

# A clinical comparative study to evaluate the efficacy of intubating doses of atracurium and cisatracurium in patients undergoing general anesthesia



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## ABSTRACT

**Background:** Skeletal muscle relaxation is integral part of general anesthesia. Non-depolarizing neuromuscular blocking drugs like cisatracurium are devoid of any signs of histamine release and can improve the quality of intubating conditions. **Aims and Objectives:** We decided to assess the efficacy of Cisatracurium when compared to atracurium in terms of intubating conditions and hemodynamic parameters in patients undergoing surgeries under general anesthesia. **Materials and Methods:** In this study, 80 patients in the age group of 20–65 years were randomly allocated into Group A received Atracurium 0.5 mg/kg and Group B received Cisatracurium 0.15 mg/kg for intubation after administration of induction agent. Intubating conditions were assessed by Cooper et al., score and hemodynamic parameters such as heart rate and blood pressure were recorded at 1, 3, 5, 10, 15, and 30 min of intubation. Any signs of histamine release were noted. **Results:** Demographic profile was comparable between the two groups. As per Cooper et al., score intubating conditions were excellent with Cisatracurium group as compared to the atracurium group which was statistically significant. Hemodynamic parameters during intubation and after intubation were comparable between two groups. No associated signs of histamine release were noted in either of the groups. **Conclusion:** From our clinical comparative study, we have observed that Cisatracurium 0.15 mg/kg provides better intubating conditions and stable hemodynamic profile with no signs of histamine release as compared to atracurium 0.5 mg/kg dose.

**Key words:** Atracurium; Cisatracurium; Endotracheal intubation

## INTRODUCTION

General anesthesia is the state produced when a patient receives medications to produce amnesia and analgesia with or without reversible muscle paralysis. Ideal neuromuscular blocking agent for intubation should have a rapid onset, brief duration of action, free from hemodynamic effects, devoid of residual paralysis, and provide excellent intubating conditions such as fully relaxed jaw, widely open vocal cords, and absence of any intubation response.<sup>1-4</sup> ED<sub>95</sub> and intubating dose of atracurium is 0.25 mg/kg for

adults<sup>5</sup> and is designed to undergo spontaneous degradation at physiological temperature and by a mechanism called Hofmann's elimination, yielding laudanosine, and monoquaternary acrylate.<sup>6</sup> Onset of action is approximately 3 min when an intubating dose is given.<sup>6</sup>

Cisatracurium besylate is a cis-cis isomer (51W89:1R-cis 1"R-cis Atracurium), one of the ten stereoisomers of atracurium that constitutes 15% of the atracurium mixture and is about 3–4 times more potent than atracurium and devoid of any cardiovascular side effects in doses of up to 8 times of ED<sub>95</sub>.<sup>5,7-9</sup>

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The ED95 of Cisatracurium is 0.05 mg/kg.<sup>1,3</sup> It undergoes Hofmann's degradation to form Laudanosine and monoquaternary alcohol. It does not lead to histamine release in humans.<sup>8,9</sup> The volume of distribution of Cisatracurium is low as it is having relatively larger molecular weight and higher polarity<sup>5-9</sup>

Atracurium is having adverse effects of histamine release such as tachycardia, hypotension, erythema, and cardiovascular instability as compared to Cisatracurium.<sup>2</sup> The ED95 of Cisatracurium is 0.05 mg/kg.<sup>1,3</sup> Studies are going on to evaluate the intubating conditions following intravenous administration of multiple doses of cisatracurium (2ED95, 3ED95, and 4ED95) and atracurium (2×ED95). We have planned to conduct this randomized prospective study to compare intubating conditions, hemodynamic profile and signs of histamine release with 2ED95 Atracurium and 3ED95 Cisatracurium. In addition, we have evaluated the neuromuscular blocking profile with train of four counts at 3 min.

### Aims and objectives

The objectives are as follows:

1. To compare the efficacy of intubating doses of Atracurium (0.5 mg/kg) and Cisatracurium (0.15 mg/kg) regarding intubating conditions and hemodynamic parameters.
2. To observe the side effects of Atracurium and Cisatracurium.

## MATERIALS AND METHODS

After obtaining approval from the hospital ethics committee and written informed consent, the present prospective randomized study was conducted on 80 patients of either sex scheduled for surgeries under general anesthesia in the Department of Anaesthesiology, G.R. Medical College and J.A Group of Hospitals, Gwalior (M.P.). The enrollment of patients was done between January 2020 and 2021.

### Inclusion criteria

The following criteria were included in the study:

1. Consent to participate in study
2. Age: 20–50 years, of both sexes.
3. American Society of Anesthesiologist Grades I & II.
4. Mallamapati classes I and II
5. Elective surgeries under general anesthesia.

### Exclusion criteria

The following criteria were excluded from the study:

1. Patient's refusal

2. Patients with disorders of cardiovascular, hepatic, renal, or neuromuscular system.
3. Pregnant and lactating women
4. Patients with airway problems suggesting difficult intubation, that is, Mallampati Grades III and IV, anticipated difficult airway
5. Patients receiving drugs known to interact with neuromuscular blocking agents, for example, antibiotics (aminoglycosides and tetracyclines), antidepressants, antiepileptics, anti-arrhythmic (calcium channel blockers and quinidine), and magnesium sulfate.
6. Allergy to any of the study drugs.

### Pre-anesthetic assessment

All the patients were examined on the day before surgery and all the required routine and special investigations including complete blood count, random blood sugar, blood urea, and serum creatinine. ECG and Chest X-ray as per hospital protocol were carried out. The purpose and protocols of the study were explained to patients and informed well written consent was obtained.

### Grouping

Selected 80 patients of ASA Grades I and II scheduled for surgeries under general anesthesia were randomly divided into two groups as below:

GROUP A (n=40)	Atracurium 0.5 mg/kg IV Bolus
GROUP CA (n=40)	Cisatracurium 0.15 mg/kg IV Bolus

On arrival of the patient in operation theatre, intravenous line access was done with 18 G cannula in a vein and intravenous fluids were started on maintenance. All routine monitors including pulse oximeter, blood pressure cuff, and electrocardiogram leads were connected and observations were recorded.

1. Preoxygenation was done with 100% oxygen for 3 min.
2. Neuromuscular monitor is attached to assess level of neuromuscular blockade. Patient was premedicated with Inj. Midazolam 1 mg IV, Inj. Glycopyrolate 0.2mg IV and Inj. Pentazocin (0.3–0.6 mg/kg). Anesthesia induced with injection Propofol 2 mg/kg intravenously followed by injection Atracurium 0.5 mg/kg in Group A and injection Cisatracurium 0.15 mg/kg in Group CA. Muscle relaxant was given over 5 s and intravenous line was flushed with normal saline over 15 s. After 3 min of mask ventilation, intubating conditions were noted clinically according to Cooper et al., score<sup>10</sup> criteria as excellent (8–9), good (6–7), fair (4–5), and poor (0–2).

TOF ratio was noted at 3 min and intubating conditions were graded as: Excellent for TOF count 0, good for TOF

count 1, fair for TOF count 2 and poor for TOF count 3 and 4. It was correlated with clinical criteria by Cooper et al., score.

Patient was intubated with appropriate size endotracheal tube after a proper laryngoscopy. If not able to intubate, next attempt was taken after 30 s. After checking bilateral air entry, endotracheal tube was secured. Post-intubation hemodynamic response was noted. Further anesthesia was maintained with 66.7% Nitrous oxide and 33.3% Oxygen, Isoflurane 0.8–1% using closed circuit system with controlled ventilation and injection Atracurium 0.1 mg/kg in Group A or with injection Cisatracurium 0.03 mg/kg in Group CA. At the end of surgical procedure, reversal was done with injection Neostigmine 0.04 mg/kg and injection Glycopyrrolate 0.08 mg/kg.

Monitoring of hemodynamic parameters such as heart rate, blood pressure, mean arterial pressure was done at 1, 3, and 5 min after intubation and throughout the procedure. Any adverse reactions to any of the administered drugs and signs of histamine release such as bradycardia, tachycardia, hypertension, hypotension, erythema, flushing, itching, urticaria, wheezing, bronchospasm, and injection reaction were noted.

### Statistical analysis

Data were statistically analyzed using SPSS-25 statistical software. Quantitative data were expressed as Mean±SD. Qualitative data were expressed as numbers and percentages. For comparison of qualitative data between two groups Chi-square or Fisher's exact test was used. Quantitative data was compared using student's "t" test or Mann-Whitney U test. (P<0.05) was considered statistically significant.

## RESULTS

In our study, it was found that demographic profiles were comparable between the two groups and statistically insignificant (P>0.05).

Intubating conditions by TOF response (as shown in Table 1) in cisatracurium group were better than atracurium group which was statistically significant (P<0.05).

With reference to Table 2, in atracurium group, easy jaw opening was seen in 31 patients. Comparatively in Cisatracurium group, jaw opening was easy in 35 patients and moderate in five patients. There was no statistically significant difference between two groups (P>0.05).

In Group A, vocal cords were found in moving condition in about 25 patients while in 15 patients they were open, easing the intubation. In Group CA, vocal cords movement was

seen in ten patients. (Table 3) It was found that vocal cord relaxation was better in Group CA, which was statistically significant (P<0.05).

As shown in Table 4, in Group A, 24 patients had slight diaphragmatic movement and 11 patients showed complete relaxation. However, in Group CA, 28 patients showed complete relaxation and only two patients had mild cough reflex.

Intubating conditions assessed clinically by Cooper et al., score was better in cisatracurium group than atracurium group which was statistically significant (P<0.05) (Table 5). Better intubation score in Group CA was found which was statistically significant (P<0.05).

**Table 1: Assessment of intubating condition by TOF response**

Grading	TOF COUNT	Group A (n=40)		Group CA (n=40)		P value
		No.	%	No.	%	
Excellent	0	7	17.5	28	70.0	<0.001
Good	1	26	65.0	10	25.0	
Fair	2	7	17.5	2	5.0	
Poor	3 and 4	0	0.0	0	0.0	

**Table 2: JAW relaxation in study subjects**

JAW relaxation	Group A (n=40)		Group CA (n=40)		P value
	No.	%	No.	%	
Impossible to Open	0	0.0	0	0.0	0.38
Open with Difficulty	1	2.5	0	0.0	
Moderate Opening	8	20.0	5	12.5	
Easy opening	31	77.5	35	87.5	

**Table 3: Vocal cord position in study subjects**

Vocal cord position	Group A (n=40)		Group CA (n=40)		P value
	No.	%	No.	%	
Closed	0	0.0	0	0.0	0.001
Closing	0	0.0	0	0.0	
Moving	25	62.5	10	25.0	
Open	15	37.5	30	75.0	

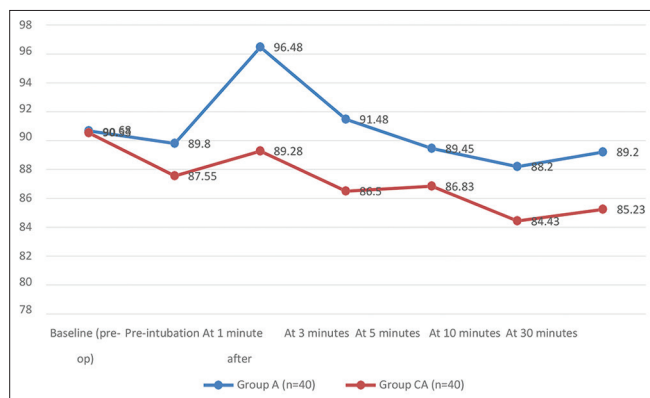
**Table 4: Response to intubation (diaphragmatic status)**

Response to intubation (diaphragmatic status)	Group A (n=40)		Group CA (n=40)		P value
	No.	%	No.	%	
Severe coughing	0	0.0	0	0.0	0.001
Mild coughing	5	12.5	2	5.0	
Slight diaphragmatic movement	24	60.0	10	25.0	
No movement	11	27.5	28	70.0	

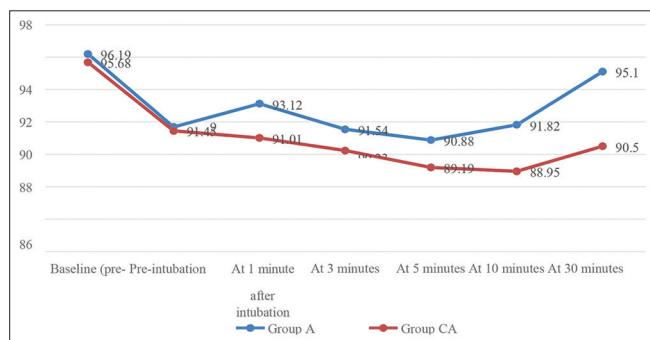
The baseline values of hemodynamic parameters were comparable. The results obtained from statistical analysis showed that there was increase in heart rate, compared to baseline in atracurium group at 1 min after intubation which gradually returned to the baseline value at 5 min and there was no statistically significant difference. Changes in hemodynamic parameters at different intervals were statistically insignificant (Graphs 1 and 2).

## DISCUSSION

In our study, the demographic data in terms of age, weight, sex as well as the ASA grades and Mallampati class were comparable between the two groups and statistically insignificant ( $P > 0.05$ ).



**Graph 1:** Heart rate comparison between study subjects at different interval



**Graph 2:** MAP comparison between study subjects at different interval

**Table 5: Intubation score (cooper et al., score) comparison in study groups**

Intubation score	Group A (n=40)		Group CA (n=40)		P value
	No.	%	No.	%	
Excellent	14	35.0	29	72.5	0.003
Good	20	50.0	9	22.5	
Fair	6	15.0	2	5.0	
Poor	0	0.0	0	0.0	

The adequacy of conditions for tracheal intubation is a function of several factors which includes depth of anesthesia and the level of neuromuscular blockade at the time of intubation attempt.<sup>11</sup> We assessed intubating conditions both clinically and correlated them with TOF count at the time of intubation. Intubation time was kept fixed at 3 min.

In our study, intubating conditions were assessed by Cooper et al., score.<sup>10</sup> Sahu et al.,<sup>12</sup> and Gogoi et al.,<sup>13</sup> also used Cooper et al., score<sup>10</sup> for clinical assessment of intubating conditions. Furthermore, the assessment of vocal cords showed better relaxation in 3ED95 dose of cisatracurium group as compared to 2ED95 atracurium which was statistically significant ( $P < 0.05$ ). In our study, we found superior intubating conditions with ED95 of cisatracurium as compared to 2ED95 dose of atracurium which was statistically significant ( $P < 0.05$ ).

In a similar study by Gogoi et al.,<sup>13</sup> TOF was elicited every 10 seconds and intubation was performed at 3 min. They found comparable intubating conditions at 3 min with 2ED95 dose of atracurium and 3ED95 cisatracurium and both showed better results than at 2ED95 dose of cisatracurium which was statistically highly significant ( $P < 0.00001$ ). When assessed clinically, similar results were found in studies conducted by Ranjan et al.,<sup>14</sup> and Khobragade and Sonwane.<sup>15</sup> Ranjan et al.,<sup>14</sup> compared the 3ED95 dose of cisatracurium with 2ED95 dose of atracurium and concluded that 3ED95 cisatracurium provides better intubating conditions as compared to 2ED94 atracurium.

El-kasaby et al.,<sup>16</sup> study found that equipotent doses of 2ED95 atracurium and 2ED95 cisatracurium are similar as regard to intubating conditions. However, higher doses of Cisatracurium (4ED95 and 6 ED95) provide better intubating conditions when assessed clinically. In another study, Bluestein et al.,<sup>17</sup> found good to excellent intubating conditions in more than 90% of patients.

Mandal<sup>11</sup> conducted a dose response study to find out ideal intubating dose of Cisatracurium. They compared 3ED95 (0.15 mg/kg), 4ED95 (0.2 mg/kg), and 5ED95 (0.25 mg/kg) doses and concluded that by clinical assessment, 4ED95 dose provided excellent intubating conditions in 90 s as compared to 3ED95 dose. However, 5ED95 dose developed very good to excellent intubating conditions in 75–90 s.

In our study 100%, patients were intubated in the first attempt, similar to Khobragade and Sonwane<sup>15</sup>, El-kasaby et al.,<sup>16</sup> and Bluestein et al.,<sup>17</sup> Niranjana et al.,<sup>18</sup> and Utpal et al.,<sup>19</sup> found better intubating conditions with 6ED95 cisatracurium as compared 2ED95 atracurium.

### Hemodynamic comparison

In our study, baseline heart rate, systolic blood pressure, diastolic blood pressure, and mean arterial pressure and at different time intervals as 0, 1, 3, 5, 10, and 30 min after intubation among the two groups were noted and compared. The mean and standard deviation of all the parameters was calculated.

The baseline values of hemodynamic parameters were comparable and remained so before intubation which was statistically insignificant ( $P > 0.05$ ).

There was increase in heart rate, compared to baseline in Atracurium group at 1 min after intubation but this may be due to stress response. They gradually returned to the baseline value at 5 min and there was no statistically significant difference. It was found out that the changes in heart rate, systolic blood pressure, diastolic blood pressure, and mean arterial blood pressure were comparable in both the groups at different intervals and had no significant difference.

This hemodynamic stability can be attributed to slow administration of injection of muscle relaxant, rapid injection of which is usually associated with fall in blood pressure and transient tachycardia and cisatracurium being devoid of release of histamine and associated with 3–4 times lesser production of Laudanosine which is responsible for cardiovascular effects and central nervous system stimulation<sup>4,6</sup>

Bhandari *et al.*,<sup>20</sup> did not notice any sudden changes in hemodynamic parameters or episodes of bronchospasm, urticaria, and erythema following injection of equipotent doses of atracurium (3ED95) and cisatracurium (3ED95) and during maintenance of anesthesia. They concluded that hemodynamic and safety profile of both the drugs were comparable. Niranjana *et al.*,<sup>18</sup> also noticed similar hemodynamic profile in both the groups. Utpal *et al.*,<sup>19</sup> and Thukral *et al.*,<sup>21</sup> found stable hemodynamics in 4ED95 and 6ED95 cisatracurium as compared to 2ED95 atracurium.

Athaluri *et al.*,<sup>22</sup> and Mohanty *et al.*,<sup>23</sup> conducted study to compare the 2ED95 and 3ED95 dose of cisatracurium with 2ED95 dose of atracurium and comparable hemodynamics in all three groups with no statistically significant alteration in baseline as well as post intubation hemodynamic parameters in all the groups. In one more similar study, Gogoi *et al.*,<sup>13</sup> compared 2ED95, 3ED95 dose of cisatracurium with 2ED95 dose of atracurium and found comparable hemodynamics in all three groups and stated that increase in hemodynamic parameters at 1 min due to intubation stress response which may

return to baseline values at 5 min and was not statistically significant.

El-kasaby *et al.*,<sup>16</sup> in their study observed that hemodynamic stability for both mean arterial pressure and heart rate was more evident when cisatracurium with higher dosage (4ED 95 and 6ED95) as compared to (2ED 95 dose of atracurium and 2ED95 dose of cisatracurium which was statistically significant ( $P < 0.05$ ) which can be attributed to absence of dose-dependent histamine release in cisatracurium group. Jammal *et al.*,<sup>24</sup> also concluded better hemodynamics with higher dose of (4ED95) cisatracurium compared to the lower dose (3ED95).

Subha *et al.*,<sup>25</sup> and Bakhshi *et al.*,<sup>26</sup> also observed better hemodynamic stability with the cisatracurium group (6ED95 and 4ED95, respectively) as compared to atracurium (2ED95).

Yazdanian *et al.*,<sup>27</sup> stated that there were comparable hemodynamic effects between atracurium and cisatracurium but atracurium was more cost-effective. Movafegh *et al.*,<sup>28</sup> studied about 100 patients for safety and cost analysis. They compared equipotent doses of Cisatracurium (3ED95) and Atracurium (3ED95) to conclude that both the drugs had similar safety profile and can be used safely during anesthesia.

As shown in table, none of our study subjects had episodes of hypotension, tachycardia, bronchospasm, erythema, rash, or urticaria. The signs of histamine release are often noted following administration of benzyliisoquinolinium class of muscle relaxants.<sup>20</sup> This effect lasts for short duration (1–5 min) which is dose related and clinically insignificant in healthy patients and this side effect can be considerably reduced by slow administration of drug. The clinical effects of histamine are observed when plasma concentration exceeds 200–300% that of the baseline values and these are due to chemical displacement of contents of mast cell granules containing histamine, prostaglandin, and other vasoactive substances.<sup>29</sup>

A study by Basta *et al.*,<sup>30</sup> reported that atracurium releases histamine when doses of 0.5 mg/kg or more are injected rapidly. A transient fall in blood pressure and facial erythema may be observed when plasma histamine levels increases more than 1000 pg/mL. This can be prevented by slower injection from 30 to 60 s. Shang Guan *et al.*,<sup>31</sup> concluded even with higher dose (8ED95) no signs of histamine release are seen due to stereospecificity.

In El-kasaby *et al.*,<sup>16</sup> study, no signs of histamine release were noted with any of the doses of (2ED95, 4ED95, and 6ED95) cisatracurium while 2 cases (one case showed flush

and other showed erythema) were noted in atracurium group which were statistically insignificant. No signs of histamine release were seen in any of the studies by Niranjana *et al.*, Khobragade and Sonwane, Bhandari *et al.*

### Limitations of the study

This study included only 0.15 mg/kg dose of cisatracurium and appropriate dose of drug is still not determined.

## CONCLUSION

From our clinical comparative study, it can be concluded that intubating conditions are better with 3ED95 dose of cisatracurium as compared to 2ED95 dose of atracurium. Both drugs provided stable hemodynamic status. None of the participant showed signs of histamine release. Hence, cisatracurium can be considered as more efficacious as compared to atracurium.

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**PH-** Interpreted the results, reviewed the literature, and manuscript preparation; **PG-** Concept and design of the study, prepared first draft, and supervision; **AG-** Interpretation and revision of manuscript; **NJ-** Concept, coordination, interpretation, statistical analysis and preparation of manuscript; **DK-** Proofreading and revision of manuscript.

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