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Cisatracurium in different doses versus Atracurium during general anaesthesia for thyroid surgery: A comparative study

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Abstract
Background & Aim: *Cisatracurium, an isomer of atracurium is a non-depolarising neuromuscular blocking drug of intermediate duration. It is devoid of histamine release when compared to atracurium. Both drug are used in liver and kidney failure. However, 2× ED95 dose of cisatracurium may not provide satisfactory intubating condition. The objective of this study was to evaluate the intubating condition, duration of action, hemodynamic effects and any adverse effects of atracurium with different doses of cisatracurium.*
Methods: *The study was designed as randomized controlled trial in which we compared atracurium (0.5mg/kg) and different doses of cisatracurium (0.1mg/kg and 0.15mg/kg) for intubation. Sixty patients were randomly assigned to one of three groups, group A received 0.5mg/kg of atracurium, group C1 received 0.1mg/kg of cisatracurium, and group C2 received 0.15mg/kg of cisatracurium. Onset time, duration of action, condition of intubation, hemodynamic effects, and signs of histamine release were recorded.*
Results: *Onset time was found to be significantly lower with group C2 compared to group C1 and group A. At the same time, 0.15mg/kg cisatracurium produced longer duration of action compared to 0.5mg/kg atracurium and 0.1mg/kg cisatracurium.*
Conclusion: *0.15mg/kg cisatracurium can provide more effective, more rapid neuromuscular blocking with longer duration of action, stable hemodynamic status without any associated signs of histamine release.*
Keywords: *Cisatracurium, Atracurium,Hemodynamic , Histamine.*

Introduction

Rapid and safe endotracheal intubation is an integral part of administration of anaesthesia during surgical procedures. It depends upon type and degree of muscle relaxation, depth of anaesthesia and skill of anaesthesiologist. Muscle

relaxant is used to facilitate endotracheal intubation and provide surgical relaxation. The ideal neuromuscular blocking agent for intubation should have a rapid onset, brief duration of action, free from hemodynamic changes, devoid of residual paralysis and provide excellent intubating conditions like fully relaxed jaw, widely open vocal cord and absence of intubation-response.[1]

Succinylcholine, which is a depolarizing muscle relaxant, has rapid onset of action and is the gold standard muscle relaxant for rapid sequence intubation. However it has several unintended side-effects such as muscle fasciculations, thereby producing postoperative myalgia, hyperkalemia, bradycardia, dysrhythmias, rise in intraocular, intragastric, and intracranial pressure. This led to the search of newer relaxants having early onset time, excellent intubating conditions but without the side effects of succinylcholine.[2]

Many non-depolarizing neuromuscular blocking drugs were introduced in the clinical practice but they had many side effects like cardiovascular instability, occurrence of recurarisation and residual paralysis and were not suitable for use in certain clinical situations like liver and kidney disorders. Atracurium is an intermediate acting NDMR, mixture of 10 optical isomers commonly used in renal failure and liver failure.It is metabolized by Hoffmann elimination and nonspecific esterhydrolysis but It is associated with histamine release leading to hypotension and anaphylaxis.[3,4,5]

Cisatracurium is a purified form of one of the 10 stereoisomers of Atracurium with a potency of approximately 3 to 4 times greater than that of Atracurium which, unlike the parent compound is not associated with dose dependent histamine release in humans.On metabolism 5 times less laudanosine is produced.[6,7] Cisatracurium may not yield satisfactory intubating conditions such as those seen with equipotent doses of Atracurium. The recommended intubating dose of Cisatracurium is $3ED_{95}$.[8]

Hence keeping in view of the above facts,we have done a study comparing different doses of Cisatracurium with Atracurium for intubation in general anaesthesia for thyroid surgery. Onset time, condition of intubation, duration of action, degree of neuromuscular blockade, hemodynamic effects and signs of histamine release were studied.

Methods

The present clinical study was performed in S.C.B Medical College and Hospital, Cuttack during the period from November2015 to October2017. The patients, scheduled for elective thyroid surgery were included in this study. After obtaining approval from Institutional ethics committee (IEC) bearing no 523/16.09.2017 the study was done.

Patients with ASA physical status class-I and II and age-18-60 years of either sex were included in the study. Patients having hepatic, renal or neuromuscular disease, asthma, COPD, and cardiovascular diseases were excluded.

The procedure of the study was explained to all patients and informed consent for anaesthesia and the procedure was obtained. The patients were randomly allocated into 3 groups of 20 patients each to receive an intubating dose of one of the study.

Gr-A:- received intubating dose of atracurium 0.5mg/kg IV.

Gr-C1:- received intubating dose of cisatracurium 0.10mg/kg IV.

Gr-C2:- received intubating dose of cisatracurium 0.15mg/kg IV

On arrival in the operating room, non-invasive monitors like electrocardiogram (ECG), non-invasive BP, and pulse oximetry were connected to the patient. Intravenous access was achieved with an 18G cannula and infusion of crystalloid solution was started. Pre-medication:-midazolam (0.04 mg/kg IV), glycopyrrolate(0.005 mg/kg iv), nalbuphine(0.3mg/kg iv).

The patients were preoxygenated with 100% oxygen for 3 minutes. Muscle relaxants (stydy drugs) were given prior to induction. Then induction was done with propofol 2mg/kg till the

loss of eyelash reflex. The electrodes of peripheral nerve stimulator were positioned over ulnar nerve on the volar side of the wrist. The supramaximal stimulus of duration 0.2 ms and frequency 2 Hz was delivered in a train-of-four (TOF) stimulation to the ulnar nerve at the wrist via surface electrodes and the resultant four twitches of adductor pollicis muscle were observed. The onset time of the muscle relaxant was determined by measuring the time from injection of muscle relaxant to abolition of all four responses to train of four stimulus. Endotracheal intubation was carried out once maximum block achieved (all four responses are ablated) and positive pressure ventilation started.

Intubating conditions were assessed using the train of four stimuli. Intubating conditions were categorized as excellent, good, poor and not possible.[9]

Excellent: Easy passage of the tube without coughing. Vocal cords relaxed and abducted.

Good: Passage of tube with slight coughing and/or bucking. Vocal cords relaxed and abducted.

Poor: Passage of tube with moderate coughing and/or bucking. Vocal cords moderately adducted.

Haemodynamic parameters like mean arterial pressure and pulse rate were recorded at base line before intubation and at 5 min, 10min and 15 minutes after intubation.

After tracheal intubation, at every 5 minutes train of four stimulation was recorded and accordingly muscle relaxants in a maintenance dose of inj. cisatracurium0.03mg/kg and inj. atracurium 0.1mg/kg was administered and maintained.

The time interval from injection of intubating dose of muscle relaxant to the recovery of the first twitch in the train-of four was taken as the duration of action, which were recorded and compared in three groups. After the end of operative procedure the reversal was done with inj. Neostigmine and inj. Glycopyrrolate after appearance of all the four twitches of TOF and extubation was done.

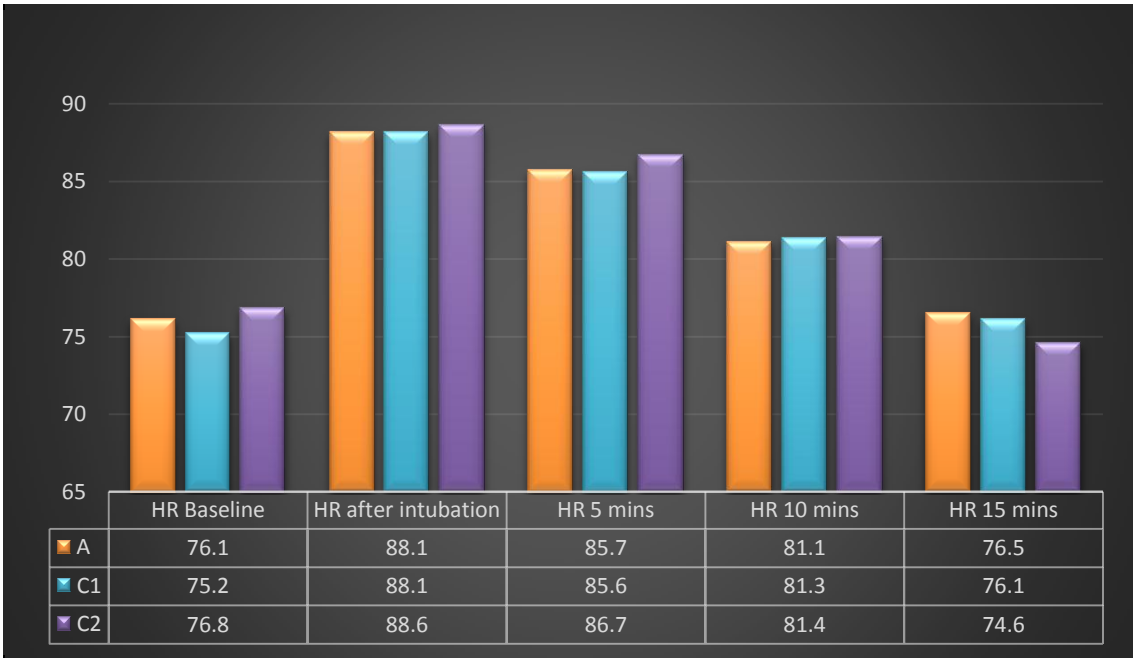
Statistical Analysis

Data were statistically analyzed using SPSS version 21.Sample size was calculated by Power analysis. Quantitative data were expressed as Mean±SD. Qualitative data were expressed as numbers and percentages. Anova test were used to test significance. P-value) <0.05 was considered statistically significant.

Results

There are no statistical differences with respect to age,sex and weight. (p>0.05) in the three groups.

Figure 1: Heart rate changes before and after administration of atracurium and cisatracurium

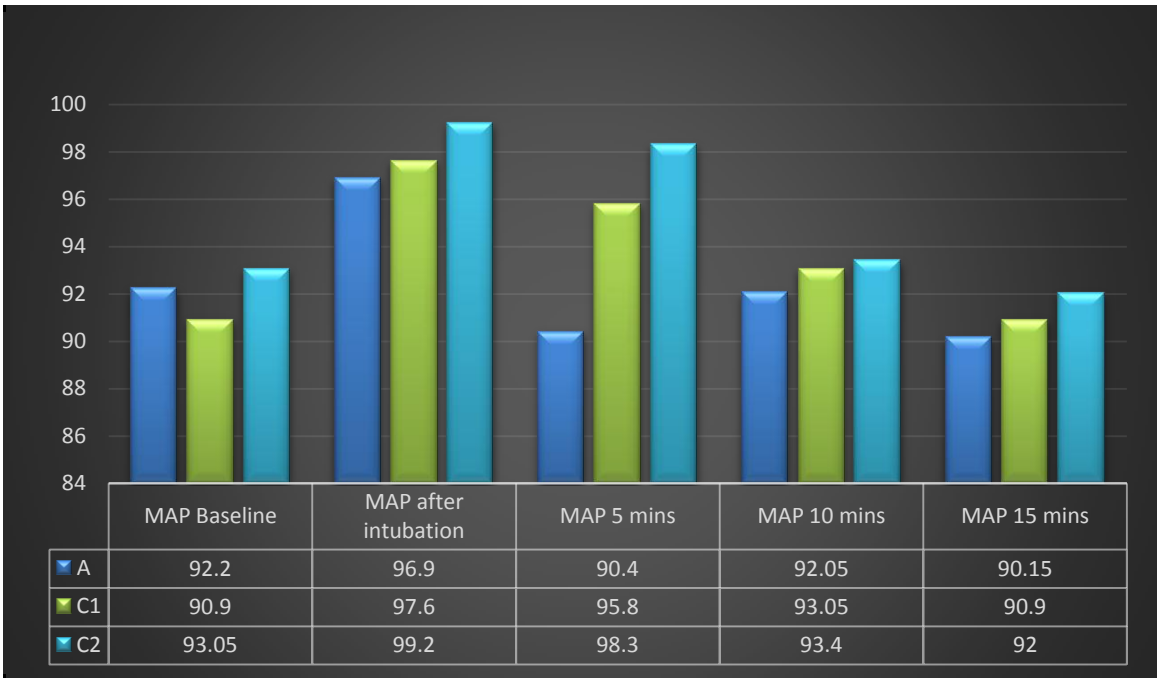


	HR Baseline	HR after intubation	HR 5 mins	HR 10 mins	HR 15 mins
A	76.1	88.1	85.7	81.1	76.5
C1	75.2	88.1	85.6	81.3	76.1
C2	76.8	88.6	86.7	81.4	74.6

The mean and standard deviation of baseline heart rate, heart rate after intubation and at different time intervals at 5,10,15 mins after intubation among three groups were compared. The results obtained from the analysis shows that there was an increase in heart rate compared to baseline in all the three groups at 5mins after intubation. It gradually returns to baseline at 15mins but this may be due to stress response and there was no statistical significant difference. (fig-1)

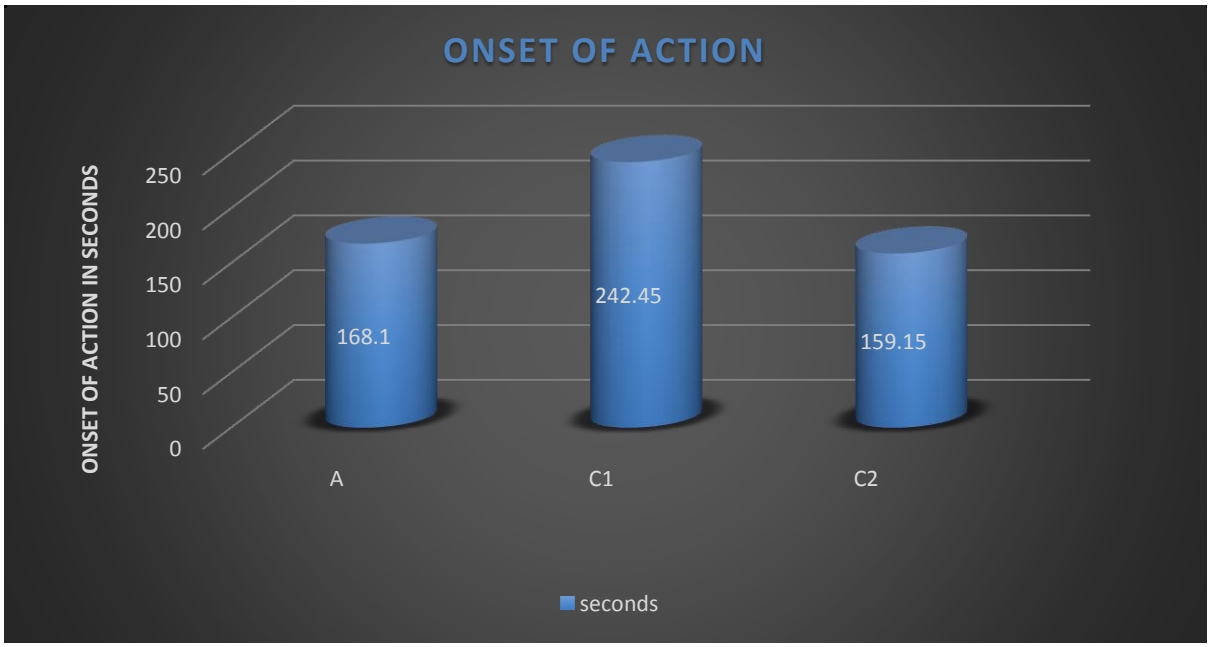
The mean and standard deviation of baseline MAP, MAP at different time intervals at 5,10,15 mins after intubation among three groups were compared. The results obtained from the analysis shows that there was an increase in MAP compared to baseline in all the three groups after intubation and at 5 mins which gradually returned to baseline at 15mins but there was no statistical significant difference.(fig-2)

Figure 2: Mean arterial pressure changes before and after administration of atracurium and cisatracurium



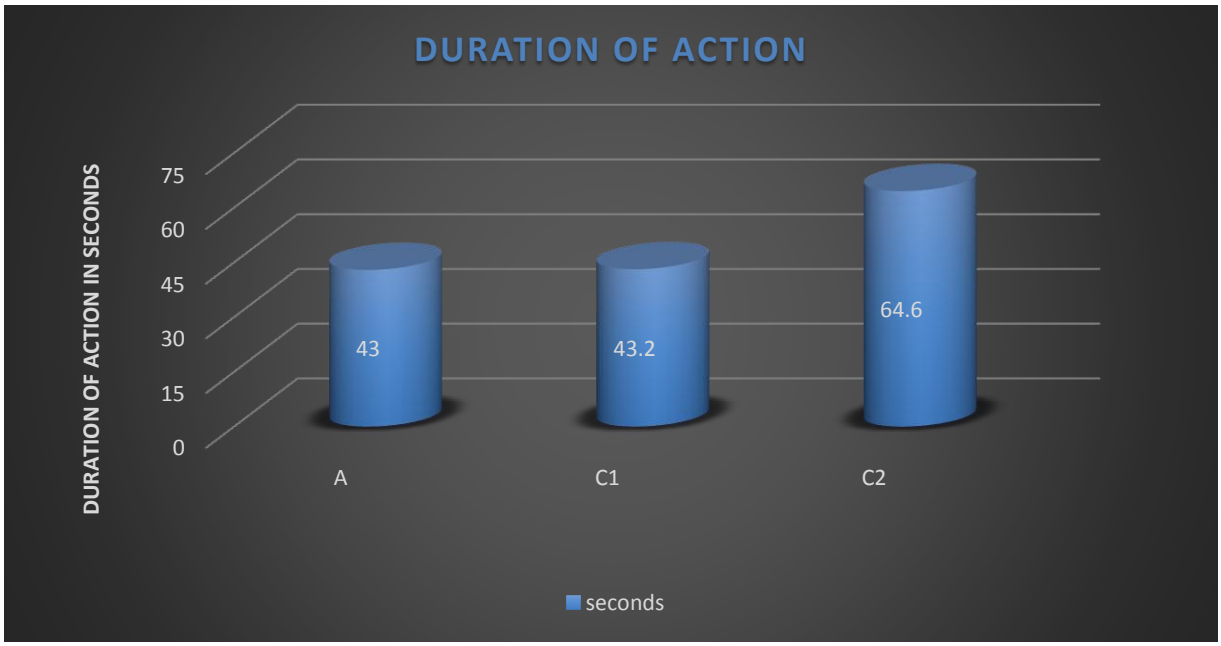
	MAP Baseline	MAP after intubation	MAP 5 mins	MAP 10 mins	MAP 15 mins
A	92.2	96.9	90.4	92.05	90.15
C1	90.9	97.6	95.8	93.05	90.9
C2	93.05	99.2	98.3	93.4	92

Figure 3: Onset of action



In present study, the mean ±SD time for onset of action for group A was 168.10±10.60 secs and group C1 was 242.45±11.64 secs and for group C2 was 159.15±10.49secs. Onset of action in group C2 was rapid compared to other two groups with statistical significance (p=0.000).(fig-3)

Figure-4 Duration of action



The mean ±SD duration of action of intubating dose in group A(Atracurium) was 43.0+2.27 min, group C1(Cisatracurium) was 43.2+2.72 min and in group C2(Cisatracurium) was 64.6±4.83 min. The duration of action was found to be more prolonged in group C2 which is statistically significant.(fig-4)

Table 1: Intubating Conditions

	Excellent	Good	Poor	Not Possible
Grp A	12 (60%)	8(40%)(40%)	0	0
Grp C1	13(65%)	7(35%)	0	0
Grp C2	14(70%)	6(30%)	0	0

Intubating conditions were either excellent or good in all the three groups and had no fair or poor intubating condition. Intubating conditions were excellent in 60% cases in group A and good in 40% cases, while in group C1 65% had excellent intubating conditions and 35% had good intubating conditions. In group C2 70% had excellent intubating conditions and 30% had good intubating conditions.

Table 2: Signs of histamine release

	No of patients
Group A	2
Group C1	0
Group C2	0

Only 2 patients out of 20 who were administered Atracurium showed signs of histamine release i.e facial flushing. However there was no such findings in patients administered Cisatracurium.

Discussion

NMBA have made anaesthesia much safer and provide efficient operating conditions. It is used to facilitate endotracheal intubation and provide surgical relaxation. Cisatracurium possess most of these properties of an "ideal" muscle relaxant. It is similar in structure and properties to Atracurium but has the added advantage of rapid onset of action, no signs of histamine release, less laudanosine production on metabolism . So, it has

an advantage over Atracurium. So the present study was undertaken to study the neuromuscular properties of Atracurium and to compare it with different doses of Cisatracurium.[10]

There have been studies conducted with various doses of these two muscle relaxants for comparison. As for intubation usually twice the ED95 dose of a NDMR is required but only for Cisatracurium 3ED95 dose is required. In present study we used 2ED95 doses i.e. Atracurium the dose of 0.5 mg / kg and compared it with Cisatracurium in the dose of 0.1 mg / kg and 0.15mg/kg as intubating dose.

In our study we used neuromuscular monitoring by Train of four because the response of neuromuscular blocking drugs is not predictable. So the monitoring of neuromuscular function by TOF provides more predictable and rational approach to the use of muscle relaxants and better and faster recovery.

According to Suresh S.N et al [11], monitoring of neuromuscular activity of the Adductor Pollicis using Train of Four to determine the appropriate tracheal intubation time and condition is clinically more relevant than monitoring the Orbicularis Oculi muscle.

In present study, the mean ±SD time for onset of action for group A was 168.10±10.60 secs and group C1 was 242.45±11.64 secs and for group C2 was 159.15±10.49secs. Onset of action in group C2 was rapid compared to other two groups with statistical significance (p=0.000).The present study concurs with the findings of the studies of Mellinghoff et al,[12] Bluestein et al [13] who have also reported the onset time similar to our present study. All the previous studies showed that time for onset of action of Cisatracurium $3ED_{95}$was faster than $2ED_{95}$ doses of Cisatracurium and Atracurium with statistical significance which is similar with our result.

Intubating conditions with Atracurium were excellent in 60% and good in 40% patients while in the Cisatracurium(C1) group, intubating condition were excellent in 65% and good in 30% patients and in (group C2) intubating condition were excellent in 70% patients and good in 30% cases which were comparable and without statistical significant difference. El kasaby et al [14] found excellent Intubating conditions of Cisatracurium in higher doses versus $2ED_{95}$ dose of cisatracurium and Atracurium. Our study finding coincides with their results. Our study finding was also similar to finding of Bluestein et al.[13]

The mean ±SD duration of action of intubating dose in group A (Atracurium) was 43.0+2.27 min, group C1 (Cisatracurium) was 43.2+2.72 min and in groupC2 (Cisatracurium) was 64.6±4.83 min. The duration of action was found to be more prolonged in group C2 with a p-value of 0.000 which is statistically significant. Our study was in agreement with study by Bluestein et al. [13] and El kasaby et al [14]. The changes in heart rate, mean arterial blood pressures at the different time intervals after intubation were also comparable in both groups and had no significant difference. This finding is in accordance with the studies of Lien et al.[15], and Basta et al.[16] 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 ED_{95} of atracurium.

Conclusion

It may be concluded that 0.15mg/kg of Cisatracurium provide more effective neuromuscular blocking than 0.10mg/kg of Cisatracurium and 0.5mg/kg of Atracurium. Cisatracurium has faster onset of action and longer duration of action.It is hemodynamically more stable and it shows no signs of histamine release.

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