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# Evaluating cis-atracurium: Comparing different doses for tracheal intubation

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**Abstract**
**Objective:** This study was designed to compare different doses of cis-atracurium (2×ED95, 4×ED95, 6×ED95) in regarding onset time, condition of intubation , duration of action, hemodynamic effects, and signs of histamine release.
**Methods:** Sixty ASA I and II adult patients undergoing abdominal surgery under general anesthesia were included in this prospective, randomised, double blind study. Patients were allocated to one of three groups:
**Group 1:** Patients in this group received with initial dose of 0.1 mg/kg (2×ED95) of cis- atracurium.
**Group 2:** Received initial dose of 0.2 mg/kg (4×ED95).
**Group 3:** Received initial dose of 0.3 mg/kg (6×ED95).
**Result:** All the demographic parameters were comparable**.**There was a statistically significant increase in HR, MABP post intubation when compared to baseline and post injection of 2× ED95 dose of cis-atracurium in group 1. Higher doses of cisatracurium (4×ED95 and 6×ED95) showed onset time that was significantly lower than cisatracurium (2×ED95). Regarding the duration of action, higher doses of cisatracurium (4×ED95 and 6×ED95) showed statistically significant longer duration of action than lower doses of cisatracurium. 4×ED95 and 6×ED95 doses of cisatracurium were significantly better than 2×ED95 dose of cisatracurium. Only 6×ED95 dose of cisatracurium was statistically significant with higher percentages of patients with excellent condition of intubation.
**Conclusion:** We can conclude that the higher doses of cisatracurium provide more effective, more rapid neuromuscular blocking with longer duration of action, stable hemodynamic status, and no associated signs of histamine release clinically.

**Keywords:** General anaesthesia, tracheal intubation, cis- atracurium, neuromuscular blocking

## 1. Introduction
Muscle relaxants is a routine drug for general anesthesia [1]. The potency of cis-atracurium besilate is about three times that of atracurium besilate, and the maximum block time is 2-3 min longer for equipotent doses as compared to atracurium besilate. The duration of action and rate of spontaneous recovery from equipotent doses are similar in comparisons clinically [2].

Cis-atracurium is more potent than at parent mixture 95% effective dose (ED95) 0.05 mg/kg v/s 0.2 mg/kg, its pharmacodynamic profile is similar to that of atracurium, except for a reportedly slower onset [3]. Cis-atracurium does not have histamine induced cardiovascular side effects like atracurium. However 2 X ED95(100 µg/kg) doses of cisatracurium does not provide ideal conditions for intubation such as seen in equipotent doses of atracurium. The recommendion for intubating dose of cis-atracurium is 3 X ED95 [4, 5].

## 2. Aim of the Works
This study was done to compare three doses of cis-atracurium (2×ED95, 4×ED95, 6×ED95) in regarding onset time, condition at the time of intubation, duration of action, haemodynamic effects, and any signs of histamine release.

## 3. Materials and Methods
### 3.1 Ethics Statement
The study was approved by Institute Ethics Committee and was registered with Clinical Trials Registry-India at www.Ctri.nic.in (CTRI/2019/05/019128). Written consent was obtained after informing the participants about the risks, the nature and scope of study.

### 3.2 Duration and type of study
This study was conducted in department of Anesthesia in Indira Gandhi Institute of Medical sciences, Patna, Bihar, India between May 2019 and December 2019. Sixty consenting adult patients were included in this double-blind, randomized, comparative study. The sampling type was randomized cluster sampling.

### 3.3 Inclusion Criteria
Patients with ASA I and II, age: between 20 to 65 years, either sexes scheduled for abdominal surgeries of an anticipated duration of at least more than one hour enrolled in this study.

### 3.4 Exclusion criteria
Pateints who refused to participate; any history of significant co-morbid disorders; anticipated difficult intubation; with known allergy to study drug and patients on medication that interact with neuromuscular blocking agent like antibiotics, antidepressants, anticonvulsants, antiarrhythmics and magnesium sulfate.

### 3.5 Preanesthesia
Pre-anesthesia evaluation of all patients was done before admission to the ward. All patients were pre-medicated with Tab Rantidine 150 mg & Tab Alprazolam 0.25 mg the night before surgery. All patients were kept fasting for 6 h prior to undergoing surgery.

### 3.6 Intervention plan
On the arrival in operation theatre, routine monitoring in the form of electrocardiography, capnography, temperature probe, non invasive blood pressure, pulse oximetry, respiration and neuromuscular monitoring was done and baseline values were noted. IV access was secured with an 18 G intravenous catheter on dorsum of non-dominant hand, and infusion plasmalyte was started. All the patients were premedicated with 2 mg midazolam IV 20 min preoperatively.
Using computer generated random numbers, patients were allocated to one of three groups:

**Group A:** 20 patients of this group received initial dose of 0.1 mg/kg (2×ED95) of cis-atracurium.

**Group 2:** 20 patients of this group received initial dose of 0.2 mg/kg (4×ED95) of cis-atracurium

**Group 3:** 20 patients of this group received initial dose of 0.3 mg/kg (6×ED95) of cis-atracurium

The first response (T1) of the train of four (TOF) stimulation was the parameter, which used for the pharmacodynamic measurements. The hand on which neuromonitoring applied was wrapped to avoid hypothermia. Patient was pre-oxygenated with 100% oxygen. General anesthesia was induced with IV fentanyl(dose:2µg/kg) and IV propofol (dose:2 mg/kg). Anesthesia was maintained with O2 + $N_2$ + isoflurane and assisted ventilation. Neuromuscular monitoring was done after obtaining the control values by supramaximal stimulus (70 mA) from relaxograph (2 Hz/0.5 s; pulse width 0.2 ms) every 20s to stimulate the ulnar nerve via surface electrodes.

Aftert 5 min, the muscle relaxant was given for according to the previously mentioned initial doses for each group and given intravenously within 5-10 s.The detectable difference between the means of the group using the onset of action (time from end of injections to 90% neuromuscular block) and its equals 0.7 minutes [6]. After 3 min, endotracheal intubation was done by using appropriate size of laryngoscope blade and endotracheal tube and the condition of intubation was assessed and recorded according to the following [7].

1) **Excellent:** Smooth passage of the endotracheal tube without coughing. Vocal cords relaxed and abducted.
2) **Good:** Passage of the endotracheal tube with slight coughing and/ or bucking. Vocal cords were relaxed and abducted.
3) **Poor:** Passage of the endotracheal tubes with moderate coughing and/ or bucking vocal cords moderately were adducted.
4) **Not possible:** Endotracheal tube could not be passed throgh Vocal cords. Vocal cords were tightly adducted.

The onset time was determined as the interval from the end of muscle relaxant injection until the maximal suppression of T1%.
Anesthesia was maintained with boluses of the muscle relaxant (10% of the initial dose) with 25% recovery of response to T1% and ventilation was controlled by the adjust end tidal $CO_2$ ($EtCO_2$) at 30-35 mmHg. Neuromuscular blockade after induction was monitored and recorded every 5 min by supramaximal train-of-four (TOF) stimuli.
The duration of the muscle relaxant **(**time from the end of injection of the drug to till 25% recovery of T1%) was recorded. Patients were monitored for any signs of histamine release clinically through skin changes graded as flush (if redness lasted > 120 s), erythema, or wheals [8] and presence of any hemodynamic changes or bronchospasm.
Intra-operative hemodynamic changes were continuously displayed on the monitor including: heart rate (HR), arterial blood pressure (BP) every 5 min, oxygen saturation (SO2), and end tidal CO2.
To avoid Hyper / Hypothermia by means of warmed IV fluids and warming blankets through nasopharyngeal probe. At the end of operation with 25% recovery of T1%, reversal agent were given of neostigmine and atropine mixture (2.5 mg neostigmine: 1 mg atropine) through slow IV injection. TOF-ratio>0.9 was sufficient for safe extubation of the trachea.

### 3.7 Blinding
The study drugs were prepared and administered by the independent anesthesiologist not involved in the study. The anesthesiologist giving general anesthesia and observing the patient was blinded to the treatment group. Neither the patient nor the attending anesthesiologist who collected the data was unaware of group allocation.

### 3.8 Rescue interventions
Rescue interventions were planned for bradycardia and hypotension:
Bradycardia (<50 beats per minute): atropine
Hypotension (<20% of baseline value): mephentermine

### 3.9 Stasticals methodes

Data were processed using SPSS version. Quantitative data were expressed as means±SD while qualitative data were expressed as numbers and percentages (%). Student *t* test and ANOVA test were used to test significance of difference for quantitative variables (HR, BP) that follow normal distribution and chi square test used to significance of difference for qualitative variables. A probability value (*P*-value) <0.05 was considered statistically significant.

## 4. Results

All the demographic parameters were comparable (>0.005) [Table 1]. There was a statistically significant increase in HR, MABP post intubation when compared to baseline and post injection of 2× ED95 dose of cis-atracurium in group 1. HR,MABP changes 5-20 minutes later were not statistically significant with administration of 4×ED95 and 6×ED95 doses of cis-atracurium in groups 2 and 3, respectively [Tables 2 and 3].

Time of onset was found to be significantly lower with 2×ED95 dose of cisatracurium. At the same time, higher doses of cisatracurium (4×ED95 and 6×ED95) showed onset time that was significantly lower then cisatracurium (2×ED95). Regarding the duration of action, higher doses of cisatracurium (4×ED95 and 6×ED95) showed statistically significant longer duration of action than lower doses of cisatracurium [Table 4].

Only 6×ED95 dose of cisatracurium was statistically significant with higher percentages of patients with excellent condition of intubation. 4×ED95 and 6×ED95 doses of cisatracurium were significantly better than 2×ED95 dose of cisatracurium. No one of the studied patients in the three groups been reported as not possible intubation. Assessment of vocal cords, 2×ED95 and 4×ED95 doses of cisatracurium were similar, while 6×ED95 dose of cisatracurium was significantly better than 2×ED95 dose of cisatracurium [Table 5]. No signs of histamine release were noted with any doses of cisatracurium.

**Table 1:** Demographic characteristics of the studied patients

| | | Cisatracurium group (n=16) 2×ED95 | Cisatracurium group (n=16) 4×ED95 | Cisatracurium group (n=16) 6×ED95 | P-value |
|---|---|---|---|---|---|
| Age | Mean ± SD | 42.7 ± 4.1 | 41.9 ± 6.8 | 36.9 ± 6.4 | 0.04(NS) |
| | Range | 33-58 | 27-50 | 29-53 | |
| Sex | Male N (%) | 8(50%) | 6(37.5%) | 6(43.75%) | 0.8(NS) |
| | FemaleN (%) | 8(50%) | 9(62.5%) | 8(56.25%) | |

NS - No statistically significant difference

**Table 2:** Heart rate changes before and after administration of cisatracurium

| Heart rate (beat/min) | | | | | | | |
|---|---|---|---|---|---|---|---|
| | Baseline reading | After injection of muscle relaxant | After attempt of intubation | 5 min | 10 min | 15 min | 20 min |
| Cisatracurium group(n=16)2×ED95 | 72.4 ± 5.71 | 75.9 ± 6.3 | 83.6 ± 547 * | 75.3 ± 6.51 | 76.4 ± 5.87 | 74.6 ± 5.78 | 75.1 ± 5.65 |
| Cisatracurium group (n=16)4×ED95 | 69.8 ± 4.43 | 72.2 ± 5.2 | 74.2 ± 3.45 | 73.9 ± 6.53 | 77.7 ± 5.56 | 74.1 ± 6.75 | 74.6 ± 5.84 |
| Cisatracurium group (n=16)6×ED95 | 71.8 ± 6.60 | 70.8 ± 7.3 | 71.9 ± 5.54 | 74.8 ± 6.65 | 74.4 ± 6.85 | 73.4 ± 4.75 | 75.7 ± 5.38 |

*Statistically significant difference versus Baseline reading (*P*-value < 0.05)

**Table 3:** Mean arterial blood pressure changes before and after administration of cisatracurium

| Mean arterial blood pressure (mmHg) | | | | | | | |
|---|---|---|---|---|---|---|---|
| | Baseline reading | After injection of muscle relaxant | After attempt of intubation | 5 min | 10 min | 15min | 20 min |
| Cisatracurium group(n=16)2×ED95 | 79.8 ± 10.5 | 79.8 ± 10.5 | 92.6 ± 7.59 * | 88.4 ± 8.64 | 84.6 ± 9.65 | 85.7 ± 7.43 | 83.5 ± 8.93 |
| Cisatracurium group (n=16)4×ED95 | 82.1 ± 8.5 | 82.1 ± 8.5 | 84.5 ± 6.73 | 83.5 ± 7.52 | 85.6 ± 8.42 | 84.9 ± 8.64 | 86.4 ± 9.24 |
| Cisatracurium group (n=16)6×ED95 | 81.7 ± 10.1 | 80.1 ± 9.6 | 85.3 ± 8.43 | 86.4 ± 9.34 | 84.9 ± 6.95 | 85.9 ± 6.58 | 82.6 ± 8.68 |

*Statistically significant difference versus Baseline reading (*P*-value < 0.05)

**Table 4:** Neuromuscular blockade after administration of cisatracurium

| | Onset time (Time to maximum suppression of T1%) (min) | Duration of action (25% recovery T1%) (min) |
|---|---|---|
| Cisatracurium group (n=16) 2×ED95 | 4.37 ± 0.46 * | 43.6 ± 4.15 |
| Cisatracurium group (n=16) 4×ED95 | 4.37 ± 0.46 * | 65.5 ± 10.5 *# |
| Cisatracurium group (n=16) 6×ED95 | 2 ± 1.2 *# | 78.4 ± 8.6 *# |

* Statistically significant difference versus 2×ED95 dose of atracurium (*P*-value < 0.05); # Statistically significant difference versus 2×ED95 dose of cisatracurium (*P*-value < 0.05)

**Table 5:** Condition of intubation and vocal cords assessment as recoded after 2 minutes of administration of cisatracurium

| | | Cisatracurium group (n=16) 2×ED95 | Cisatracurium group (n=16) 4×ED95 | Cisatracurium group (n=16) 6×ED95 |
|---|---|---|---|---|
| Vocal cords | Open N (%) | 6(37.5) | 11(68.75) | 16*#(100) |
| | Abducted N (%) | 8(50) | 5(31.25) | 0(0) |
| | Adducted N (%) | 2(12.5) | 0(0) | 0(0) |
| Condition of intubation | Excellent N (%) | 2(12.5) | 10#(62.5) | 13#*(81.25) |
| | Good N (%) | 9(56.25) | 5(31.25) | 3(18.75) |

| | | | | |
|---|---|---|---|---|
| | Poor N (%) | 5(31.25) | 1(6.25) | 0(0) |
| | Not Possibile N (%) | 0(0) | 0(0) | 0(0) |

* Statistically significant difference versus 2×ED95 dose of atracurium (*P*-value < 0.05); # Statistically significant difference versus 2×ED95 dose of cisatracurium (*P*-value < 0.05); Figures in parenthesis are in percentage

**Table 6:** Histamine release among the studied patients

| | Cisatracurium group (n=16) 2×ED95 | Cisatracurium group (n=16) 4×ED95 | Cisatracurium group (n=16) 6×ED95 | P-value |
|---|---|---|---|---|
| Flush N (%) | 0 | 0 | 0 | 0.5 (NS) |
| Erythema N (%) | 0 | 0 | 0 | |
| Wheals N (%) | 0 | 0 | 0 | |

NS - No statistically significant difference; Figures in parenthesis are in percentage

## 5. Discussion

All patients were assessed for hemodynamic state (heart rate, mean arterial blood pressure), onset time, duration of action, and signs of histamine release clinically, condition of intubations, and vocal cords assessment. The three groups of the study were matched regarding patients' age and sex.

Hemodynamic stability for both heart rate and mean arterial blood pressure were more evident among higher doses of cisatracurium (4×ED95, 6×ED95).

There was a statistically significant increase in HR, MABP, post-intubation 120 s post-injection of the muscle relaxant when compared to baseline and postinjection of 2×ED95 dose of cisatracurium in group 1 because of stress intubation and the patients were not fully relaxed. However, changes in HR and MABP 5-20 minutes later were not statistically significant in 4×ED95 and 6×ED95 doses of cisatracurium in groups 2 and 3, respectively. Lien *et al.*, [9] and Basta *et al.*, [10] concluded that the maximal MABP and HR changes of patients receiving cisatracurium were small and similar to those observed in patients receiving two times the ED95 of atracurium. In his study no patient developed a decrease in blood pressure >20% or an increase in heart rate >20% that was attributable to muscle relaxant administration.

The time of onset was determined as the interval from the end of muscle relaxant injection until the onset of the maximal suppression of T1 and the duration of action of the muscle relaxant was defined as time from disappearance of TOF stimulation till 25% recovery of T1.

Bluestein and colleagues [11], studied 80 patient in four groups. Group A received Cisatracurium 0.1 mg/kg (2×ED95), Group B received Atracurium 0.5 mg/kg (2×ED95). Patients in Group C 0.2 mg/kg (4×ED95) and Group D 1.5 mg/kg (3×ED95), were treated with Cisatracurium. They assessed the mean time of onset, mean time of clinically effective duration, and condition of intubation. As regarding the mean time of onset and mean time of clinically effective duration there results were in accordance with ours. They reported that increasing the initial dose of cisatracurium (from 0.1 to 0.15 and 0.2 mg/kg), decreased the mean time of onset (from 4.6 to 3.4 and 2.8 min, respectively) and increased the mean time of clinically effective duration (45 to 55 and 61 min, respectively). Mandal [12] conducted a study in 60 adult patients in three group to find out the minimum possible dose of cisatracurium for achieving excellent to good intubating conditions within 90 s of its administration under general anesthesia. After induction of anesthesia with the group I (n=20) received 0.15 mg/kg, group II (n=20) received 0.20 mg/kg, and group III (n=20) received 0.25 mg/kg of cisatracurium. For each group laryngoscopy and intubation was tried at either 75 or 90s, thereby patients were further divided into six subgroups. Subgroup 'a' denotes the procedure at 75s and, 'b' denotes at 90s. For grading the intubating conditions, the ease of laryngoscopy, the position or movement of the vocal cords and the degree of coughing were evaluated. Excellent to good intubating conditions could be achieved only in group IIb (0.20 mg/kg at 90 s) and both sub-groups (0.25 mg/kg at 7 5s and 90 s) in group III patients. Hence the minimum dose required to achieve excellent to good intubating conditions with cisatracurium is 0.20 mg/kg at 90 s after its administration. The adequacy of conditions for tracheal intubation is a function of several factors, such as the depth of anesthesia and the level of neuromuscular block at the time of attempt [13].

One of two intubating doses 0.15 mg/ kg (3×ED95) and 0.2 mg/kg (4×ED95) of cisatracurium, as components of a propofol /nitrous oxide/oxygen induction intubation technique, may produce generally good or excellent conditions of intubation in 2.0 and 1.5min, respectively [14].

## 6. Conclusion

We can conclude that the higher doses of cisatracurium provide more effective, more rapid neuromuscular blocking with longer duration of action, stable hemodynamic status, and no associated signs of histamine release clinically.

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