International Journal of Medical Anesthesiology

E-ISSN: 2664-3774
P-ISSN: 2664-3766
www.anesthesiologypaper.com
IJMA 2020; 3(1): 122-126
Received: 24-11-2019
Accepted: 28-12-2019

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A prospective randomized comparative study of the efficacy of atracurium and cisatracurium during general anaesthesia

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DOI: https://doi.org/10.33545/26643766.2020.v3.i1b.80

Abstract
Introduction: The neuromuscular blocking drugs (NMBDs) has revolutionized the management of balanced General Anaesthesia (GA). Atracurium and Cisatracurium are intermediate-acting muscle relaxants without any much side effects and recovery due to non-organ dependent elimination.
Aim: To compare the efficacy of Atracurium and Cisatracurium in general anaesthesia with endotracheal intubation.
Methods: In this prospective randomized comparative study 156 patients who fulfilled the eligibility criteria were systematically randomized into two groups of 78 each, Group. A (Atracurium) and Group B (cisatracurium). Patients' duration of surgery, vital parameters, intubation score were recorded.
Results: Cisatracurium Besylate subjects had a mean onset time of 165.95 seconds, mean duration of action of 57.41 minutes and mean recovery time of 121.62 minutes. Similarly group Atracurium Besylate subjects had a mean onset time of 196.95 seconds, mean duration of action of 34.58 minutes and mean recovery time of 150.65 minutes. Cisatracurium Besylate subjects had a mean jaw relaxation score of 2.90, mean vocal cord score of 2.77, mean intubation response score of 2.85 and mean intubating score of 8.51. Similarly, group Atracurium Besylate subjects had a mean jaw relaxation score of 2.55, mean vocal cord score of 2.42, mean intubation response score of 2.43 and mean intubation score of 7.38. There were no adverse drug reactions observed in both groups
Conclusion: Cisatracurium with lesser side effects and a better hemodynamic profile is safe and more efficacious as compared to atracurium.

Keywords: Atracurium, cisatracurium, general anesthesia, neuromuscular block

Introduction
Neuromuscular blocking drugs are widely used in anesthesia and intensive care to provide. Skeletal muscle. Paralysis. Neuromuscular effects are required to produce immobility during surgery, to improve ventilation and to facilitate airway management [1]. Cisatracurium is a new intermediate duration, non-depolarizing, benzylisoquinolinium neuromuscular blocking drug which 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 up to 0.4mg/kg (8×ED95) [2, 3].
The recommended intubating dose is 0.15mg/kg (3×ED95) & higher. Higher doses of Cisatracurium 0.2mg/kg and 0.3mg/kg provide more effective, more rapid neuromuscular blocking with longer duration of action, stable hemodynamic status and no signs of histamine release [4-6].

Aim
To compare the efficacy of Atracurium and Cisatracurium in general anaesthesia with endotracheal intubation.

Materials and Methods
It is a comparative prospective randomized single-blinded control study. The study was approved by the ethical committee and conducted during the period between December 2017 to May 2018 in the Department of Anesthesiology, Government Kilpauk Medical College, and Chennai. The surgeon was also duly informed of the study.

Inclusion Criteria

1. Patients undergoing elective surgeries under general anesthesia Age between 18 to 50years
2. Males and females
3. ASA class 1 and 2
4. Patients who have given valid informed consent

Exclusion *Criteria*

1. Patients not satisfying inclusion criteria.
2. Uncooperative patients
3. Patients with the disorder of cardiovascular, hepatic, renal or neuromuscular systems.

156 patients who fulfilled the eligibility criteria were enrolled for the study. Preoperatively informed, written consent was obtained from these patients. These patients were systematically randomized into two groups of 78 each. Group. A (Atracurium) and Group B (cisatracurium).

In all patients, age, baseline vital parameters were recorded. History regarding previous anaesthesia, surgery, any significant medical illness medications and allergy were recorded. Complete physical examination and airway assessment were done. Haemoglobin% Urine- Albumin and sugar, packed cell volume Bloodurea, sugar, creatinine, Liver Function Tests, E.C.G and X-Ray Chest laboratory investigations were done.

The patient was premedicated with Inj. Glycopyrrolate 0.2mg, Inj. Midazolam 1mg iv, Inj. Fentanyl 100mcg iv preoxygenated for 3 minutes and then induced with Inj. Propofol 2mg/kg given over 60 seconds. Following the loss of consciousness, the ulnar nerve was stimulated at the wrist using a peripheral nerve stimulator. The current strength was progressively increased and the single twitch elicited. When the maximal thumb adduction was obtained the current strength was noted and one and half times the strength was used for the elicitation of Train of Four Stimulus. The HR and B.P. with supramaximal stimulus were noted. A bolus IV dose of Atracurium (0.5mg/kg) or Cisatracurium 0.3mg/kg was given. The patient was ventilated with 100% oxygen. TOF was elicited every 10 seconds and the trachea was intubated after attaining TOF score "0" with appropriate size endotracheal tube after direct laryngoscopy. The endotracheal tube was secured after confirming bilateral air entry. The conditions of intubation were evaluated and scored according to the scoring system described by Cooper *et al*.

The time from the end of injection of the relaxant to the time when all four responses of TOF were abolished was taken as onset time. After intubation and observation of the intubating conditions and haemodynamic profiles, anaesthesia was maintained with 33.3% oxygen and 66.7% nitrous oxide and sevoflurane 1% using a closed-circuit system with controlled ventilation. Neuromuscular function was monitored using TOF stimuli every 15minutes. The interval between the administration of the bolus dose of the relaxant and the reappearance of the two responses to TOF was taken as the duration of action.

Statistical Analysis was done by Statistical Package for Social Sciences (SPSS Version 16.0) statistical analysis software. The values were represented in number (%) and mean ± standard deviation. Suitable statistical tests of comparison were done. Continuous variables were analysed with the unpaired t-test. Categorical variables were analysed with the Chi-Square Test and Fisher Exact Test. Statistical significance was taken as $P < 0.05$.

Results

In the group, Atracurium Besylate majority were in 31-40 years age category (41.03%) with a mean age of 36.79 years. (p= 0.388). In the Cisatracurium Besylate group, 52.56% of subjects were males and in the group, Atracurium Besylate both males and females were equally distributed (50.00%) (p= 0.751).

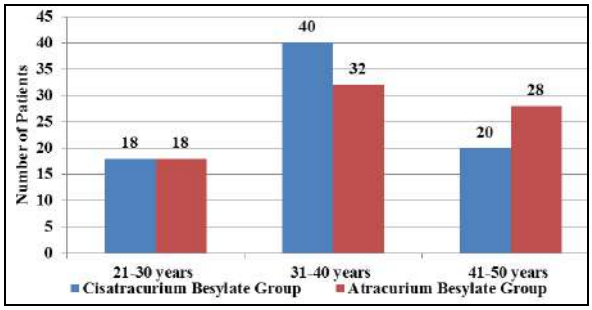

Fig 1: Distribution of Age group

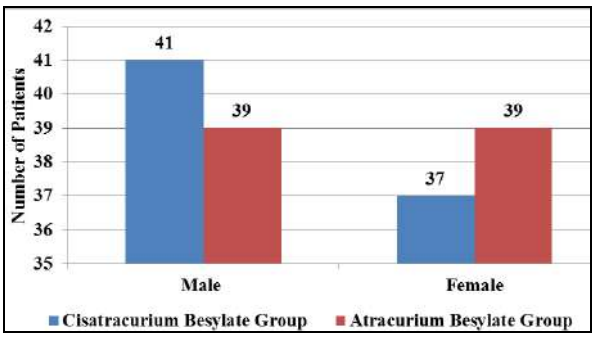

Fig 2: Distribution of Gender

In Cisatracurium Besylate group, subjects were in the 51-60 kgs weight category (73.08%) with a mean weight of 56.54 kgs. In the group, Atracurium Besylate majority were in the 51-60 kgs weight category (67.95%) with a mean weight of 56.59 kgs. (p=0.944).

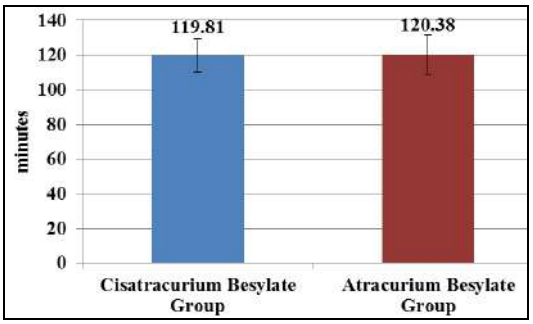

Fig 3: Distribution of Duration of Surgery

In the Cisatracurium Besylate group, subjects were in the 91-120 mins duration category (80.77%) with a mean duration of 119.81 mins. In the group, Atracurium Besylate majority were in the 91-120 mins duration category (73.08%) with a mean duration of 120.38 mins. (p= 0.944).

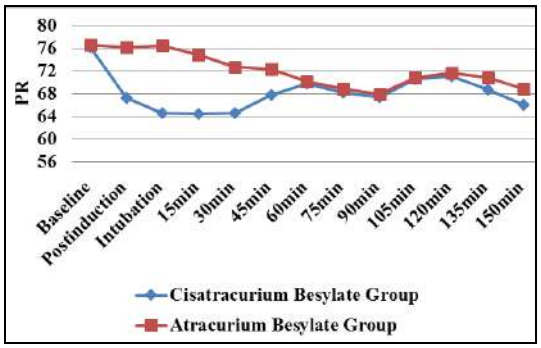

Fig 4: Distribution of Pulse rate

The intraoperative pulse rate distribution table that group Cisatracurium Besylate subjects had 68.20 bpm and group Atracurium Besylate subjects had 72.16 bpm.

The intraoperative systolic BP distribution table that group Cisatracurium Besylate subjects had an overall mean of 126.10 mm Hg and group Atracurium Besylate subjects had an overall mean of 130.64 mm Hg.

The intraoperative diastolic BP distribution table that group Cisatracurium Besylate subjects had an overall mean of 57.76 mm Hg and group Atracurium Besylate subjects had an overall mean of 59.19 mm Hg.

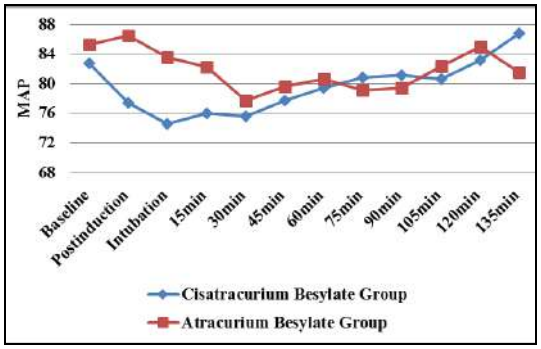

Fig 5: Distribution of MAP

The intraoperative MAP distribution table that group Cisatracurium Besylate subjects had an overall mean of 79.67 mm Hg and group Atracurium Besylate subjects had an overall mean of 59.19 mm Hg.

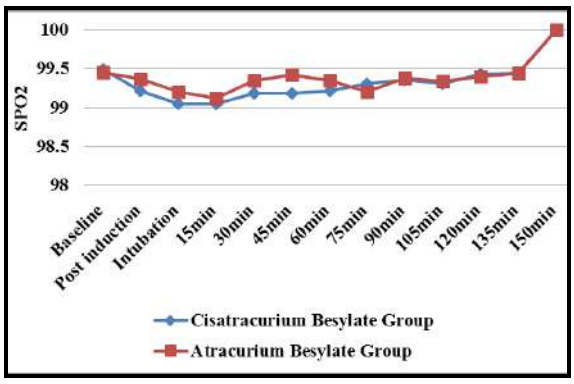

Fig 6: Distribution of SPO2

The intraoperative SPO2 distribution table that group Cisatracurium Besylate subjects had an overall mean IO SPO2 of 99.33% and group Atracurium Besylate subjects had an overall mean IO SPO2 of 99.39%.

Table 1: Distribution of anesthetic effects

Anaesthetic Effects	Cisatracurium Besylate Group		Atracurium Besylate Group		P-value
	Mean	SD	Mean	SD	
Onset Time (seconds)	165.95	17.92	196.95	13.05	<0.001
Duration of Action(minutes)	57.41	2.37	34.58	2.92	<0.001
Recovery Time (seconds)	121.62	11.49	150.65	29.84	<0.001

The anesthetics effects table that group Cisatracurium Besylate subjects had a mean onset time of 165.95 seconds, mean duration of action of 57.41 minutes and mean recovery time of 121.62 minutes. Similarly, group Atracurium Besylate subjects had a mean onset time of 196.95 seconds, mean duration of action of 34.58 minutes and mean recovery time of 150.65 minutes.

Table 2: Distribution of Intubation Scoring

Intubation Scoring	Cisatracurium Besylate Group		Atracurium Besylate Group		P-value
	Mean	SD	Mean	SD	
Jaw Relaxation	2.9	0.31	2.55	0.5	<0.0001
Vocal Cords	2.77	0.42	2.42	0.5	<0.0001
Intubation Response	2.85	0.43	2.43	0.5	<0.0001
Intubation Score	8.51	0.94	7.38	1.1	<0.0001

The intubation scoring table that group Cisatracurium Besylate subjects had a mean jaw relaxation score of 2.90, mean vocal cord score of 2.77, mean intubation response score of 2.85 and mean intubation score of 8.51. Similarly, group Atracurium Besylate subjects had a mean jaw relaxation score of 2.55, mean vocal cord score of 2.42, mean intubation response score of 2.43 and mean intubation score of 7.38.

Discussion

Two non-depolarizing muscle relaxants of the intermediate duration of action, atracurium and cisatracurium besylate were compared in this study in terms of onset of action, duration of action first dose and recovery. Hemodynamic parameters including systolic blood pressure, diastolic blood pressure, mean arterial pressure and heart rate were monitored every 15 minutes till the end of the surgical procedure. The onset time and duration of the neuromuscular blockade were studied by electrical nerve stimulation. The most commonly used pattern of electrical nerve stimulation for evaluation of neuromuscular function is the train-of-four. The study was conducted by using the peripheral nerve stimulator NS- 100 to elicit TOF response and visual recording of the evoked responses were made.

The time from the end of injection of the relaxant to the time when all four responses of TOF were abolished was taken as onset time. Neuromuscular function was monitored using TOF stimuli every 5minute after giving the bolus dose of the relaxant. The interval between the administration of the bolus dose of the relaxant and the reappearance of the two responses to TOF was taken as the duration of action.

The speed of onset is directly proportional to the potency of non-depolarizing neuromuscular blocking agents. In previous studies, it was concluded that atracurium in 2xED95 dose has a faster onset of action as compared to cisatracurium 4xED95. Cisatracurium in higher doses will presumably have a faster onset of action as compared to atracurium.

In our study mean onset of action in the cisatracurium group (6x ED95) was 2.46 minutes as compared to 3.17 minutes in the atracurium group (2xED95) which was statistically significant. In the other study by M. El-kasa by *et al*., [4] where 3 doses of cisatracurium were compared, it was observed that the onset of action was significantly faster with higher doses of cisatracurium when compared to atracurium. M.T. Carroll *et al*. also had similar observations in their study [7]. In another study conducted by Bluestein and colleagues, similar results were observed. Neuromuscular block was continuously monitored every 15 minutes until the end of the procedure. The maximum duration of action of atracurium is likely to be about 25-30 minutes and 30-35 minutes for cisatracurium. In our study mean duration of action after the first dose of atracurium is 35 minutes with a dose of 0.5 mg/kg and 57 minutes for cisatracurium with a dose of 0.3mg/kg which was more and statistically significant when compared to atracurium. Similar observations were found in studies done by M.El-kasaby *et al*. and Bluestein & colleagues [4, 8].

In our study, the intubation score for tracheal intubating conditions was based on the degree of jaw relaxation, vocal cord movement, and intubation response. From our observations, the mean intubation score was 8.5 for cisatracurium besylate and 7.38 for atracurium besylate which was clinically significant. Cisatracurium besylate in higher doses gives better intubating conditions than atracurium besylate. The decrease in plasma concentration of neuromuscular blocking drugs which partly occurs due to redistribution determines the recovery from neuromuscular blocking drugs. It is dependent upon the drug elimination than distribution.

Anticholinesterase administration contributes to the recovery of neuromuscular function by antagonism of anticholinesterase at NMJ and secondly by the natural decrease in plasma concentration of the drug. In our study, reversal was achieved with neostigmine in both group A and group B and results were comparable and statistically significant. In our the study, meantime of recovery after giving reversal was 121 seconds with patients receiving cisatracurium besylate compared to 150.6 seconds with patients receiving atracurium besylate which was significant. Adequate reversal was clinically assessed by sustained head lift, handgrip for 5 seconds, spontaneous eye-opening, protrusion of tongue, normal tidal volume and maximum inspiratory pressure 40-50cm H_2O or greater was confirmed and patient was shifted Mellingh off, Hermann MD *et al*. [9] conducted study in which continuous infusion for a constant neuromuscular block was given at the rate of 1.5 ±0.4 (range, 1-3) mg kg-1min-1and 6.6 ±1.7 (range, 3-11) mg kg-1 min-1 for Cisatracurium and Atracurium, respectively. It was observed that after continuous infusion of NMBA recovery was almost identical between atracurium and cisatracurium Bergeron *et al*. in his study while comparing 3 different doses of cisatracurium 0.05mg/kg,0.15mg/kg and 0.3 mg/kg; observed that onset time was not significantly different between the doses in adults, but recovery time increased, 23, 24 and 26 minutes respectively Shang Guan in his study, reported that with the increasing doses of NMBA, the duration of clinical action was prolonged and the risk of postoperative residual block increases. Cisatracurium is four times more potent as compared to atracurium and does not cause histamine release which indicates that the phenomenon of histamine release is stereospecific. In our study, we did not notice any signs of histamine release in both groups. M. El–kasaby *et al*. in his study has observed that hemodynamic stability for both heart rate and mean arterial pressure was more evident even with higher doses of cisatracurium [4].

Similarly in our study better hemodynamic stability was observed with the cisatracurium group. Yazdanian F *et al*. [10] in his study has reported that there were comparable hemodynamic effects between atracurium and cisatracurium, but atracurium was more cost-effective. The use of muscle relaxants has common adverse reactions such as any cardiovascular effects, allergic reactions and inadequate reversal as safety issues. Laudanosine, one of the major metabolites of atracurium has a central nervous system stimulating property and cardiovascular effects which includes mainly bradycardia and hypotension. Peak plasma concentration of Laudanosine occurs 2 minutes after IV injection of atracurium and 75% peak occurs at 15 minutes. Laudanosine is mainly eliminated by the kidney and liver. Plasma concentration of Laudanosine after a single dose of Atracurium 0.5mg/kg is higher in patients with renal failure when compared to normal patients. Cisatracurium besylate cis isomer of atracurium besylate has five times less production of laudanosine which might be the cause of lesser side effects.

In a study conducted by Shang guan *et al*., it was observed that cisatracurium even with higher doses (8x ED95) did not have sins of histamine release and no significant hemodynamic effects. In our study with the dose of cisatracurium (6xED95), there were no signs of histamine release and a better hemodynamic profile. Similar observations were made in the study by A. M. El-Kasaby *et al*. Basta SJ *et al*. in his study had observed that atracurium in doses of 0.5mg/kg or more when administered rapidly releases histamine and when the plasma level of histamine increases over 1000pg/ml transient decrease in blood pressure, facial erythema may be noted. This phenomenon can be attenuated by injecting the drug slowly over 30 to 60 seconds [4, 11].

Conclusion

Cisatracurium is a dose of 0.3mg/kg had a faster onset time and prolonged duration of action as compared to Atracurium (0.5mg/kg) better intubating conditions were observed with Cisatracurium group as compared to Atracurium group. Significant hemodynamic stability was observed with the Cisatracurium group. There were no adverse drug reactions observed in both groups.

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