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# Comparative Study of Different Doses of Cisatracurium for Endotracheal Intubation

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***Abstract***

***Background***

*Cisatracurium, an intermediate duration, non-depolarisingbenzylisoquinolinium neuromuscular blocking drug, appear to have potential clinical advantages, faster onsetwhile retaining hemodynamic stability without chemically mediated histamine release or its associated symptoms.So we planned to design a study to evaluate and compare the intubating conditions and onset of action of the different doses of this drug.*

***Materials and methods***

*The study was a randomized, prospective, double blinded one in which sixty adult patients of ASA I & II, aged 19-65 years, undergoing various surgeries under general anaesthesia were randomized into three equal groups of twenty patients each as to receive 10 ml of cisatracurium -viz 3×$ED_{95}$(1.5mg/kg), 4×$ED_{95}$(2.0mg/kg) and 5×$ED_{95}$(2.5mg/kg) in the group A, B& C respectively. The onset time, intubation score, TOF, haemodynamics parameter and side effects were recorded and analysed.*

***Results***

*Demographic parameterssuch as age, sex, weight, height and ASA were comparable in the three groups.The mean onset time was longest in group A at 123.50±26.64 seconds, 93.15±25.18 seconds with group B and least with 76.05±15.64 seconds in the group C(P=0.00).Good to excellent intubating condition was observed in 95% in group C,80% in group B and 70% in group A (P=0.102). Train of four in percentage was least (12.7%) in higher dose of cisatracurium or group C. There were no side effects recorded.*

***Conclusion.***

*Cisatracurium 0.25mg/kg produces better significant intubating condition than 0.20mg/kg & 0.25mg/kg eventhough they provide acceptable intubation score at the cost of increased onset time.*

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## I. Introduction

Neuromuscular blocking agents is an integral component of modern day anaesthesia practice. These agents have been widely used and none of the currently available drugs is ideal.Cisatracuriumbesilate is a new intermediate duration, non-depolarising, benzylisoquinolinium neuromuscular blocking drug which is one of the ten stereoisomer of atracurium consisting 15% of the atracurium mixture and about three to four times more potent than atracurium.[1,2]Compared to other neuromuscular blocking drugs, it appears to have potential clinical advantages, onset time is faster while retaining same hemodynamic stability without chemically mediated histamine release or its associated symptoms.[3]

Cisatracurium does not alter heart rate or blood pressure, nor does it produce autonomic effects, even at doses as high as eight times $ED_{95}$.[2,3] The principal advantage of cisatracurium is that there has been no evidence of histamine release at doses up to eight times the $ED_{95}$ whereas atracurium causes histamine release in humans at doses greater than 2.5 × $ED_{95}$.[1-3]The $ED_{95}$ dose ofcisatracurium is 0.05mg/kg.[2]

The rate limiting step in the degradation of cisatracurium is Hoffmann degradation (organ independent elimination) to form laudanosine and monoquaternary alcohol. 77% of drug is cleared via Hoffmann degradation which is a pH and temperature dependent process, rest 23% of drug get cleared through organ dependent means, and renal elimination accounts for 16% of this.Faster onset and longer duration of action with larger doses of cisatracurium ($4\times ED_{95}$ and above) and more cardiovascular stability, predictable recovery from neuromuscular block make cisatracurium a more promising alternative muscle relaxant agent for tracheal intubation in clinical practice.[2]

In literature, we found there is paucity of work evaluating the intubating condition of this drug and no such study has been done in this part of the country. So we planned to design a study to evaluate and compare the intubating conditions and onset of action of the different doses of this drug.

**Aims and objects:**

The aim of this study was to evaluate the intubating condition and compare the onset time of different doses of cisatracurium.

## II. Materials And Methods

The study was a prospective, randomized, double blinded one conducted at a tertiary care centre, Imphal, Manipur, India, over a period of two years from September 2017 to December 2019. After getting approval from the Institutional research ethics board and written informed consent from sixty adult patients aged 19-65 years, ASA I & II, scheduled to undergo various elective surgical procedure under general anaesthesia requiring endotracheal intubation were recruited for the study. Pregnant or lactating women, patient with known sensitivity to neuromuscular blocking drugs, history of alcoholism, neurologic, psychiatric or respiratory diseases, patient on medication with antidepressants, anticonvulsants or antihistamine within one week before the study, etc were excluded from the study.

Patients were randomly allocated, based on computer generated randomization into three groups of twenty patients each to receive equal volume(10 ml) of either-

Group A-injection cisatracuriumin the dose of $ED_{95}\times 3$,i.e 0.15 mg/kg

Group B-injection cisatracuriumin the dose of $ED_{95}\times 4$,i.e 0.2 mg/kg and

Group C-injection cisatracuriumin the dose of $ED_{95}\times 5$,i.e 0.25 mg/kg.

After thorough routine preanaestheticcheck up, patients were premedicated with inj glycopyrrolate. Intravenous access was established with 20G cannula and crystalloid I.V solution was given and patient was taken to the operating room, where routine monitors were applied including three leads electrocardiogram (ECG), non invasive blood pressure, pulse oximetry, capnography, temperature probe and baseline values of these variable measurement, train of four (TOF) watch for neuromuscular monitoring.A uniform anaesthetic technique was advocated for all the patients. General anaesthesia was induced with fentanyl (2μ/kg) followed by propofol (2mg/kg) i.v till the loss of eye lash reflex and TOF baseline was measured and anaesthesia maintained with a mixture of 35% $O_2$/65% nitrous oxide and inhalation anaesthetic with assisted ventilation. Once the baseline response had been noted, the different doses of the muscle relaxant (in a standardised solution volume of 10ml) was injected over 5-10 seconds, 30 seconds after administration of propofol according to the group assigned.Double blinding was achieved by making the principle investigator and co-investigator not involved in the preparation of the study drug and preparing a standardised solution volume of 10ml by a colleague (anaesthesiologist) not involved in the observation of the study.

Sixty seconds after the injection of the muscle relaxant, the first intubation attempt was made by an anaesthesiologist who was blinded to the muscle relaxant administration. Onset time along with intubating score suggested by Cooper R et al[4] was noted.

| Score | Jaw relaxation (laryngoscopy) | Vocal cords | Response to Intubation |
|---|---|---|---|
| 0 | Poor (impossible) | Closed | Severe coughing or bucking |
| 1 | Minimal (difficult) | Closing | Mild coughing |
| 2 | Moderate (fair) | Moving | Slight diaphragmatic movement |
| 3 | Good (easy) | Open | None |

At the same time TOF was measured (60 seconds after administration of cisatracurium, then every 12 seconds and at the time of intubation). In the event of the unsuccessful laryngoscopy and intubation, ventilation was continued for another 30-45seconds until the next attempt was made. Once the intubation was achieved, this study was taken as completed at this point and further anaesthetic procedure was not influenced by this study.

The vital parameters such as systolic/diastolic blood pressure (BP), heart rate (HR), oxygen saturation ($SPO_{2)}$ were monitored for every minute to 5 minutes after the administration of muscle relaxant.
Anaesthesia was maintained with a balanced technique with $N_2O/O_2$ in a ratio of 65:35 with systemic analgesics and inhalation agents. Any signs of histamine release like skin changes will be graded as flush (if redness >120s), erythema or wheals.
Sample size was determined based on study conducted by Doenicke AW et al[3]where we recruited twenty patients for each groups considering 5% droupouts. Data was entered in IBM SPSS Statistics 21 for Windows (IBM Corp. 1995,2012).Categoricaldatas were analysed using chi-square test, and for continuous variable ANOVA for three or more variables&t-test for two variables, etc whichever were appropriate were utilized. A P-value of <0.05 was taken as significant.

## III. Results And Observation

Sixty patients completed the study protocol. The demographic parameters such as age, weight, sex, height, ASA were comparable in the three groups and did not affect the study outcome as shown in table 1.

**Table 1: Socio-demographic characteristics of the patients in each group (N=60)**

| Variable | Groups | | | p-value |
|---|---|---|---|---|
| | A n=20 | B n=20 | C n=20 | |
| Age (in yr) [mean± SD] | 40.05±11.44 | 40.05±12.34 | 39.05±12.51 | 0.956* |
| Weight (in Kg) [mean± SD] | 55.95±8.76 | 56.65±4.28 | 56.65±7.41 | 0.937* |
| Height (in cm) [mean ± SD] | 156.90±4.48 | 157.90±5.28 | 159.30±6.74 | 0.399* |
| Sex, n (%) | | | | |
| Male | 5 (25.0) | 4 (20.0) | 7 (35.0) | 0.551† |
| female | 15 (75.0) | 16 (80.0) | 13 (65.0) | |
| ASA, n (%) | 17 (85.0) | 16 (80.0) | 18 (90.0) | 0.676† |
| I | 3 (15.0) | 4 (20.0) | 2 (10.0) | |
| II | | | | |

*One-way ANOVA; †Chi-square test

The mean onset time was significantly shorter (76.05±15.64 seconds) in the higher dose group C (0.25mg/kg) of cisatracurium and longest in the lowest dose group A (0.15mg/kg) with 123.50±26.64 secondsand this distribution was statistically significant(P=0.000), as shown in table 2. However, intergroup comparison showed significant differences only between group A and C

**Table 2: Distribution and comparison of onset time of the drugs (in seconds) in the three groups (N=60)**

| Groups | Onset time of drug (mean±SD) | p-value* |
|---|---|---|
| Group A | 123.50±26.64 | 0.000 |
| Group B | 93.15±25.18 | |
| Group C | 76.05±15.64 | |

*One-way ANOVA

Intubating conditions were considered acceptable if they were scored between 6 and 9 (good or excellent). Group A recorded 70% of acceptable score while Group B & C recorded 80% and 95% intubating score respectively, as shown in table 3. However, none of the patient recorded poor and fair intubating condition in the three groups. Their intergroup comparison also showed significant differences except between group A & B.

**Table 3: Distribution of intubating condition level-wise in three groups (N=60)**

| Intubating score | Groups, n (%) | | | p-value* |
|---|---|---|---|---|
| | A n=20 | B n=20 | C n=20 | |
| Poor (0-2) | 0 | 0 | 0 | 0.102 |
| Fair (3-5) | 0 | 0 | 0 | |
| Good (6-7) | 6 (30.0) | 4 (20.0) | 1 (5.0) | |
| Excellent (8-9) | 14 (70.0) | 16 (80.0) | 19 (95.0) | |

*Chi-square test

Intubation scores were higher for the larger dose of cisatracurium (group C) with significantly better intubating condition in shorter time than for the lower doses of cisatracurium (group A and group B) which is shown in table 4.

**Table 4. Comparison of intubation condition and time at intubation after the administration of different dosage of cisatracurium (N=60)**

| **Outcomes** | **Group A(n=20) (0.15 mg/Kg)** | | | **Group B (n=20) (0.20 mg/Kg)** | | | **Group C(n=20) (0.25 mg/Kg)** | | | **p-value*** |
|---|---|---|---|---|---|---|---|---|---|---|
| **Intubating condition** | <90 sec | 90-120 sec | >120 sec | <90 sec | 90-120 sec | >120 sec | <90 sec | 90-120 sec | >120 sec | |
| 0-2 Poor | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0.000 |
| 3-5 Fair | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | |
| 6-7 Good | 1(5%) | 4(20%) | 1(5%) | | 4(20%) | | 1(5%) | | | |
| 8-9 Excellent | | 8(40%) | 6(30%) | 8(40%) | 5(25%) | 3(15%) | 14(70%) | 5(25%) | | |

* Chi square value of 22.49

The TOF percentage at intubation (123.50±26.64 seconds)was highest in group A 26.05±28.41 percentage and least in group C (76.05±15.64 seconds) 12.70±16.56 percentage even though not statistically significant (P = 0.162), whereas at 3 minutes it showed statistically significant (P= 0.001) differences in the three group as it approach to near zero percentage (shown in table 5). The intergroup comparison also recorded significant defferences except between group B & C.

**Table 5: Comparison of train of four (TOF) % among the three groups**

| **TOF %** | **Groups (mean±SD)** | | | **p-value*** |
|---|---|---|---|---|
| | **A n=20** | **B n=20** | **C n=20** | |
| Baseline | 100.00±0.00 | 100.00±0.00 | 100.00±0.00 | - |
| At Intubation | 26.05±28.41 | 19.40±18.47 | 12.70±16.56 | 0.162 |
| 3 minute | 1.80±2.04 | 0.60±1.47 | 0.00±0.00 | 0.001 |
| 5 minute | 0.00±0.00 | 0.00±0.00 | 0.00±0.00 | - |

*One-way ANOVA

The haemodynamics parameters such as systolic and diastolic blood pressure, heart rate, $SPO_2$ etc were all comparable at different time points. There were no incidence of any side effects recorded in any of the groups.

## IV. Discussion

Endotracheal intubation is one of the important components of general anesthesia.[5] Neuromuscular blocking drug is used to facilitate endotracheal intubation and provide surgical relaxation. Many non-depolarizing neuromuscular blocking drugs were introduced in the clinical practice but they had many side effects like cardiovascular instability, occurrence of recurarisation and residual paralysis and were not suitable for use in certain clinical situations like liver and kidney disorders.[6]

Cisatracurium, besylate (Nimbex) is a new benzylisoquinoline introduced to clinical use in 1995, it is purified from one of the 10 stereo-isomers of atracurium. It is eliminated mainly by Hofmann degradation, and has one metabolite laudanosine which has no neuro-muscular blocking effect. It does not trigger histamine release, and has no direct cardiovascular effect.[7,8] The adult $ED_{95}$ is 0.05 mg/kg.[7]Cisatracurium has been considered a drug with a relatively slow onset but that has the significant benefit of having faster onset time when used at higher doses.[9] The present study was performed to compare the onset time and intubating conditions produced by three doses of cisatracurium during induction of anesthesia using fentanyl and propofol .

Selecting the time for intubation can either be by clinical method or neuromuscular monitoring method. Complete neuromuscular block at the adductor pollicis muscle was not a prerequisite for optimal intubating conditions.[10,11]Kim K S et al[12] reported shorter lag time, onset time and recovery time at larynx than at the adductor pollicis with cisatracurium 0.1mg/kg. So, in our study intubating conditions was assessed using clinical criteria such as jaw relaxation, vocal cord movements and diaphragmatic relaxation.

The main finding of the current study was that, by increasing the dose of cisatracurium from 0.15 to 0.25mg/kg in adult patients had shortened onset time andprovide better intubating condition. Our study observed onset time of 123.50±26.64s in group A patients receiving 0.15mg/kg dose, whereas the mean onset time was 93.15±25.18s in group B receiving 0.2mg/kg and as 76.05±15.64s in group C patients receiving 0.25mg/kg dose. Comparable results were recorded with the study of Doenicke et al[3]as onset time of 105.3±41.2s with 0.15mg/kg and 68.2±19.5s with 0.25mg/kg dose of cisatracurium . Little john et al[13] also reported onset time of

120s and 90s with a dose of 0.15mg/kg and 0.2mg/kg respectively which were similar to our study. Our onset time was also correlated with MT Caroll et al[14]showing time of onset 132 seconds with 0.15mg/kg dose of cisatracurium .

Our onset times correlate well with our intubation scores, as well as those reported by other investigators.[3,13,14] Our data indicate that the vocal cords were relaxed and the trachea of all patients could be intubated at onset time of 123.50±26.64s following 0.15 mg/kg cisatracurium and at onset time of 93.15±25.18s in group B receiving 0.2mg/kg and 76.05±15.64s in group C patients receiving 0.25mg/kg dose. Rimaniol et al[15] reported good to excellent intubating conditions at 2 minute in 80% of patients receiving 0.15mg/kg but in 97% of patients after receiving 0.2mg/kg of cisatracurium, which was almost similar to our study.

Hence, our study showed that higher dose of cisatracurium produce shorter onset of time as well as higher percentage of excellent intubating condition compared to lower doses. The difference between an intubation score of good or excellent was the occurrence of a slight diaphragmatic movement or mild coughing upon passage of the endotracheal tube.

Our results showed that in all the three groups, patient's mean arterial pressure, systolic blood pressure, diastolic blood pressure and heart rate were maintained within acceptable limits as it didn't changed significantly from the baseline at any time point. There was no clinical evidence of histamine release in all the three groups who received different doses of cisatracurium. None of the patients show any side effects.

**Limitations of our study**

1. There was a poor correlation between intubation score and degree of neuromuscular block in most patients, which may be due to the difference in sensitivity to neuromuscular block and muscle flow at the adductor pollicis and the vocal cords or the diaphragm[1]. So, study based on intubation criteria due to TOF value need to be determined.
2. The study need to be prolonged during the intraoperative period to determine its duration of action with the different doses.

## V. Conclusion

Cisatracurium is a potent intermediate acting non-depolarizing neuromuscular blocking agent and tracheal intubating condition can be accomplished with good to excellent intubating conditions following 0.15mg, 0.2mg/kg and 0.25mg/kg of cisatracurium. However, significant, faster onset time and higher percentage of good to excellent intubating conditions with increasing doses of cisatracurium, lack of histamine release side effects and more cardiovascular stability make cisatracurium a more promising alternative muscle relaxant agent for tracheal intubation.

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