

# Comparison of Two Doses of Cisatracurium Besylate (0.15 mg / Kg and 0.2 mg / Kg) in Adult Patients Undergoing General Anesthesia with Endotracheal Intubation by Studying Ease of Intubation

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## ABSTRACT

### INTRODUCTION

Cisatracurium is a potent Neuron Muscular Blocking Agent [NMBA], its ideal onset time is of 4 minutes. Cisatracurium may be used to facilitate tracheal intubation at doses equivalent to 3 to 4 times the ED<sub>95</sub> (0.15 to 0.2 mg / kg) and when the duration of the procedure is expected to exceed 1 hour. Duration is shorter with lower doses, but onset time is prolonged and intubating conditions are less ideal.

### METHODOLOGY

The patients coming to Breach Candy Hospital trust during period 2018 - 2019 for surgery under general anaesthesia, who met the Inclusion Criteria.

### RESULTS

Distribution of subjects between groups with regards to Age, Weight, Gender, ASA grade or MPC grade was not statistically significant. In hemodynamics changes in both groups heart rate showed increasing trend. The difference was statistically significant at every time interval except at 6 min. (p value < 0.05) similarly, in systolic BP, diastolic BP and mean BP in two group difference was statistically significant above baseline.

### DISCUSSION

There are many neuromuscular blocking agents available to be used for general anesthesia. Cisatracurium has delayed onset of action compared to Atracurium. Better intubating conditions can be achieved early with Cisatracurium by increasing its dose, but increasing dose will increase duration of neuromuscular block. While selecting neuromuscular agent for tracheal intubation or skeletal muscle relaxation, main aim of an Anesthesiologist is to select an agent which will give better intubating conditions and does not cause much of hemodynamics response and other side effects.

### KEYWORDS

Cisatracurium, Anaesthesia, Endotracheal intubation, hemodynamics

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**INTRODUCTION**

Cisatracurium is a potent Neuro Muscular Blocking Agent (NMBA), its ideal onset time is of 4 minutes.<sup>1</sup> Cisatracurium may be used to facilitate tracheal intubation at doses equivalent to 3 to 4 times the ED<sub>95</sub> (0.15 to 0.2 mg / kg) and when the duration of the procedure is expected to exceed 1 hour. Duration is shorter with lower doses, but onset time is prolonged and intubating conditions are less ideal.<sup>2</sup> The above dose is well below the threshold for histamine release, but the duration of action is prolonged to 45 to 60 minutes. Less laudanosine and less acrylate byproducts are produced.<sup>3,4</sup> Thus, the concerns raised by the potential toxic effects of these metabolites are virtually eliminated. There is no need to adjust dosage in the elderly, children, infants or in obese individuals and the dose of Cisatracurium should be calculated on the basis of ideal body weight.<sup>5</sup> However, NMBA's are said to be responsible for a major (58 %) of anaphylactic and anaphylactic reactions.<sup>6</sup> There is lack of a significant cumulative drug effect and lack of dependence on renal and or hepatic clearance mechanisms.<sup>7</sup> Standard Recommendation by manufacturer is to use 3 ED<sub>95</sub> (0.15 mg / kg) or 4 ED<sub>95</sub> (0.2 mg / kg) dose. The rate of recovery is independent of the dose of Cisatracurium and the duration of the administration, as Cisatracurium does not depend on end - organ function for its elimination.<sup>8</sup> In patients with unstable hemodynamics parameters Cisatracurium was said to be the appropriate choice.<sup>9</sup> Cisatracurium is devoid of histamine releasing properties even at high doses (8 × ED<sub>95</sub>). It is also devoid of cardiovascular effects.<sup>10</sup> Elimination half - life is 22 to 25 minutes, so the duration of action for 2 X ED<sub>95</sub> doses (0.1 mg / kg) is 30 to 45 minutes. This study we started for Post graduate student dissertation, even at the lower dose of 0.15 mg / kg an experienced Anesthetists was comfortably able to intubate so we decided to carry out a larger study with the same parameters and study the advantages and pitfall of both doses.

**MATERIALS AND METHODS**

**Study population:** The patients coming to Breach Candy Hospital trust during period 2018 - 2019 for surgery under general anaesthesia, who met the inclusion criteria.

**Inclusion criteria:**

- Patient age between 20 - 65 years of either sex.
- Patient of ASA [American Society of Anesthesiologist's Physical Classification] Grade I or II.
- Patients scheduled for elective surgery.
- Patients with BMI 18 to 29.9. Patients with MPC Grade 1 and 2.

**Exclusion criteria:**

- Asthmatics.
- Patients on antihistamines and anticonvulsants.
- Patients with history suggestive of sleep apnea.
- Patients with known and anticipated difficult airway (MPC III or IV).
- Allergies to food, drug and dust.
- History of GERD.

A single - center, prospective, comparative, and parallel - group, randomization method study was done after approval from the Ethics Committee of Breach Candy hospital. Group a (50) in which patients received Cisatracurium 0.15 mg / kg (3 ED<sub>95</sub>) and Group B (50) received Cisatracurium 0.20 mg / kg (4 ED<sub>95</sub>). Patients were allotted to Groups by computer generated random numbers. All the patients were pre - oxygenated with 100 % oxygen and were given Fentanyl 2 mcg / kg, Midazolam 2 mcg / kg, Propanolol till abolition of eyelash reflex, Cisatracurium 0.15 mg / kg or 0.20 mg / kg was given after checking ease of ventilation by IPPV with Oxygen under mask. Intubation was done by same Anesthesiologist in all 100 patients, 3 minutes after Cisatracurium bolus.<sup>11</sup> Heart rate, Blood pressure, Systolic, Diastolic, Mean, SpO<sub>2</sub>, ET CO<sub>2</sub>, TOF monitoring at the adductor pollicis Pulse width 200 microseconds at 1 Hz and BIS were monitored every 1 min from Cisatracurium bolus dose till TOF disappear (Table 1).<sup>12</sup> Study was concluded at 7 min as in our pilot study 95 to 100 % (Group B) patients had no response to TOF at that point. Intubating conditions in both the groups evaluated and scored according to the Steyn's modification of Helbo - Hansen Scoring system.<sup>13</sup>

Points	1	2	3	4
Laryngoscopy	Easy	Fair	Difficult	Impossible
Vocal cords	Open	Moving	Closing	Closed
Coughing	None	Slight	Moderate	Severe
Jaw relaxation	Complete	Slight	Stiff	Rigid
Limb movements	None	Slight	Moderate	Severe [Jerky]

**Table 1. Steyn's Modification of Helbo - Hansen Scoring System.**

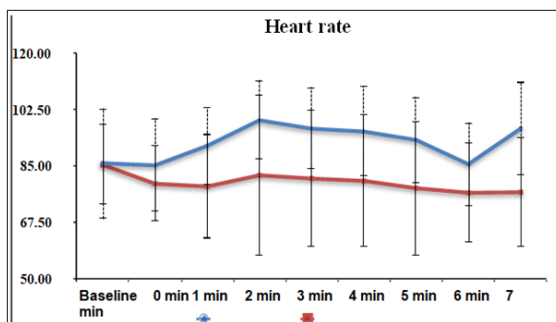
Total score of 5 was considered excellent, 6 - 10 good, 11 - 15 poor, and 16 and beyond - bad. Comparison of quantitative variables between the study groups was done using Student t test for independent samples if normally distributed. Mann Whitney U test was used for non - normally distributed quantitative data. For comparing categorical data, *Chi Square* test was performed. A probability value (p value) less than 0.05 was considered as statistically significant. Statistical calculations were done using computer programs

Microsoft Excel 2013 (Microsoft Corporation, NY, and USA) and SPSS (Statistical Package for the Social Science, SPSS Inc, Chicago, IL, USA) version.

**RESULTS**

Distribution of subjects between groups with regards to age, weight, gender, ASA grade or MPC grade was not statistically significant. In hemodynamics changes in both groups heart rate showed increasing trend. The difference was statistically significant at every time interval except at 6 min. (p value < 0.05) Similarly, in systolic BP, diastolic BP and mean BP in two group difference was statistically significant above baseline. Group A, mean baseline heart rate was 85.94 ± 12.54 and at 0 minute was 85.26 ± 11.74. The mean value of heart rate in group A was increasing at 1 min (91.32), 2 min (99.28), 3 Minute (96.66), 4 Minute (95.76), 5 Minute (93.16), 7 Minute (96.62) and in group B the trend was decreasing from baseline (85.44 ± 17.14) to 6 minutes (76.74 ± 13.08) with a minor increase at 2 minutes (82.18 ± 12.40).

**Intra - group comparison:** The above difference was statistically significant at 1 min, 2 min, 3 min, 4 min, 5 min, 7 min in group A and 0 min, 1 min, 3 min, 4 min, 5 min, 6 min, 7 min in group B when compared with baseline (Figure 1).



**Figure 1. Comparison of Heart Rate within and between the Groups.**

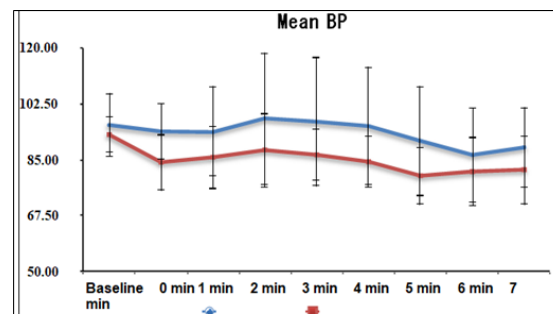
**Inter group comparison:** The difference was statistically significant at 0 min, 1 min, 2 min, 3 min, 4 min, 5 min, 6 min, 7 min. (p value < 0.05).

Mean BP reflects both Systolic and Diastolic BP in groups at different time. In group a, mean BP was lower at 0 min, 1 min, 4 min, 5 min, 6 min, 7 min and was higher at 2 min, 3 min when compared to baseline. In group B it was lower at all - time intervals when compared to baseline.

**Intragroup comparison:** In group A it was statistically significant at 6 min, 7 min and in Group B it was significant at 0, 1, 2, 3, 4, 5, 6 and 7 min when compared with baseline (P value < 0.05).

**Intergroup comparison:** In between two groups it was statistically significant at all point of

observation (P value < 0.05) (Figure 2).



**Figure 2. Comparison of Mean BP within and between the Groups.**

There were hemodynamic changes in both groups but group B (0.2 mg / kg) was more stable than group A (0.15 mg / kg) (Table 2).

Score	Group A (%)	Group B (%)	P value
Excellent (5)	07 (14)	31 (62)	
Good (6 - 10)	28 (56)	16 (32)	
Poor (11 - 15)	15 (30)	03 (06)	
Bad (16 - 20)	00 (00)	00 (00)	< 0.05
Total	50 (100)	50 (100)	

**Table 2. Comparison of Steyn's Modification of Helbo - Hansen Score between the Groups.**

The above table shows Steins' Modification of Hellbox - Hansen Score of two groups. In Group A maximum participants were having good score *i.e.* 28 (56 %) in number followed by poor (30 %) and excellent (14 %) whereas in Group B excellent score was maximum *i.e.* 31 (62 %) in number followed by good (32 %) and poor (6%). This difference was statistically significant. (P value < 0.05). Even those in Group A who had poor hellbox - Hansen score did not have any residual sore throat after 24 hours (Table 3).

Time	Group A				Group B				P value		
TOF	0	1	2	3	4	0	1	2	3	4	
Basal	0	0	0	0	5	0	0	0	0	0	-
0 min	0	0	0	0	5	0	0	0	0	0	-
1 min	0	0	0	0	5	0	0	0	0	0	-
2 min	0	0	0	0	5	0	0	0	0	0	-
3 min	0	0	0	0	4	0	0	0	0	0	-
4 min	0	0	1	0	9	0	0	0	9	1	0.003
5 min	1	4	4	0	1	0	0	1	7	2	< 0.001
6 min	2	2	5	8	9	8	0	6	3	3	0.007
7 min	6	2	1	3	1	4	0	6	0	0	0.0001
7 min	4	5	0	0	0	0	0	0	0	0	0.056

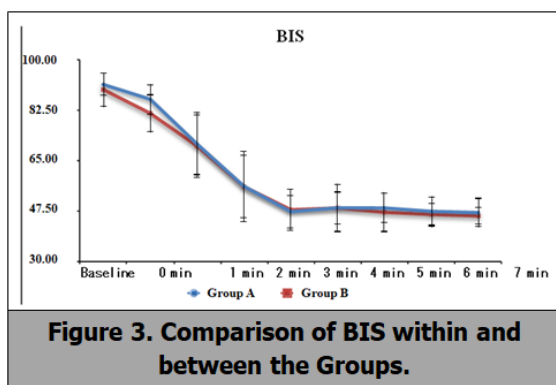
**Table 3. Comparison of TOF within and between the Groups.**

The above table shows train of four in two groups at different time. The difference was statistically

significant at 3 min, 4 min, 5 min and 6 min. ( $p$  value  $< 0.05$ ) Proportion of patients with TOF 3 was significantly higher in group B as compared to group A at 3 minutes ( $p$  value = 0.003), proportion of patients with TOF 2 was significantly higher in group B as compared to group A at 4 minutes ( $p$  value  $< .0001$ ) and proportion of patients with TOF 0 was significantly higher in group B as compared to group A at 5 and 6 minutes ( $p$  value  $< 0.05$ ). Group B showed decreased response to neuron muscular stimulation from 3 minute onwards compared to Group A. However by 7<sup>th</sup> minute both groups were comparable. Spectral index monitoring, in both groups showed decreasing trend at every time interval.

**Intragroup comparison:** In both groups difference was statistically significant at every time interval. ( $P$  value  $< 0.05$ ).

**Intergroup comparison:** In between groups the difference was statistically significant at 0 min. ( $p$  value  $< 0.05$ ) (Figure 3).



**Figure 3. Comparison of BIS within and between the Groups.**

## DISCUSSION

There are many neuromuscular blocking agents available to be used for general anaesthesia. Cisatracurium has delayed onset of action compared to Atracurium. Better intubating conditions can be achieved early with Cisatracurium by increasing its dose, but increasing dose will increase duration of neuromuscular block. While selecting neuromuscular agent for tracheal intubation or skeletal muscle relaxation, main aim of an Anesthesiologist is to select an agent which will give better intubating conditions and does not cause much of hemodynamic response and other side effects. SpO<sub>2</sub> was maintained above 95 % throughout the apneic period during induction, ET CO<sub>2</sub> monitored through closed circuit during IPPV with tidal volume of 6 - 8 ml / kg with respiratory rate adjusted to keep it between 30 - 35 mm of Hg and laryngoscopy was attempted at 3 minutes after NMBA. Best practice is always to monitor TOF for assessment of neuron - muscular block onset.<sup>14</sup> BIS was maintained below 65 and not below 40 and 20 mg of protocol was planned as a bolus if it went above that which was never required during the

study period of 7 minutes after giving the NMBA.<sup>15</sup> Similarly if BIS went below 40 at the time of induction, we had decided to exclude the case from our study; however such a situation did not arise. In present study, we have studied Cisatracurium in two different doses for its ease of Intubation at given time and hemodynamic stability. There were no statistical difference between two groups in terms of age, gender, ASA grade and MPC grade hence groups were comparable. ( $P$  value  $> 0.05$ ) When you compare both the groups statistically significant difference in Heart rate was observed from the beginning onwards between the two groups. Neuromuscular blockade develops faster, lasts a shorter time and recovers faster at the laryngeal and diaphragm muscles compared with the peripheral thumb muscle because the effective plasma concentration of the drug necessary to achieve 50 % of the intended effect (EC<sub>50</sub>) for almost all drugs studied is between 50 % and 100 % higher at the diaphragm or larynx than it is at the adductor pollicis.<sup>16</sup> The difference was statistically significant at 3, 4, 5 & 6 minutes ( $p$  value  $< 0.05$ ) which shows that a higher dose of muscle Relaxant gives a faster lower TOF score. The adequacy of conditions for tracheal intubation is a function of several factors, such as the depth of anaesthesia at the time of the intubation attempt and the level of neuromuscular block at the time of attempt.<sup>17</sup> In our case we had kept the depth of Anaesthesia constant between 40 to 65. This does suggest that a larger dose of Cisatracurium shows reduced intubation response. Spectral index monitoring in both groups was decreasing trend at every time interval till 7 minutes. The study was stopped at 7 min since TOF reached zero in all cases by then. Ideally TOF ratio should have been studied, but our PNS [Peripheral Nerve Stimulator] did not have that facility when the study was carried out. We would like to say that Cisatracurium in a dose of 0.15 mg / kg (3 ED<sub>95</sub>) it is possible to intubate comfortably, however 0.2 mg / kg (4 ED<sub>95</sub>) gives better comfort and virtually no intubation response. Since we did not study duration of action, we can say that if duration of action is not the concern, 0.2 mg / kg of Cisatracurium can be used for better comfort and minimal intubation response.

## CONCLUSION

- Cisatracurium is a potent non - depolarizing neuromuscular blocking agent and tracheal intubation can be accomplished with good to excellent intubating conditions according to Steins' Modification of Helbo - Hansen Scoring System at 3 minutes following 0.15 mg / kg and 0.2 mg / kg of Cisatracurium.
- From the study of 100 patients in 2 groups we found that Cisatracurium in dose of 3 ED<sub>95</sub> (0.15 mg / kg) has hemodynamic stability in view of Heart rate and Blood Pressure. But Cisatracurium in dose of 4 ED<sub>95</sub> (0.2 mg / kg) was more aerodynamically stable than Cisatracurium 3 ED<sub>95</sub> (0.15 mg / kg)

during intubation.

- Our observations are based on our study of 100 patients and to come to such conclusion more and larger studies are required.

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