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Original Research Article

A Comparative Study of the Efficacy of Intubating Doses of Atracurium and Cisatracurium in Adults Undergoing Elective Surgeries under General Anaesthesia

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Abstract:

Introduction: Neuromuscular blocking drugs help with endotracheal intubation and surgical relaxation by interrupting nerve impulse transmission at the neuromuscular junction. The triad of narcosis, analgesia, and muscle relaxation has been reinterpreted as anaesthesia. Atracurium is an intermediate acting NDMR which is often used in renal and hepatic failure. Cisatracurium is 3 to 4 times more potent than Atracurium and may not produce the same excellent intubating results as equipotent dosages of Atracurium.

Materials And Methods: This prospective, randomized, double blinded study was conducted between December 2019 to June 2021 on 60 patients of ASA PS I and II undergoing elective surgery under General anaesthesia. Patients fulfilling the inclusion criteria were randomly were randomly divided into 2 groups of 30 in each group; Group A - Atracurium 0.5 mg/kg and Group C - Cisatracurium 0.15 mg/kg .The drug was administered by an anaesthesiologist unrelated to the study by closed envelope method. The mean onset and duration of action of neuromuscular blockade was calculated for both the groups.

Results: The Statistical analysis showed that the mean onset of blockade was found to be significantly longer in Atracurium group (3.32± 0.35 min) compared to Cisatracurium group (3.03±0.36 min).Duration of action was significantly longer in group C (40.60 ± 4.70 minutes) when compared to group A (32.50 ±4.17 minutes).

Conclusion: Based on the present clinical comparative study, 0.15mg/kg (3× ED95) of Cisatracurium provides more effective neuromuscular blocking than 0.5mg/kg (2× ED95) of Atracurium in terms of time of onset and duration of neuromuscular blockade.

Keywords: Atracurium; Blockade; Cisatracurium; Efficacy.

Introduction

The widespread use of neuromuscular blocking drugs constituted a watershed moment in anaesthesia's evolution. Neuromuscular blocking drugs help with endotracheal intubation and surgical relaxation by interrupting nerve impulse transmission at the neuromuscular junction. The triad of narcosis, analgesia, and muscle relaxation has been reinterpreted as anaesthesia.

The introduction of d- tubocurarine and succinylcholine to the field of neuromuscular blockade has paved the way for substantial advancements. Muscle relaxation does not ensure analgesia, amnesia, or unconsciousness. Except for succinylcholine, they do not cross the blood-brain barrier; hence there is no increase in intracranial pressure. These drugs have little adverse effects, are quickly broken down into inactive metabolites, and their effects are primarily limited to the neuromuscular junction. The ideal Neuromuscular blocking drug for intubation must have a rapid onset of action, brief duration of action, free from hemodynamic changes,

devoid of residual muscle paralysis and should have excellent intubating conditions.

Atracurium is an intermediate acting NDMR which is often used in renal and hepatic failure. It is metabolized by Hoffmann elimination and nonspecific ester hydrolysis. It is associated with the release of histamine. Cisatracurium is 3 to 4 times more potent than Atracurium and is not linked with the release of histamine. Cisatracurium may not produce the same excellent intubating results as equipotent dosages of Atracurium [1]. Cisatracurium is recommended at a dose of 2×ED95 (0.1mg/kg) to 3×ED95 (0.15 mg/kg) for intubation [2]. Equipotent dosages of Cisatracurium and Atracurium had similar effective durations of action and rates of spontaneous recovery [3].

Materials and Methods:

This prospective, randomized, double blinded study was conducted in the Department of Anaesthesiology in Siddhartha medical college, Vijayawada between December 2019 to June 2021 ; on 60 patients of ASA PS I and II undergoing elective surgery under General anaesthesia.

Institutional ethical committee approval and informed written consent was obtained. Detailed preanaesthetic evaluation and routine investigations like Complete blood count ,Blood glucose, Renal function tests, Liver function tests BT, CT,ECG, Chest X ray were done as per institution protocol.

Inclusion criteria:

1. Age 18 to 60 years of both sexes
2. ASA physical status 1 and 2
3. MPC 1 and 2
4. Elective surgeries under General Anaesthesia

Exclusion criteria:

1. Patients not willing to enroll for the study
2. Patients with COPD, Asthma
3. Patients with Neuromuscular disorders
4. Known or anticipated difficult airway
5. Moderate to severe anaemia
6. Pregnant and Lactating women
7. Patients with Cardiovascular, Renal or Hepatic disorders
8. Emergency surgeries
9. Family history of malignant hyperthermia

Patients fulfilling the inclusion criteria were randomly divided into 2 groups of 30 in each group; Group A - Atracurium 0.5 mg/kg and Group C - Cisatracurium 0.15 mg/kg.

The drug was administered by an Anaesthesiologist unrelated to the study by closed envelope method. The mean onset and duration of action of neuromuscular blockade was calculated for both the groups.

The heart rate, systolic blood pressure, diastolic blood pressure and mean arterial pressure were recorded before induction, 1 min, 2 min and 5 min after intubation and compared between both the groups.

To determine the statistical significance, all recorded data was input into MS Excel and analysed using SPSS version 21 software. Analysis of variance (ANOVA) was used to study the significance of mean. On the mean values of various parameters, an independent 't' test was employed to compare the two groups. P-values less than 0.05 were considered statistically significant.

Results:

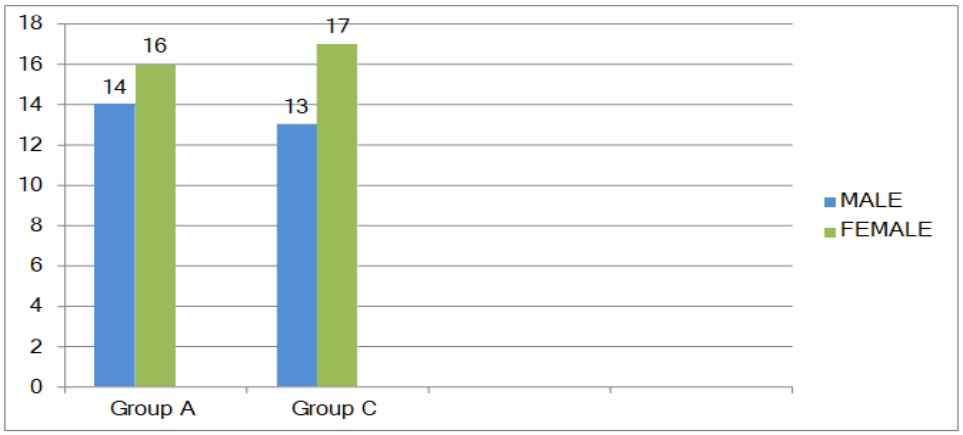

Figure 1: Gender Distribution

Out of 30 (100%) subjects in group A, 14 (46.7%) subjects were males and 16(53.3%) were females. Out of 30 (100%) study subjects in group C, 13 (43.3%) were males and 17 (56.7%) were females as evident from Figure 1.There was statistically no significant difference in the distribution of subjects based on gender between the two groups (P= 0.795).

Table 1: Comparison of ASA Grades

ASA		Group		Total
		Group A N (%)	Group C N (%)	
ASA I	Count	22	22	44
	Percentage	73.3	73.3	73.3
ASA II	Count	8	8	16
	Percentage	26.7	26.7	26.7
Total	Count	30	30	60
	Percentage	100.0	100.0	100.0

Table 1 depicts association between the study groups on the basis of American Society of Anesthesiologists grading. There was no significant association between the study groups from Pearson's Chi square test (P=1.000).

Table 2: Comparison of Various Parameters at Baseline

Parameter	Group		P value
	Group A Mean ± SD	Group C Mean ± SD	
Heart rate (bpm)	82.93±7.36	83.70±7.79	0.697
Systolic blood pressure (mm Hg)	118.96±6.60	120.86±6.69	0.273
Diastolic blood pressure (mm Hg)	75.23±5.47	76.56±7.54	0.437
Mean arterial pressure (mm Hg)	89.53±5.30	91.03±6.85	0.347

Table 2 shows comparison of various parameters of study subjects in the two groups at baseline. None of these differences between both groups at baseline were found to be significant (p>0.05).

Table 3: Comparison of Various Parameters at the Time of Induction

Parameter	Group		P value
	Group A Mean ± SD	Group C Mean ± SD	
Heart rate (bpm)	83.80±5.85	84.90±7.53	0.530
Systolic blood pressure (mm Hg)	119.66±6.03	120.53±5.73	0.571
Diastolic blood pressure (mm Hg)	75.63±5.12	76.50±6.58	0.572
Mean arterial pressure (mm Hg)	90.00±4.57	90.76±5.59	0.564

Table 3 depicts comparison of various parameters of study subjects in the two groups at the time of induction. None of these differences between both groups at the time of induction were found to be significant (p>0.05).

Table 4: Comparison of Various Parameters during Intubation

Parameter	Group		P value
	Group A Mean ± SD	Group C Mean ± SD	
Heart rate (bpm)	93.56±5.31	90.80±8.07	0.123
Systolic blood pressure (mm Hg)	126.90±4.30	127.56±4.51	0.561
Diastolic blood pressure (mm Hg)	81.86±5.25	82.56±6.09	0.635
Mean arterial pressure (mm Hg)	96.53±4.35	97.20±4.86	0.578

Table 4 shows comparison of various parameters of study subjects in the two groups during intubation. The results obtained from the analysis showed that there was an increase in heart rate, systolic blood pressure, diastolic blood pressure and mean arterial pressure during intubation compared to the baseline. None of these differences between both groups during intubation were found to be significant (p>0.05).

Table 5: Comparison of Various Parameters One Minute after Intubation

Parameter	Group		P value
	Group A Mean ± SD	Group C Mean ± SD	
Heart rate (bpm)	85.53±6.14	88.13±7.10	0.135
Systolic blood pressure (mmHg)	119.03±4.90	121.63±4.23	0.062
Diastolic blood pressure (mmHg)	76.93± 4.83	78.93± 4.91	0.118
Mean arterial pressure (mmHg)	90.66±4.17	92.86± 3.91	0.089

Table 5 shows comparison of various parameters of study subjects in the two groups one minute after intervention. The results obtained from the analysis showed that there was an increase in heart rate, systolic blood pres-

sure, diastolic blood pressure and mean arterial pressure compared to the baseline. None of these differences between both groups one minute after intervention were found to be significant (p>0.05).

Table 6: Comparison of Various Parameters Two Minutes After Intubation

Parameter	Group		P value
	Group A Mean ± SD	Group C Mean ± SD	
Heart rate (bpm)	83.86±5.72	85.66±5.92	0.236
Systolic blood pressure (mm Hg)	117.76±4.93	120.00±5.50	0.103
Diastolic blood pressure (mm Hg)	75.90±4.18	77.60±5.30	0.173
Mean arterial pressure (mm Hg)	89.46±3.65	91.36±4.74	0.088

Table 6 shows comparison of various parameters of study subjects in the two groups two minutes after intervention. None of these differences between both groups two minutes after intervention were found to be significant (p>0.05).

Table 7: Comparison of Various Parameters Five Minutes After Intubation

Parameter	Group		P value
	Group A Mean ± SD	Group C Mean ± SD	
Heart rate (bpm)	82.66±4.88	82.83±6.03	0.907
Systolic blood pressure (mm Hg)	117.70±5.49	120.73±4.84	0.067
Diastolic blood pressure (mm Hg)	74.50±4.49	78.10±4.50	0.053
Mean arterial pressure (mm Hg)	88.56±4.04	91.96±3.93	0.072

Table 7 shows comparison of various parameters of study subjects in the two groups five minutes after intervention. None of these differences between both these groups five minutes after intervention were found to be significant (P>0.05).

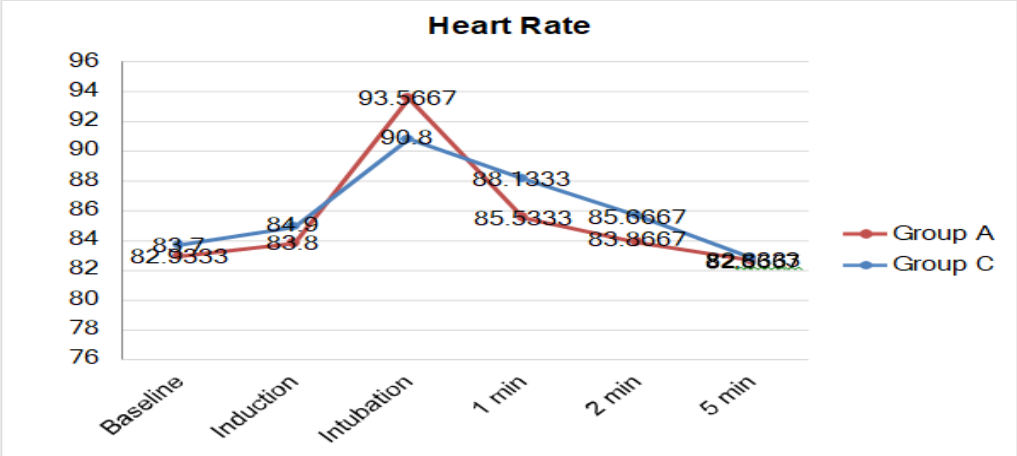

Figure 2: Line Diagram Showing Heart Rate

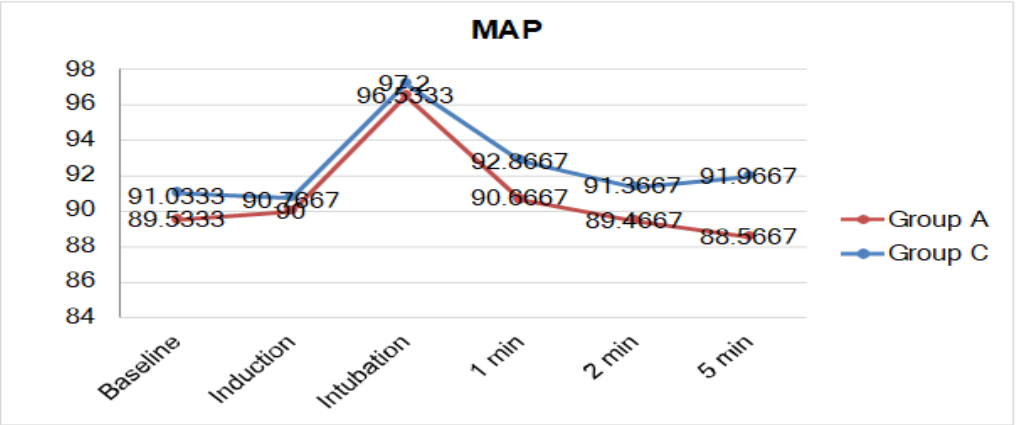

Figure 3: Line Diagram Showing Mean Arterial Pressure

The results obtained from the analysis showed that the increase in heart rate, systolic blood pressure, diastolic pressure and mean arterial pressure observed during intubation gradually returned to baseline at 5 min and it may be due to stress response as depicted in Figures 2 and 3.

Table 8: Comparison of Mean Onset and Duration of Blockade

Parameter	Group		P value
	Group A Mean ± SD	Group C Mean ± SD	
Onset of blockade (in min)	3.32±0.35	3.03±0.36	0.004
Duration of blockade (in min)	32.50±4.17	40.60±4.70	<0.001

Table 8 shows that the mean onset of blockade was found to be significantly longer in group A (3.32±0.35 min) compared to group C (3.03± 0.36 min) (p=0.004).The mean duration of blockade was found to be significantly longer in group C (40.60±4.70 min) compared to group A (32.50±4.17 min) (p<0.001). None of the subjects in the two study groups had allergic reactions to the intervention.

Discussion:

Endotracheal intubation is an important step for the administration of General Anaesthesia during controlled ventilation. Muscle relaxants have made Anaesthesia much safer and provide good relaxation during endotracheal intubation and for surgical relaxation.

The popularity of Succinyl choline is questioned by its side effects which range from muscle pains after recovery to dangerous arrhythmias and hyperkalemia, and it is contraindicated in many instances. An ideal muscle relaxant reduces the time for intubation and also minimizes the untoward hemodynamic stress response.

Cisatracurium, an isomer of Atracurium is a potent muscle relaxant and has the properties of an ideal muscle relaxant. It has an added advantage of rapid onset of action, no histamine release and less Laudanosine production. It is a nondepolarizing muscle relaxant (ED95 estimated to be 0.05mg/kg). It is known to produce good intubating conditions following a dose of 0.1mg/kg to 0.15mg/kg in two minutes[2].In present study, we compared the hemodynamic effects, onset of action and duration of action of intubating doses of Atracurium (0.5 mg/kg) and Cisatracurium (0.15mg/kg)[2].

The selection of non-depolarizing muscle relaxant to be used for surgical anaesthesia depends mainly on onset time, intubating conditions, duration of action, cardiovascular effects, pharmacokinetic profile and reversal of neuromuscular blockade. To avoid discrepancy between the two groups, similar anaesthetic techniques were employed in both the groups. 60 patients were randomly divided into two groups of 30 each (Group A and Group C). All patients in both the groups induced with Propofol (2mg/ kg) and then,

Group A: Received 0.5mg/kg Atracurium bolus. Group C: Received 0.15 mg/kg Cisatracurium bolus.

Both the groups were compared for the following parameters: Onset of action, Duration of action, Hemodynamic effects, and Allergic reactions. 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 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 at regular intervals using TOF monitor. 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 results obtained were noted and data for different parameters were analysed sequentially.

Demographic Data: The two groups were comparable and there was no statistically significant difference between the mean ages, sex and weight. In this study the optimum age range was 18 to 60 years of ASA physical status 1 and 2, which was also not statistically significant.

Hemodynamic Changes During and After Intubation: In general, bisbenzylquinolinium compounds promote histamine release, which can cause face flushing and hemodynamic abnormalities. A reduction in mean arterial pressure and a compensatory increase in heart rate are the most common cardiovascular consequences associated with histamine release.

These responses normally are transient and are related to both the dose of the relaxant administered and the time course over which the relaxant is given [13]. The circulatory changes are brief, lasting 60-90 seconds after Atracurium administration and then disappearing within 5 minutes. Cisatracurium has no histamine-releasing properties, hence even large dosages (8ED 95) of Cisatracurium do not cause cardiovascular abnormalities [12]. In a study

conducted by Wolfgang M. Schramm et al [8] cisatracurium demonstrated fewer cerebral and cardiovascular hemodynamic side effects in sedated adult neurosurgical patients.

In present study the statistical analysis showed that in both the groups mean heart rate, mean systolic pressure, mean diastolic pressure and mean arterial pressure during intubation, 1min and 2 min after intubation was significantly higher when compared to the baseline values. They gradually returned towards the baseline values 5 min after intubation. These hemodynamic changes may be due to stress response to intubation.

The analysis showed that systolic blood pressure, diastolic blood pressure, mean arterial pressure at different time intervals after intubation were comparable. There was no statistical difference between the groups.

El-Kasaby AM et al [1] compared Atracurium (2ED95) to various doses of Cisatracurium (2ED95, 4ED95, 6ED95) and found that small changes in mean blood pressure and heart rate occurred post induction and post intubation, but that these changes were not statistically or clinically significant at higher doses of Cisatracurium. Higher doses of Cisatracurium (4ED95, 6ED95) showed more hemodynamic stability for both heart rate and mean arterial blood pressure. When compared to baseline and following injection of 2ED95 dose of Atracurium in group 1 and the same dose of Cisatracurium in group 2, there was a statistically significant rise in HR and MABP due to stress reaction to intubation, even after 120 s of injection of the muscle relaxant. Agavelian EG and Arkharova TB14 (1999) reported that Cisatracurium in a dose of 0.15mg did not produce fluctuation in hemodynamic parameters.

Jean-Yves Lepage et al [10] (1996) reported in their study that bolus administration of Cisatracurium at doses up to 5×ED 95 caused no dose-related clinically significant effects on HR or MAP. In present study, the mean± SD time for onset of blockade for group A was 3.32± 0.35 (Atracurium 0.5 mg/kg) and group C was 3.03 ± 0.36 (Cisatracurium 0.15 mg/kg). Onset of blockade was rapid with Cisatracurium 0.15 mg/kg than Atracurium 0.5 mg/kg with statistical significance (P<0.05).This is in concurrence with the findings of the studies of Mellinghoff et al [6]and Bluestein et al [11] who reported the time of onset similar to present study. These studies showed that time of onset of action of 3× ED 95 was faster than 2× ED 95doses of Cistracurium and Atracurium with statistical significance which is similar to present study. Hyunjung Lee et al [7] report shows that the onset time of cisatracurium was significantly longer, compared to rocuronium. However, a small dose of 0.15 mg/kg of cisatracurium, supplementing a remifentanil-propofol combination, provides excellent or good endotracheal intubating conditions in 96% of patients, a rate similar to those achieved by rocuronium 0.9 mg/kg (100%), while using the same anesthetic technique and similar induction time.

Linda S. Bluestein MD, et al [11], studied 80 patients with ASA physical category I or II who underwent abdominal surgery between the ages of 18 and 70 in 1996. They were divided into four groups at random (A-D). Group A received Cisatracurium 0.1 mg/kg (2×ED95), Group B received Atracurium 0.5 mg/kg (2×ED95). Patients in group C received Cisatracurium 0.2mg/kg (4×ED95) and group D 0.15 mg/kg (3×ED95). They found that same dose of Atracurium had onset time of 3.2 minutes and Cisatracurium had onset time of 4.6 minutes. They also found on further increasing the doses of Cisatracurium (0.15 and 0.2 mg/kg), the onset time decreased.

In a study by M. El-kasaby et al. [1], where 3 doses of Cisatracurium were compared, it was observed that the onset of action was substantially faster with higher doses of Cisatracurium when compared to Atracurium. The onset of neuromuscular blockade with a 2ED95 dose of Atracurium was shown to be substantially lower than with a 2ED95 dose of Cisatracurium. . At the same time, greater Cisatracurium dosages (4ED95 and 6ED95) had a faster onset and a longer duration of action than Atracurium (2ED95) and a lower Cisatracurium dose (2ED95).The mean and standard duration of action of the intubating dose in group A was 32.50± 4.17 min and group C was 40.60± 4.70. The mean duration of blockade was found to be significantly higher in Cisatracurium group compared to Atracurium group (P< 0.001).

The study finding was in concurrence with study by M.T. Carroll et al[9] where different doses of Cisatracurium (0.1mg/kg and 0.15 mg/kg) were compared with Atracurium (0.5 mg/kg) and concluded that the time for median duration of muscle relaxation, i.e. the time from drug administration to recovery of T1 to 25%, with Cisatracurium 0.15 mg.kg (51–59 min) was longer compared with both Cisatracurium 0.1 mg.kg (45–48 min) and Atracurium (47– 48 min).

Bluestein and colleagues [11], studied 80 patients of ASA physical status I or II, 18 — 70 years of age, who were randomly allocated to four groups (A-D) Cisatracurium 0.1 mg/kg (2ED95) was given to group A, while Atracurium 0.5 mg/kg (2ED95) was given to group B. Cisatracurium 0.2 mg/kg (4ED95) and 0.15 mg/kg (3ED95) were given to patients in groups C and D, respectively.

They assessed the mean time of onset, mean duration of effect, and intubation conditions. They found that increasing the initial dose of Cisatracu-

rium (from 0.1 to 0.15 and 0.2 mg/kg, respectively) decreased the mean time of onset (from 4.6 to 3.4 and 2.8 min, respectively) and increased the mean time of clinically effective duration of action (from 4.6 to 3.4 and 2.8 min, respectively) (45 to 55 and 61 min, respectively).

In a study conducted by Arun kumar mohanty and colleagues4 where a randomized controlled trial was conducted to compare 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.

The time of onset, duration of action, condition of intubation, hemodynamic effects, and signs of histamine release were recorded. The onset time was found to be significantly lower with group C2 compared to group C1 and group A. There was significantly increased duration of action with 0.15mg/kg Cisatracurium compared to 0.5mg/kg Atracurium and 0.1mg/kg Cisatracurium.

Amini Shahram et al [20] studied effects of different doses of Cisatracurium on appropriate time for endotracheal intubation and hemodynamic changes during anaesthesia and found that the mean clinical duration of action (recovery of evoked response to 25% 0f control) with 0.15 mg/kg was 44.93±5.40 minutes while with 0.2 mg/kg was 57.03±4.21 minutes

Luc Bergeron et al [21] found that mean clinical duration of action with 0.15 mg/kg body wt. was 58.9±10.4 minutes. No signs of histamine release like flushing at the site of injection, tachycardia, hypotension, erythema or wheals were noted in both the groups. As a benzylisoquinoline molecule, Atracurium has the ability to produce histamine. When doses of 0.5 mg/kg (2ED95) or more are injected rapidly, it becomes clinically obvious. A transient hypotension and facial erythema may occur when plasma histamine levels exceed 1000 pg/ml. The phenomenon of histamine release may be minimized by slower injection from 30 to 60 sec. Combined H1 and H2 receptors blockers can be used to prevent the release of histamine with Atracurium.

In a study by Hosking et al [15], individuals were given diphenylhydramine 1 mg/kg and cimetidine 4 mg/kg intravenously 30 minutes before receiving a very large dosage of Atracurium (1.5 mg/kg). The Atracurium-induced fall in mean arterial blood pressure was decreased to 30 mmHg (37 percent below baseline) in treated patients. Atracurium is non-vagolytic and does not inhibit autonomic ganglia despite a 10- to 20-fold increase in plasma histamine levels.

In a study conducted by Kasaby et al [1], no signs of histamine release were noted with any doses of Cisatracurium (2×ED95, 4×ED95 and 6×ED95), while it was noted with Atracurium 0.5 mg/kg (2 cases; 1 case showed flush and the other case showed erythema), however the patients did not experience any hypotension or tachycardia.

Laudanosine is one of the major metabolite of Atracurium metabolism. Peak plasma concentration of Laudanosine occurs about 2minutes after i.v. injection of Atracurium. It depends on liver and kidney for its elimination.

Plasma concentration of Laudanosine after single dose of Atracurium 0.5mg/kg are higher in patient with renal failure compared with the normal patients. So patients with liver disease and those who receive Atracurium for long time in ICU are found to have elevated concentration of Laudanosine, as high as 5-6µg/ml. It has CNS stimulating properties and cardiovascular effects, can cause bradycardia and hypotension. Cisatracurium, an isomer of Atracurium it is five times more potent than Atracurium and about five times less Laudanosine is produced and lesser side effects.

In a study by Rochana G Bakhshi and colleagues [5], they observed that with the dose of Cisatracurium (0.2mg/kg; 4× ED95) there was no signs of histamine release while skin rashes were noted in 2 patients who received Atracurium (0.5mg/kg: 2× ED95). Infants are more sensitive to the effects of neuromuscular blockers than children. Taivanen T et al [16] studied the safety and efficacy of 0.15mg/kg of Cisatracurium in children during and found that onset of action is more rapid in infants than children. Duration of action was also prolonged in infants than children. Sarooshan SS et al [19] also found that young patients have more rapid onset of block than elderly patients, but clinical duration of action were similar.

According to Suresh S.N et al [17], monitoring of neuromuscular activity of adductor pollicis using Train of four to determine the appropriate tracheal intubation time and duration is clinically more relevant than monitoring the Orbicularis oculi muscle. Woo Jong Shin et al [18] compared the dose response relationship and time course of neuromuscular blockade of Cisatracurium at laryngeal adductor and adductor pollicis muscle and found that onset of action and recovery is faster at the laryngeal adductors than adductor pollicis.

Conclusion:

Based on the present clinical comparative study, the following conclusions can be made 0.15mg/kg (3× ED95) of Cisatracurium provides more effective neuromuscular blocking than 0.5mg/kg (2× ED95) of Atracurium in terms of time of onset and duration of neuromuscular blockade. Both Atracu-

rium (0.5mg/kg) and Cisatracurium (0.15 mg/kg) produced stable hemodynamics without clinically significant changes in PR and BP. No allergic reactions were noted with both the drugs.

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