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A clinical comparative study of different doses of cisatracurium for intubation in patients undergoing general anaesthesia

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Abstract
Cisatracurium is a new non-depolarizing, benzylisoquinolinium neuromuscular blocking drug with intermediate duration of action. It is a stereoisomer of atracurium with a potency of approximately 3 to 4 times greater than that of atracurium. Despite the higher potency, cisatracurium is associated with more stable hemodynamics than atracurium and does not cause histamine release even at doses of upto 0.4mg/kg (8×ED95). The recommended intubating dose is 0.15mg/kg (3×ED95) & High Most of the previous clinical studies have compared equipotent doses of atracurium and cisatracurium and concluded that atracurium is more effective than cisatracurium at same dose (2×ED95). However, few studies have shown that increasing the dose of cisatracurium to 4×ED95 (0.2mg/kg) and 6×ED95 (0.3mg/kg) provided more effective neuromuscular blockade and excellent cardiovascular stability with no marked histamine release clinically. Hence the present study was done in order to test the intubating conditions and hemodynamic stability of cisatracurium at 2 ×ED95 and 4×ED95 doses.
Methods: Randomised controlled trial conducted, after ethical committee clearance and informed written consent from patient. Sixty patients of ASA 1 and 2 aged 20 -60 yrs of both sexes coming for elective surgeries under general anaesthesia. Patients were divided into two groups, so each, group A received 0.1mg/kg (2*ED95) and group B received 0.2mg/kg(4*ED95) loading dose of cisatracurium.
Results: Intubating conditions were satisfactory with group B compared to group A and was statistically significant. Better hemodynamic stability with respect to mean pulse rate, systolic blood pressure and mean arterial pressure in group B compared to group A and was statistically significant.
Conclusion: 4*ED95 doses of cisatracurium provides better intubating conditions and more stable hemodynamic status than 2*ED95. There was no untoward effects noted clinically.

Keywords: Cisatracurium, intubating conditions, general anaesthesia, histamine release

Introduction
The introduction of neuromuscular blocking drugs into clinical practice represents one of the most significant advances in the development of Anaesthesiology and has revolutionized the practice of Anaesthesia. The use of neuromuscular blocking drugs has increased the safety and improved the results of many established surgical procedures as well as many new ones.
Cisatracurium first synthesized by D.A. Hill and G.L.T urner in 1989 as an individual isomer molecule and the pharmacological research of Cisatracurium was further by R. Brandt Maehr and William. B. Wastila [1].
Cisatracurium approval for human use by the US Food and Drug Administration in 1995. It is a non-depolarizing, benzylisoquinolinium neuromuscular blocker with intermediate duration of action [2]. It is a Atracurium stereoisomer having 3 to 4 times more potency than Atracurium [2, 3] and it is associated with more stable hemodynamics and cause no release of histamine compared to Atracurium at equipotent doses [4].
The recommended intubating dose is 3times ED_{95} (0.15mg/kg) & higher [5, 6].
At equipotent doses of Atracurium and Cisatracurium, atracurium is more effective than cisatracurium at 2 times ED95 dose as per previous clinical studies .However, few studies have shown that increasing the dose of Cisatracurium to 0.2mg/kg (4 times ED_{95}) and 0.3mg/kg (6 timesED_{95}) provided excellent cardiovascular stability and effective neuromuscular blockade clinically [5, 7]
Hence the present study was done in order to evaluate the intubating conditions and hemodynamic stability of Cisatracurium at 2 times ED_{95} and 4 times ED_{95} doses.

Objectives of the Study

This study was designed to compare between two different doses of Cisatracurium 0.1mg/kg and 0.2mg/kg regarding,

1. Intubating conditions.
2. Untoward effects
3. Hemodynamic response:

Materials and Methods

Source of Data

A randomized controlled trial titled "A Clinical comparative study of different doses of cisatracurium for intubation in patients undergoing general anaesthesia"

- Study Design: Randomized controlled trial
- Sample Size: Two groups of 30 subjects each.
- Sampling Method: Random sampling.
- Statistical Analysis were done using SPSS (statistical package for social science) for windows version 20.
- Test of significance: Unpaired T test and chi square test. To compare between the 2 groups of Cisatracurium (0.1 & 0.2 mg/kg) and results were given in necessary tables and graphs.
- A 'p'value of <0.05 will be considered as statistically significant at 5% level.

Method of Collection of Data

- Sixty patients between 20 to 60 years of age with ASA grade 1 and ASA grade 2 physical status posted for elective surgeries under general anaesthesia were considered for the study after ethical committee clearance.
- Each patient were visited pre-operatively and the procedure explained and informed written consent were obtained. All the routine investigations required for pre operative evaluation and for the proposed surgery were done. Pre-medications were given to all patients included in the study, tabl*et al*prazolam 0.5mg at night before surgery and tablet Ranitidine 150mg at night before and the morning on the day of surgery. Period of absolute fasting of at least 8 hours were allowed.

Inclusion Criteria

1. Age 20 -60 years of both sexes.
2. American society of anaesthesiologist grade 1 and 2.
3. Patients coming for elective surgeries.

Exclusion Criteria

1. Patients other than ASA 1 and 2.
2. Patients with anticipated difficult airway.
3. Patient with history of allergy
4. Pregnant and lactating women.
5. Patients receiving drugs known to interact with neuromuscular blocking agents.
6. Patients with cardiovascular, neuromuscular, hepatic or renal disorder.

Methodology

- On arrival in the operating room, patients were randomly divided into two groups and drug to be given were decided on the basis of sealed envelope technique, which were picked randomly and administered by the anaesthesiologist unrelated to study.
- Group A: Cisatracurium of 0.1mg/kg 30 patients
- Group B:Cisatracurium of 0.2mg/kg 30 patients

- Intra venous cannula (18G / 20G) were secured and standard monitoring - NIBP, SPO2, ECG were done .
- Baseline hemodynamic parameters recorded. (SBP, DBP, MAP, HR).
- All patients were premedicated with inj. Glycopyrolate 0.005mg/kg intra venously.
- After preoxygenation, general anesthesia technique was standardized for both the groups, induced with Inj Propofol 2mg/kg and Inj fentanyl 2mcg/kg intravenously.
- Muscle relaxant were given for patients according to previously mentioned initial doses for each group and ventilated with gas Oxygen for two minutes.
- At the end of two minutes, endotracheal intubation were done using appropriate size Macintosh laryngoscope blade and endotracheal tube.
- The condition of intubation were assessed by the degree of jaw relaxation, resistance to laryngoscopy, vocal cord position, limb movements, and coughing.

Table 1: Criteria for determining intubating conditions [8]

Scoring	1	2	3	4
Jaw Relaxation	Complete	Slight tone	Stiff	Rigid
Resistance to laryngoscope	Easy	Fair	Difficult	Impossible
Vocal cords movements	Open	Moving	Closing	Closed
Coughing	None	Slight	Moderate	Severe
Limb movements	None	Slight	Moderate	Severe

Intubation conditions were assessed using a scoring system, where

Excellent condition means all criteria scoring 1.

Acceptable condition means all criteria equals or less than 2.

Unacceptable condition means any of the five variables scoring more than 2.

- Anaesthesia was maintained with oxygen, nitrous oxide, volatile anaesthetic (Sevoflurane or Isoflurane), and intermittent positive pressure ventilation. Intermittent doses of Cisatracurium were given as and when required.
- Reversal were given with Inj Neostigmine 0.05mg/kg and Inj Glycopyrolate 0.01mg/kg intravenously.
- The following routine pre-operative investigations were carried out in both the group of patients after taking informed written consent.

Observations and Results

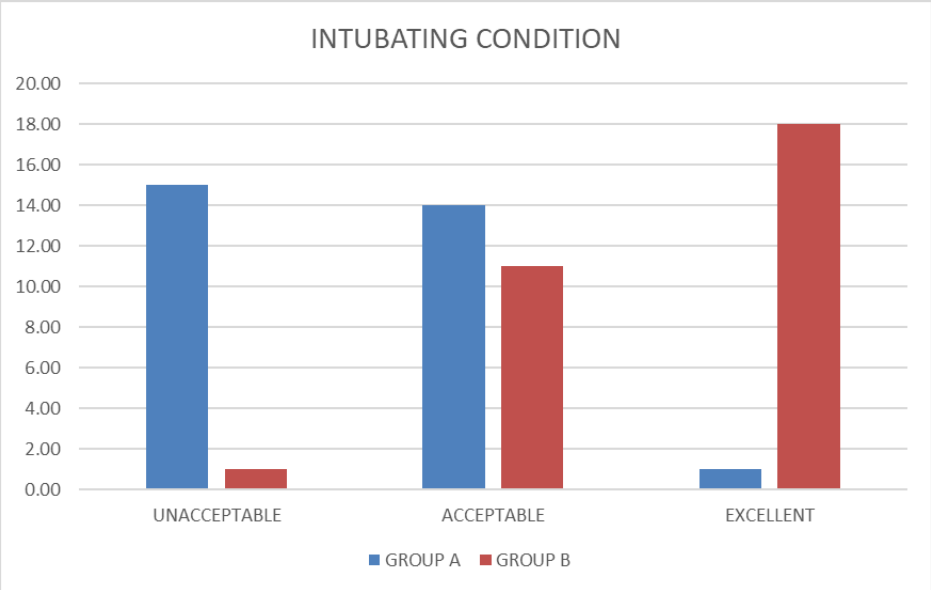
Study design: A comparative two group double blind randomized clinical study done with 0.1mg/kg and 0.2mg/kg Cisatracurium to assess the intubating conditions, hemodynamic responses and any untoward effects.

Table 2: Demographic variables comparing between two groups

Serial nos	Demographic variables	Group A %	GroupB%	P value
1	Gender :male female	14 (23.3) 16 (26.7)	13 (21.7) 17 (28.3)	0.8
2	Age	33.93±6.88	32.23±6.65	0.698
3	Weight	51.63±7.75	57.10±8.39	0.089

Table 3: Intubating conditions among the patients studied

	Group A		Group B		P value
Unacceptable	15	50%	1	3.33%	<0.01
Acceptable	14.00	46.66%	11	36.67%	
Excellent	1.00	3.33%	18	60%	

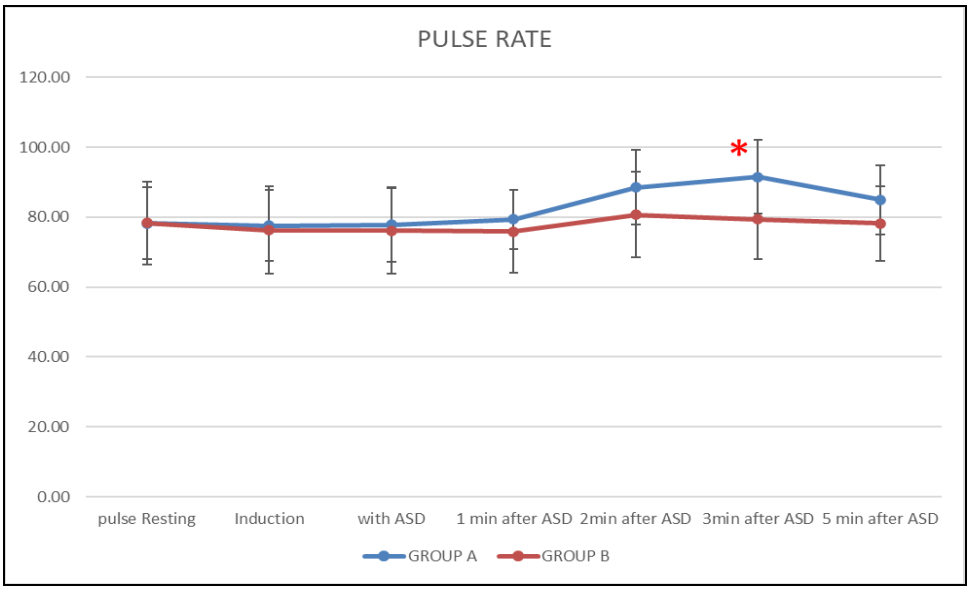


Graph 1: Bar diagram showing intubating conditions among two groups

Excellent intubating conditions were observed in 3% of group A patients and 60% of patients in group B patients.
Acceptable conditions were observed in 46% of group A patients and 36% of patients in group B patients.
Unacceptable conditions were observed 50% of group A patients and 3% of patients in group B patients.
Intubating conditions noted between two groups was statistically significant with 'p' value of <0.01.

Table 4: Comparison of Mean heart rate of patients studied

	Group A		Group B		P Value
	Mean	Sd	Mean	Sd	
Resting pulse rate	78.23	±10.21	78.27	±11.96	0.45
Induction	77.57	±10.20	76.27	±12.43	0.29
with ASD	77.87	±10.60	76.07	±12.16	0.46
1 min after ASD	79.33	±8.55	75.90	±11.75	0.16
2min after ASD	88.53	±10.76	80.67	±12.24	0.78
3min after ASD	91.53	±10.55	79.43	±11.54	0.04
5 min after ASD	84.93	±9.90	78.17	±10.62	0.97



Graph 2: Time specific changes in mean pulse rate among two groups.

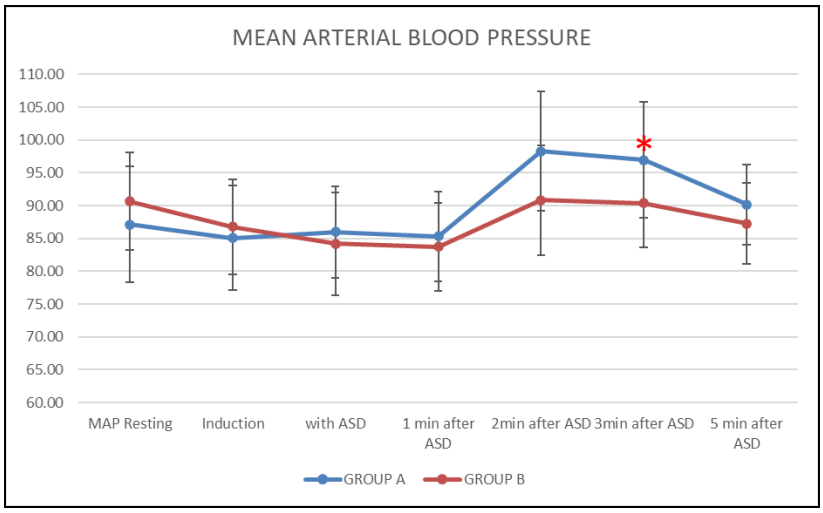
Mean pulse rate from resting to study drug administration mean among the two groups were comparable and clinically insignicant.

At 3 minutes after administration of study drug, mean pulse rate was 91.53±10.55 in group A and 79.43±11.54 in group B patients.

This was statistically significant with p value of 0.04.

Table 5: Comparison of MAP (mmHg) of patients studied

Map	Group A		Group B		P Value
	Mean	SD	Mean	SD	
MAP Resting	87.14	8.78	90.63	7.41	0.42
Induction	85.08	8.00	86.76	7.24	0.59
with ASD	85.98	6.97	84.20	7.81	0.88
1 min after ASD	85.36	6.83	83.72	6.69	0.70
2 min after ASD	98.26	9.08	90.80	8.41	0.26
3 min after ASD	96.97	8.86	90.37	6.75	0.01
5 min after ASD	90.17	6.10	87.27	6.22	0.95



Graph 3: Time specific changes of MAP (mmHg) among two groups

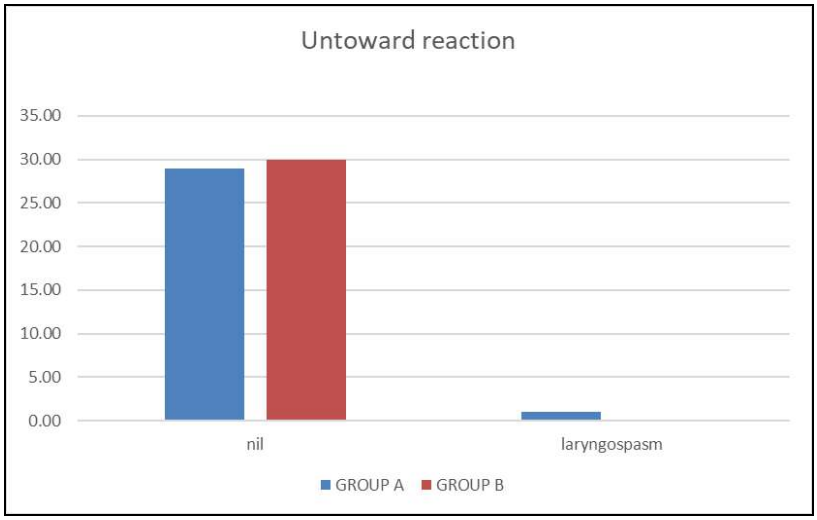
Mean arterial pressure from resting to study drug administration among the two groups were comparable and clinically insignicant.

At 3 minutes after administration of study drug, mean blood pressure was 96.97±8.86 in group A and 90.37±6.75 in group B.

This was statistically significant with 'p' value of 0.01.

Table 6: Untoward effects among patients studied

Untoward reaction	Group A	Group B	p value
nil	29.00	30.00	0.51
laryngospasm	1.00	0.00	



Graph 4: Bar diagram showing untoward effects.

As shown in the table there is no untoward effects in group A and B respectively, except for one case in group B

This was statistically insignificant with 'p' value of 0.51

Discussion

While selecting neuromuscular blockade agent for intubation or skeletal muscle relaxation, main aim of an

Anesthesiologists is to select an agent with rapid onset, excellent intubating conditions, better haemodynamic stability and good spontaneous reversal. Cisatracurium is one such non depolarizing muscle relaxant, new isomer of Atracurium with greater potency and stable hemodynamics without histamine release.

Cisatracurium is a newer and infrequently used drug with wide range of intubating doses [2×ED_{95} to 8×ED_{95}] described in literature. So in the present study we used two doses [2×ED_{95} and 4×ED_{95}], to show the increased potency of the drug with desired clinical effects and to avoid any adverse effects associated with increased/decreased dosage of any drug.

In present study, we clinically compare between two doses 0.1mg/kg [2×ED_{95}] and 0.2mg/kg [4×ED_{95}] of non depolarizing benzylisoquinolinium muscle relaxant Cistracurium with respect to its intubating conditions, hemodynamic response and any untoward effects.

The above non equipotent doses of the drugs were selected because as many studies were not done and to know the efficacy of the drug at minimal possible doses.

To avoid discrepancy between two groups, similar anesthetic techniques were employed. 60 patients were randomly divided into 2 groups of 30 each.

Group A: Included patients receiving 0.1mg/kg Cisatracurium.

Group B: Included patients receiving 0.2mg/kg Cisatracurium.

Both doses of the drug were compared for the following parameters:

- Intubating condition at fixed time 120 seconds.
- Hemodynamic response.
- Untoward effects.

The results obtained were noted and data for different parameters analyzed sequentially.

Intubating conditions

In the present study, intubation was done at the end of 2minutes after study drug administration. It was graded as excellent, acceptable, unacceptable based on the degree of jaw relaxation, vocal cord movement, resistance to laryngoscopy, limb movements, and coughing.

Excellent intubating conditions were seen in 3% and 60% of patients in group A and group B respectively.

Intubating conditions were excellent with Cisatracurium in group B: "p" value 0.01 Our findings are in consonance with Carrol MT, Mirakhur RK, *et al* (1998) who found that the increasing the dose of cisatracurium from 0.1 to 0.15mg/kg increased the excellent intubations from 17% to 54% [9].

Bluestein LS, Stinson LW, *et al* (1996) concluded that by increasing the dose of cisatracurium from 0.1 to 0.2mg/kg provides good to excellent intubation conditions could be achieved earlier (2 min vs 1.5min) [10].

Littlejohn IH, Abhay K, *et al* (1995) suggested that Cisatracurium provided acceptable intubating conditions at 2 min following 0.15mg/kg and at 1.5 min following 0.2mg/kg [11].

Mandal.P, *et al* (2002) conducted a study to find out the minimum possible dose of Cisatracurium for achieving excellent to good intubating conditions and suggests that a higher dose of Cisatracurium 0.25mg/kg (5times ED95 dose) provides excellent to good intubating conditions faster [12].

Schmautz E, Deriaz H, *et al* (1994) concluded that doses of 0.15 mg/ kg (3times ED95) and 0.2 mg/kg (4times ED95) of Cisatracurium produce generally good or excellent conditions of intubation in 2.0 and 1.5 min, respectively [13].

A. M. El-Kasaby, H. M. Atef, *et al* (2010) who observed that 4times ED_{95} dose and 6times ED_{95} doses of cisatracurium showed excellent and good intubating conditions compared to 2times ED_{95} dose. (2 min after administering the drug) [14].

Houman Teymourian, *et al* (2014) observed that 4times ED_{95} and 6dose ED_{95} dose of Cisatracurium provide more effective and rapid neuromuscular blocking effect compared to 2times ED_{95} dose at 90 seconds [15].

Prakash Jammar, *et al* (2017) observed good to excellent intubating conditions at 2 minutes following 0.15mg/kg and 0.2mg/kg of cisatracurium [16].

All these study findings correlate well with this study.

Hemodynamic responses

In our present study mean pulse rate, SBP, DBP and MAP changes were noted at 1min, 2min, 3min and 5min after the muscle relaxant Cisatracurium was administered.

In our study, basal resting mean pulse rate and MAP was comparable between

Group A and B and were statistically insignificant.

When compared between the two groups, change in the mean pulse rate and MAP at 1min, 2min and 5min were comparable and statistically insignificant.

But the change in mean pulse rate and MAP at 3min after study drug administration showed much greater change in group A compared to group B and were statistically significant.

El-Kasaby AM, H. M. Atef, *et al*. [14] (2010) stated that hemodynamic stability for both HR and MAP response were more evident among higher doses of Cisatracurium (4 timesED95 dose and 6times ED95 dose).

Agavelian EG and Arkharova TB (1999) reported that Cisatracurium in a dose of 0.15 mg/kg did not produce fluctuation in hemodynamic parameters [17].

Taivainen. T *et al*, Shahram. A *et al*. (1995) who observed the hemodynamic effects of cisatracurium and showed that, group B (0.2 mg/kg=4×ED95) found to be hemodynamically more stable than group A (0.15 mg/kg=3×ED95) [18, 19].

Schramm NM, Papousek A, *et al* (1998) stated that after Cisatracurium (0.15mg/kg), MAP and HR did not change significantly and no release of histamine was observed [20].

Correa. C.M, *et al* (2010) [21] reported in their study that 0.2mg/kg of Cisatracurium did not cause significant reduction in mean blood pressure and mean pulse rate.

Houman Teymourian, *et al* (2014) [15] observed that there was no significant changes in MAP and HR in patients receiving 0.3mg/kg and 0.4mg/kg of Cisatracurium.

Prakash Jammer, *et al* (2017) showed that hemodynamic stability maintained better with group B receiving 4 times ED_{95} dose compared to group A patients receiving 3 times ED_{95} dose [16].

Untoward effects

In our study, patients were monitored for any signs of histamine release clinically through skin changes graded as flush, erythema, wheals or broncospasm.

None of the patient in group A and B showed signs of

histamine release.

Only one patient in group A presented with laryngospasm due to inadequate laryngeal muscle relaxation. The difference was statistically insignificant.

El-Kasaby AM, H. M. Atef, *et al* (2010) reported that no histamine release signs were noted in many doses of cisatracurium [5].

Bluestein LS, Stinson LW, *et al* (1996) reported that flushing occurred in 2out of 20 patients treated with Atracurium (0.5mg/kg) and in no 60 patients treated with Cisatracurium [10].

Jean-Yves Lepage, Jean-Marc Malinovsky, *et al* (1996) reported that there were no plasma histamine concentration changes during the initial five minutes after administration of Cisatracurium at doses up to 5times the ED95 dose injected over 5-10 seconds. No cutaneous flushing or bronchospasm was noted [3].

Cynthia A. Lien, Matthew R. Belmont, *et al* (1995) stated that no cutaneous flushing was noted after rapid injection of Cisatracurium doses up to 8×ED95 [4].

Littlejohn IH, Abhay K, *et al* (1995) concluded that there was no clinical evidence of histamine release in the groups receiving different doses of Cisatracurium as compared to 2/19 patients who had cutaneous flushing following the administration of Atracurium (0.5mg) [11].

Prakash Jammer,*et al* (2017), observed that there was no signs of histamine release with 3times ED_{95} and 4times the ED_{95} dose of Cisatracurium [16].

All the above studies correlates with our study.

Conclusion

Cisatracurium, a relatively new drug, rarely used in Indian scenarios, has wide range of intubating doses. To evaluate the potent doses of Cisatracurium with desirable clinical effect, lower doses of Cisatracurium were used in the study with different doses.

Cisatracurium at a higher dose (4× times theED95 dose) provide with excellent intubating conditions, stable hemodynamic status with no signs of histamine without clinically significant changes in HR and MAP.

Hence Cisatracurium, though more costly, is more effective and a better isomer of Atracurium.

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

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