0.001) There was no statistically significant difference between the two groups regarding haemodynamic parameters (systolic blood pressure, diastolic blood pressure, mean arterial pressure and heart rate), duration of action and signs of histamine release clinically.

Badole U et al 2021 ⁽⁷⁾ compared the effects of cisatracurium and atracurium during general anaesthesia for abdominal surgery. 60 patients, ASA I&II, 20 - 60 years old underwent elective abdominal surgical procedure under general anaesthesia (GA) were randomly assigned into 2 equal groups. Group A where 0.5mg/kg atracurium was given and Group C, where 0.3mg/kg cisatracurium was given. Neuromuscular monitoring was done by stimulating ulnar nerve and recording the action potential of adductor pollicis using TOF count. Standardized GA was given to all patients as follows, fentanyl 2mcg/kg, propofol 2mg/kg, followed by NMB agent of corresponding group at designated dose, patient will be ventilated till TOF count reaches 0, intubation was tried by the anaesthesiologist who was blind to the given NMB, intubation was done if the intubating condition was acceptable (excellent or good), and it was re-attempted every 30 sec if it was poor or inadequate. Anesthesia was maintained by N2O, O2 and sevoflurane to a total MAC 1, controlled ventilation was adjusted to normocarbida. Mean arterial blood pressure (MAP), heart rate, and intubating conditions were recorded. Interpretation of TOF count for the onset of action, clinical duration, recovery index was done.

Our study were a prospective, randomized, single blind study conducted on 60 patients scheduled for elective surgery under General anaesthesia aimed to determine whether. In this study patients were randomly divided in three groups with 20 patients in each group:
Group 1 (n=20) comprising of patient whom we have given

ATRACURIUM 0.5MG/KG loading dose.

Group 2 (n=20) comprising of patient whom we have given CISATRACURIUM 0.15MG/KG loading dose

Group 3 (n=20) comprising of patient whom we have given CISATRACURIUM 0.2MG/KG loading dose.

Intubating conditions, Coughing after intubation and cuff inflation, Apnea after induction were noted. Heart rate, Systolic blood pressure, Diastolic blood pressure, Mean arterial pressure were measured at baseline, after induction, after intubation and at 1, 5 min after intubation and side effects if any are present. We summarize that: -

The demographic data (age, weight, height) was comparable in both the groups and this difference was not statistically significant.

Optimal intubating conditions were better in cisatracurium dose 0.2mg/kg (group 3) 100% 20/20. that which was comparable in all the groups and this difference was statistically significant. (P value =0.041). satisfactory intubating conditions were found in only group 1 and 2. Cough after intubation and Cough after cuff inflation was less in group 3 patient which was comparable in all the three groups and this difference was statistically significant.

Hemodynamic parameters (heart rate, systolic blood pressure, diastolic blood pressure and mean blood pressure) measured at baseline, after induction, after intubation and at 1, 5 min after intubation were comparable in both the groups and this difference was not statistically significant. Response to intubation with limb movement were zero for severe category in all three groups. Best response to intubation was seen in group 3 patient. In our study, Hypotension was observed in 1/20 patients in group 1 and group 2 as compared to group 3 0/20. Apnea was observed in all three groups which were not significant. other side effect like bradycardia, Bronchospasm, seizures/myoclonus, allergic reactions are not observed in both the group.

8. Conclusion

Higher doses of cisatracurium provide efficient, more rapid onset, with longer duration of action, excellent intubating conditions stable hemodynamic status with no signs of histamine release clinically. Recovery was normal in all the three groups. Hence Cisatracurium, though more costly, is more effective and a better isomer of Atracurium and without any residual muscle paralysis compared to atracurium.

Future studies of Cisatracurium using various doses for intubation can be considered to know the pharmacodynamics better.

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