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Original Article

Comparision of Atracurium Versus Cisatracurium Regarding Onset Time, Intubating Conditions and Haemodynamic Parameters During General Anaesthesia

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Abstract

Introduction: Cisatracurium unlike atracurium is devoid of histamine-induced cardiovascular effects and this would be the greatest advantage in replacing atracurium for the facilitation of endotracheal intubation.

Aim: The aim of the study was to compare the effectiveness of atracurium 0.5 (2 ED_{95}) mg/kg IV versus two different doses of cisatracurium, i.e., 0.1 (2 ED_{95}) and 0.15 (3 ED_{95}) mg/kg IV for intubation with regard to onset time for intubation, intubing conditions, duration of blockade, and hemodynamic parameters.

Materials and Methods: In this study, 150 patients of the American Society of Anesthesiologists Grades 1 and 2 undergoing elective surgeries under general anesthesia were taken up and divided into three groups of 50 each by computer-generated randomization. Group A received Inj. atracurium besylate 0.5 mg/kg IV, Group B received Inj. cisatracurium besylate 0.1 mg/kg IV, and Group C received Inj. cisatracurium besylate 0.15 mg/kg IV.

Results: The three groups were compared regarding the onset of blockade, duration of blockade, condition of intubation, hemodynamic effects, and results analyzed.

Conclusion: Cisatracurium 0.15 mg/kg provides excellent intubating conditions with rapid onset of action, with longer duration of action and no significant hemodynamic changes when compared with cisatracurium 0.1 mg/kg and atracurium 0.5 mg/kg and hence cisatracurium 0.15 mg/kg can be used as an ideal non-depolarizing muscle relaxant for intubation.

Key words: Atracurium, Cisatracurium, General anesthesia, Intubation

INTRODUCTION

Endotracheal intubation is an integral part of the administration of general anesthesia during the surgical procedure. Succinylcholine, introduced by Thesleff and associates in 1952, a depolarizing muscle relaxant with rapid onset of action and short duration is still the relaxant of choice to facilitate tracheal intubation. However, in addition to fasciculations, succinylcholine has many side effects such as bradycardia, dysrhythmias, increased release of potassium, post-operative myalgia, increased intra ocular pressure, intracranial tension, intragastric pressure, prolonged recovery in patients with pseudocholinesterase deficiency, masseter spasm, and triggering malignant hyperthermia.[1-6] Since these side effects are due to the depolarizing mechanism of action of succinylcholine, search has been focused onto find an ideal non-depolarizing muscle relaxant (NDMR) with rapid onset time and offering excellent intubating conditions.

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Classification of non-depolarizing muscle relaxants:

	Long-acting (>50 min)	Intermediate-acting (20–50 min)	Short-acting (10–20 min)
Steroidal compounds	Pancuronium	Vecuronium Rocuronium	
Benzylisoquinolinium compounds	Tubocurarine	Atracurium Cisatracurium	Mivacurium

Cisatracurium is one of the 10 isomers of atracurium. The neuromuscular blocking potency of cisatracurium is approximately three-fold that of atracurium besylate. Cisatracurium has ED_{95} of 50 μg/kg and atracurium has ED_{95} of 0.2 mg/kg. The principal advantage of cisatracurium is lack of histamine release, which provides better cardiovascular stability in comparison to atracurium and other histamine-releasing neuromuscular blocking agents. Hence, these two drugs are compared in this study.

Aim of the Study

The aim of the study was to compare the effectiveness of atracurium 0.5 (2 ED_{95}) mg/kg IV versus two different doses of cisatracurium, i.e., 0.1 (2 ED_{95}) and 0.15 (3 ED_{95}) mg/kg IV for intubation following induction with etomidate (0.3 mg/kg), with regard to

- Onset time for intubation
- Intubating conditions
- Duration of blockade
- Hemodynamic parameters.

MATERIALS AND METHODS

Adult patients of both sexes in the age group of 18–60 years belonging to the American Society of Anesthesiologists (ASA) I/II posted for various surgeries requiring genera anesthesia at Rangaraya Medical College, Government General Hospital Kakinada were taken up for the study. The study was a prospective randomized double-blind study.

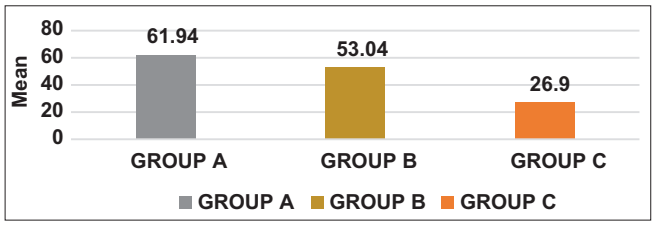

Figure 1: Distribution of study participants based on train-of-four % AT 60 s

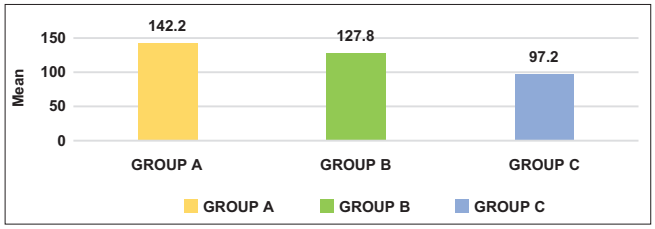

Figure 2: Comparison of time to maximum blockade between three groups

The study was performed after obtaining the Institutional Ethical Committee approval. Pre-study assessment was done, procedure explained and informed consent obtained, and patients requiring general anesthesia were randomly allocated into three groups based on computer-generated randomization.

Groups:

1. Group A: Fifty patients receiving Inj. atracurium besylate 0.5 mg/kg IV
2. Group B: Fifty patients receiving Inj. cisatracurium besylate 0.1 mg/kg IV
3. Group C: Fifty patients receiving Inj. cisatracurium besylate 0.15 mg/kg IV.

Patient Selection

Inclusion criteria

A total of 150 patients of ASA Grades I and II of age between 18 and 60 years of both genders posted for elective surgery requiring general anesthesia with endotracheal intubation without any comorbid illness are included in this study.

Exclusion criteria

The following criteria were excluded from the study:

- ASA Grade – III and Grade – IV
- Mallampati Grade – III and mallampati Grade – IV
- Anticipated difficult airway
- Comorbid systemic conditions, i.e., cardiovascular system, hepatic, and renal impairment along with neuromuscular disorders
- Patients who are on aminoglycosides, $MgSO_4$
- Known history of allergy to any of the study drugs
- Pregnant women.

Monitoring

Heart rate (HR), systolic blood pressure (SBP), diastolic blood pressure (DBP), mean arterial pressure (MAP), SPO_2, five lead electrocardiogram (ECG), and train-of-four (TOF)-Watch SX 100 were recorded with space labs multipara monitor in the operating room.

Methodology

Preanesthetic evaluation and counseling for surgery were done the day before surgery and reviewed on the day of surgery. A detailed medical history was taken and systemic examination carried out and relevant investigations advised.

Table 1: Distribution of study groups based on demographic data

	Group A	Group B	Group C	*P*-value
Age (mean±standard deviation)	36.16±9.90	35.86±9.76	34.9±9.59	0.79
Sex (M: F)	25:25	23:27	26:24	0.83
Weight (kg)	59.84±7.1353	58.18±7.0093	59.94±7.04	0.37

Demographic data are not significant as *P*>0.05

An informed written consent was taken from all the patients and was informed about known effects, and side effects of study drug and consent are taken for the study.

The night before surgery tab. Diazepam 5 mg was given. On the day of surgery in operation theater,

1. IV line secured with 18G canula
2. All the ASA monitors such as ECG, non-invasive blood pressure, SpO_2, end-tidal carbon dioxide ($EtCO_2$), and temperature were connected
3. All baseline parameters noted such as HR, SBP, DBP, MAP, and SpO2 were noted.

Premedication

All patients are given Inj. glycopyrrolate. 2 mg IV, Inj. ondansetron. 1 mg/kg IV, Inj. ranitidine 50 mg 1 h before surgery, Inj. fentanyl 1 μg/kg, and Inj. phenergan 0.5 mg/kg IM 45 min before surgery.

Preoxygenation

It is done with 100% O_2 for 3 min.

- TOF–Watch SX 100 nerve stimulator attached.

TOF Watch SX turned on. Once the current and twitch height were standardized, instrument switched to TOF mode where supra maximal TOF stimuli are applied to ulnar nerve every 15 s. Calibration and baseline responses obtained before administering the neuromuscular blocking drug (NMBD). Randomization was done on computer-generated lottery method.

All patients received priming dose ($1/10^{th}$ of the bolus dose) of the study drug according to the allocated group,

- Group A: Received priming dose of atracurium (i.e., 0.05 mg/kg)
- Group B: Received priming dose of cisatracurium (i.e., 0.01 mg/kg)
- Group C: Received priming dose of cisatracurium (i.e., 0.015 mg/kg).

Just before induction to shorten the onset time.

Induction

Induction of general anesthesia for all patients was done with Inj. Etomidate 0.3 mg/kg with loss of eyelash reflex/loss of verbal response considered to be the endpoint of induction. This was followed by an intubating dose of study drug, i.e., NDMR, over 5 s

- Group A received remaining bolus of an intubating dose of atracurium (0.45 mg/kg)
- Group B received remaining bolus of an intubating dose of cisatracurium (0.09 mg/kg)

Table 2: Distribution of study participants based on train-of-four % AT 0 s

Groups	Mean±standard deviation	*P*-value
A	104.73±5.365	0.577
B	103.4±3.225	
C	105.27±5.958	

P=0.577 not significant

Table 3: Distribution of study participants based on train-of-four % AT 30 s

Groups	Mean±standard deviation	*P*-value
A	71.94±4.98	0.001
B	73.96±5.29	
C	68.92±6.64	

P<0.05 significant

Table 4: Distribution of study participants based on train-of-four % AT 60 s

Groups	Mean±standard deviation	*P*-value
A	61.94±4.6397	0.001
B	53.04±4.4307	
C	26.9±7.2005	

P=0 is significant

Table 5: Distribution of study participants based on train-of-four % AT 90 s

Groups	Mean±standard deviation	*P*-value
A	35.00±7.60	0.001
B	26.86±7.22	
C	8.54±7.68	

P=0 is significant

Table 6: Distribution of study participants based on train-of-four % AT 120 s

Groups	Mean±standard deviation	*P*-value
A	24.82±6.26	0.001
B	9.56±8.10	
C	1.32±1.99	

P=0 is significant

- Group C received remaining bolus of an intubating dose of cisatracurium (0.135 mg/kg).

TOF–Watch SX showed TOF ratio as percentage and results recorded at 30 s interval.

Time to Maximum Blockade

- Time interval between administration of the dose of relaxant and disappearance of all four twitches in TOF monitor
- Intubation was done when the TOF ratio was 0%
- Assessment of intubation was done by scoring system given by Cooper *et al.*

Cooper *et al.*, scores

Criteria	0	1	2	3
Jaw relaxation	Complete	Moderate	Minimal	None
Vocal cord status	Open	Slight moving	Closing	Closed
Diaphragmatic status	None	Slight moving	Coughing	Bucking

Intubating conditions and time required for intubation were graded by a senior anesthesiologist blinded to group allocation. Intubation confirmed by $EtCO_2$ and connected to a ventilator for intermittent positive pressure ventilation until completion of surgery.

Maintenance

Maintenance of anaesthesia done with N_2O 60% and Sevoflurane.

Onset time and intubating conditions for atracurium and cisatracurium assessed in allocated groups, respectively. The number of attempts of intubation was assessed and compared in between three groups. Hemodynamic parameters such as HR, SBP, DBP, and MAP were recorded before induction, immediately after induction, during laryngoscopy and intubation and immediately after 1, 2, 3, 5, 10, and 15 min after tracheal intubation. After procedure patient was reversed with neostigmine (0.05 mg/kg) and glycopyrrolate (0.01 mg/kg). Any adverse events during intubation were recorded in all the three groups.

Table 7: Distribution of study participants based on train-of-four % AT 150 s

Groups	Mean±standard deviation	*P*-value
A	8.30±7.93	0.001
B	0.84±2.09	
C	0.00±0.00	

P=0 is significant

Statistical Analysis

The data are presented as mean and standard deviation. All categorical data analyzed using Fischer exact test and Chi-square test as required and continuous variables using Student's *t*-test. Value of $P < 0.05$ was considered significant. GraphPad prism version 7 (California corp.inc) was used for statistical analysis.

RESULTS

Demographic data analysed and found not significant as p value>0.05 [Table 1].

Hence, Group C provides good to excellent intubating conditions than the other two groups [Table 2-8].

Hence, Group C has a rapid onset of action than the other two groups [Table 9].

Hence, intubation time was found to be significantly faster in Group C than two other groups [Table 10 and Figure 1].

Hence, the duration of the blockade was found to be significant in Group C, which has a long duration of action than two other groups [Table 11 and Figure 2].

- Data expressed as mean±standard deviation in both groups
- $P > 0.05$ statistically not significant.

The baseline hemodynamic parameters between the three groups are not significant statistically as $P > 0.05$ [Table 12].

Baseline hemodynamic parameters (HR, SBP, DBP, and MAP) are recorded and compared between three groups. There is no significant difference between them [Table 13]. Our study found no differences in hemodynamic parameters (SBP, DBP, and MAP) between three groups.

Table 8: Comparison of intubating conditions between three groups

	Intubating conditions (Cooper *et al.*, score)					
	Excellent (0)	Good (1)	Poor (2)	Not possible (3)	Mean±standard deviation	*P*-value
Group A (*n*=50)	19	21	10	0	0.82±0.7475	0.00001
Group B (*n*=50)	20	21	9	0	0.78±0.7365	
Group C (*n*=50)	36	12	2	0	0.24±0.4314	

P=0.00001 which is <0.05 significant

DISCUSSION

In 1942, Griffith and Johnson described d-tubocurarine (dTc) as a safe drug to provide skeletal muscle relaxation during surgery.[7] In 1954, Beecher and Todd reported a six-fold increase in mortality in patients receiving dTc compared with patients who had not received muscle relaxant.[8]

In 1952, Thesleff,[9] foldes and associates,[10] introduced succinylcholine, changed anesthetic practice drastically because the drug's rapid onset of effect and ultrashort duration of action allowed for both rapid endotracheal intubation and rapid recovery of neuromuscular strength.

In 1967, Baird and Reid first reported on the clinical administration of the first synthetic aminosteroid, pancuronium.[11] The development of the intermediate-acting NMBDs built on the compounds metabolism and resulted in the introduction of vecuronium,[12] an aminosteroid, and atracurium,[13] a benzylisoquinolinium, into clinical practice in the 1980s. Vecuronium was the first muscle relaxant to have an intermediate duration of action and minimal cardiovascular actions. Mivacurium, the first short-acting non-depolarizing NMBD, was introduced into clinical practice in the 1990s,[13] as was rocuronium,[14] an intermediate-acting non-depolarizing blocker with a very rapid onset of neuromuscular blockade. These include pipecuronium, doxacurium, cisatracurium, and rapacuronium. Although all do not remain in use, each represented an advance or improvement in at least one aspect over its predecessors.

Endotracheal intubation is an integral part of the administration of general anesthesia during the surgical procedure.

Succinylcholine, a depolarizing muscle relaxant with rapid onset of action and short duration, is still the relaxant of choice to facilitate tracheal intubation. However, in addition to fasciculations, succinylcholine has many side effects such as bradycardia, dysrhythmias, increased release of potassium, post-operative myalgia, increased intraocular pressure, intracranial tension, intragastric pressure, prolonged recovery in patients with pseudocholinesterase deficiency, masseter spasm, and triggering malignant hyperthermia.[1-6]

Since these side effects are due to the depolarizing mechanism of action of succinylcholine, search has been focused on to find an ideal NDMR with rapid onset time and offering excellent intubating conditions.

Cisatracurium is one of the 10 isomers of atracurium. The neuromuscular blocking potency of cisatracurium is approximately three-fold that of atracurium besylate. Cisatracurium has ED_{95} of 50 μg/kg and atracurium has ED_{95} of 0.2 mg/kg. The principal advantage of cisatracurium is lack of histamine release which provides better cardiovascular stability in comparison to atracurium and other histamine-releasing neuromuscular blocking agents. Hence, these two drugs are compared in this study. In this study, non-depolarizing, intermediate-acting, benzylisoquinolinium compounds atracurium and cisatracurium were chosen, and their neuromuscular function was monitored using TOF-Watch SX 100.

Table 9: Comparison of time to maximum blockade between three groups

Group	Mean±standard deviation (s)	*P*-value
A	142.2±14.504	0.001
B	127.8±14.2914	
C	97.2±14.9202	

P=0.0 which is <0.05 significant

Table 10: Comparison of intubation time between three groups

Group	Mean±standard deviation (s)	*P*-value
A	144±9.4761	0.001
B	145.2±11.292	
C	135.2±11.102	

P=0 which is significant

Table 11: Comparison of duration of blockade between three groups

Group	Mean±standard deviation (min)	*P*-value
A	43.34±3.4736	0.001
B	43.06±4.3632	
C	52.06±3.8778	

P=0 which is <0.05 significant

Table 12: Comparison of baseline hemodynamic parameters

Parameters	A *n*=50 (mean+SD)	B *n*=50 (mean+SD)	C *n*=50 (mean+SD)	*P*-value
Heart rate	76.26±6.8148	76.02±97.5119	78.16±8.1375	0.2984
Systolic blood pressure	121.22±10.1966	122.8±9.8229	123.94±9.1147	0.37514
Diastolic blood pressure	75.16±7.9651	77.78±7.4458	76.88±7.8132	0.23161
Mean arterial pressure	90.42±8.0232	92.76±7.7921	92.62±7.7746	0.25168

SD: Standard deviation

Table 13: Comparison of heart rate between the three groups

Time	Groups	HR (mean±standard deviation)	*P*-value
Base line	A	76.26±6.8148	0.29
	B	76.02±7.5119	
	C	78.16±8.1375	
During laryngoscopy	A	97.94±6.4441	0.17
	B	97.18±6.986	
	C	99.7±7.2906	
After intubation 1 min	A	95.94±6.5072	0.30
	B	96.18±7.403	
	C	97.94±7.101	
2 min	A	90.88±5.9544	0.84
	B	90.22±6.7349	
	C	90.8±6.1246	
3 min	A	78.88±6.8053	0.15
	B	78.92±7.6394	
	C	81.4±7.7985	
5 min	A	79.72±6.8662	0.68
	B	80.08±7.5643	
	C	80.98±7.746	
10 min	A	79.82±7.2272	0.92
	B	79.8±7.7728	
	C	80.2±7.9076	
15 min	A	77.26±6.8148	0.23
	B	76.22±6.2639	
	C	78.62±8.0328	

P>0.05 in all three groups. Hence, heart rate changes are not significant

Cisatracurium, the 1R *cis*–1' R *cis* isomer of atracurium, comprises approximately 15% of atracurium by weight but more than 50% in terms of neuromuscular blocking activity like atracurium, cisatracurium is metabolized by Hofmann elimination. It is approximately 4 times as potent as atracurium, and in contrast to atracurium, it does not cause histamine release, thus indicating that histamine release may be stereospecific. The principal advantage of cisatracurium is that there has been no evidence of histamine release at doses up to 8 times the ED_{95}[49], whereas atracurium causes histamine release in humans at doses greater than 2.5 × ED_{95}. The onset time or time to maximum blockade for 2 × ED_{95}, 4 × ED_{95}, 8 × ED_{95} are 5.2 min, 2.7 min, and 1.9 min, respectively, and as dose increases clinical duration also increases from 45 min, 68 min, and 91 min, respectively. The intubating dose cisatracurium is 0.15–0.2 mg/kg provides excellent intubating conditions. Doses of 0.1 mg/ kg and 0.15 mg/kg of cisatracurium are used in this study.

Laryngeal adductors are more resistant to the action of cisatracurium than adductor pollicis, but onset and recovery are faster at the larynx. Adductor pollicis is most commonly used to monitor neuromuscular blockade, ulnar nerve was used to monitor in this study.

Atracurium is a bisquaternary ammonium benzylisoquinoline compound of intermediate duration of action. Atracurium has histamine-releasing properties. Laryngeal adductors and orbicularis oculi have faster onset than adductor pollicis. An intubating dose of 2 × ED_{95} is 0.5 mg/kg onset of action is 3.2 min and clinical duration of action is 46 min. 2 × ED_{95}, i.e., 0.5 mg/kg is used this study.

To reduce the onset time priming technique has been used, when priming, a small, subparalyzing dose of the non-depolarizer (≈20% of the ED_{95} or ≈10% of the intubating dose) is administered 2–4 min before the intubating dose of the compound. This procedure accelerates the onset of blockade for most non-depolarizing NMBDs only by 30–60 s, thereby indicating that intubation can be performed within 90 s of the second dose. Hence, in this study, two equipotent doses of cisatracurium and atracurium, i.e., 2 × ED_{95} (0.1 mg/kg, 0.5 mg/kg, respectively) and 3 × ED_{95} doses of cisatracurium are compared for onset time, intubating conditions, and hemodynamic parameters.

Duggappa *et al.* have studied that the onset time of atracurium on priming with 0.05 mg/kg, i.e., $1/10^{th}$ of the intubating dose 0.5 mg/kg was 147 s.

Deepika *et al.* have studied that the onset time of cisatracurium on priming with 0.01 mg/kg and 0.015 mg/ kg, i.e., $1/10^{th}$ of the intubating dose 0.1 mg/kg and 0.15 mg/kg was found to be 126 s and 103 s, respectively.

El-Kasaby *et al.* have studied that the duration of action of 0.1 mg/kg of cisatracurium and 0.5 mg/kg of atracurium was 44 min and 43 min, respectively.

Bluestein *et al.* have studied that the duration of action of 0.1 mg/kg, 0.15 mg/kg of cisatracurium, and 0.5 mg/kg of atracurium was found to be 44 min, 55 min, and 43 min, respectively.

Teymourian *et al.* have compared modified and high dose of cisatracurium for rapid sequence intubation and found that 0.3 versus 0.4 mg/kg cisatracurium had the same effect in providing appropriate laryngoscopy condition for rapid sequence induction (RSI) after 90 s. It is safer to use 0.3 mg/kg instead of 0.4 mg/kg cisatracurium to achieve acceptable condition for RSI.

In this prospective randomized double-blind study, 150 patients satisfying selection criteria underwent general anesthesia with cisatracurium 0.1 mg/kg, 0.15 mg/kg, and atracurium 0.5 mg/kg. The onset of action, which was the disappearance of all four twitches and TOF ratio 0%, the duration of action and hemodynamic variables were assessed.

The mean onset of action or the time to maximum blockade was significantly faster in Group C (cisatracurium 0.15 mg/kg) than Group B (cisatracurium 0.1 mg/kg) than Group A (atracurium 0.5 mg/kg), the onset of action was 97 s for Group C, 128 s for Group B, and 142 s for Group A, as shown by Deepika *et al.* and Duggappa *et al.*

The mean duration of action was significantly longer in Group C (cisatracurium 0.15 mg/kg) than Group B (cisatracurium 0.1 mg/kg) and Group A (atracurium 0.5 mg/kg), the duration of action was 52 min in Group C, 43 min in Group B, and 43 min in Group A which were consistent with the El-Kasaby *et al.* and Bluestein *et al.*

The hemodynamic variables such as pulse rate, SBP, and DBP were not significantly altered in all the three groups. There were no significant changes in the hemodynamic variables during pre-operative, at the time of injecting the drug, during laryngoscopy and 1, 2, 3, 5, 10, and 15 min after laryngoscopy in all the three groups (A, B, and C) as shown in Jammar *et al.* and Amini *et al.*

No adverse reaction or complication occurred in any of the three groups.

CONCLUSION

Cisatracurium 0.15 mg/kg provides excellent intubating conditions with rapid onset of action, with a longer duration of action and no significant hemodynamic changes when compared with cisatracurium 0.1 mg/kg and atracurium 0.5 mg/kg and hence cisatracurium 0.15 mg/kg can be used as an ideal non-depolarizing muscle relaxant for intubation.

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