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CISATRACURIUM IN DIFFERENT DOSES VERSUS ATRACURIUM DURING GENERAL ANESTHESIA FOR ABDOMINAL SURGERY A PROSPECTIVE, RANDOMIZED CLINICAL TRIAL

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ABSTRACT

Background and objective: This study was aimed at comparing the efficacy of atracurium and cisatracurium (in different doses) regarding onset time, intubating conditions and hemodynamic effects in patients undergoing elective abdominal surgery.

Methods: - This Randomized, double-blind, single Hospital, Prospective study, was carried out after institutional ethical committee clearance. Hundred and twenty patients aged 18 to 60 years belonging to ASA classes I and II undergoing, elective abdominal surgery were randomly allocated into 3 groups- Group A (n=40): Inj cisatracurium 0.1 mg/kg(2 ED 95),Group B(n=40): Inj Cisatracurium 0.15mg/kg(3 ED 95) and Group C(n=40): Inj Atracurium 0.5mg/kg(2 ED 95). Onset time, Intubating conditions and hemodynamic parameters were compared between the 3 groups.

Results: The demographic parameters and baseline hemodynamic variables were comparable and statistically not significant. The intubating condition and onset time of Group A when compared to Group B and Group C were statistically significant, whereas in-between Group B and C were nonsignificant. Hemodynamic parameters at 0,1,3,5 mins after intubation were comparable and nonsignificant.

Conclusion: From our clinical comparative study, we have observed that intubating conditions with 3 ED 95 cisatracurium and 2 ED 95 atracurium are comparable and significantly better than 2 ED 95 cisatracurium. The onset time in 2 ED 95 Cisatracurium was significantly longer when compared to 3 ED 95 cisatracurium and 2 ED95 Atracurium. No significant hemodynamic changes were noted in any of the three groups.

KEYWORDS : Cisatracurium, atracurium, different ED95 dose and neuromuscular monitoring

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 ester hydrolysis 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 3ED95.[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 abdominal surgery.

AIM & OBJECTIVES

1. To compare the efficacy of atracurium and cisatracurium (in different doses) regarding
   a. Onset time
   b. Intubating conditions
   c. Hemodynamic effects
2. To evaluate whether cisatracurium is more effective than atracurium with regards to the above criteria

MATERIALS AND METHODS

After approval by the institutional ethical committee, this study is conducted under the Department of Anaesthesiology and Critical Care, GMCH.

In this Randomized, Single Hospital, Prospective study, adult patients of both sexes meeting the following inclusion and exclusion criteria, was selected as the study population

Inclusion criteria

1) Age 18 to 60 years, of both sexes.
2) American Society of Anesthesiologist Grade I & II.
3) MPS I and II
4) Patients coming for elective abdominal surgeries

Exclusion Criteria

1) Unwilling patients.
2) ASA physical status III & IV.
3) Emergency surgeries.
4) Patients with disorder of cardiovascular, hepatic, renal or neuromuscular systems
5) Pregnant & lactating women.
6) Patients with airway problems suggesting difficult intubation.
7) Patients receiving drugs known to interact with neuromuscular blocking agents

The calculated sample size is 40 per group with total sample size 120 for the three groups of the study.

The patients were randomly allocated into three groups
Group A—Inj Cisatracurium 0.1mg/kg
Group B—Inj Cisatracurium 0.15mg/kg
Group C—Inj Atracurium 0.5mg/kg

On arrival in the operating room, non-invasive monitors like electrocardiogram (ECG), non-invasive BP, pulse oximetry, a peripheral nerve stimulator for neurological monitoring was also

attached to the patient. Intravenous access was achieved with an 18G cannula and infusion of crystalloid solution was started.

The patient was preoxygenated for 3 minutes and premedication with Fentanyl (1µg/kg), Glycopyrrolate 0.2 mg and ondansetron 4mg, induction was done with propofol (2mg/kg). After fixing the electrodes near the wrist, assessment of adductor pollicis response for 1 Hz single twitch stimulation of ulnar nerve was carried out starting from the minimum intensity of current, intensity of supra maximal stimulus was fixed as 20-25% more than the current strength required to produce a max single twitch response.

A bolus i.v. dose of Inj. Cisatracurium 0.1mg/kg (2× ED95) or Inj.Cisatracurium 0.15mg/kg (3× ED95) or Inj. Atracurium 0.5mg/kg (2×ED95) depending on the group was given over a period of in 5 seconds.

Patient was ventilated with 100% oxygen. TOF was elicited every 10 seconds and the trachea was intubated after 3 mins with appropriate size endotracheal tube after doing a proper laryngoscopy by an experienced anaesthetist. Endotracheal tube was secured after confirming bilateral air entry.

Intubating conditions were assessed clinically and scored as excellent (8-9), good (6-7), fair (3-5) or poor (0-2) as per the scoring method described by Cooper et al[9].[Table 1]

Based on the pattern of sequential disappearance TOF twitches (fade of TOF response in AP), the intubating conditions were classified as excellent (count 0), good (count 1), fair (count 2) and poor (count 3,4) [Table 2]

Disappearance of twitch (Fade) in AP	%NMB	TOF Count	Assessment of intubating conditions by TOF
4th	75	3	Poor
3rd	80	2	Fair
2nd	90	1	Good
1st	100	0	Excellent
[Table 1] Correlation of sequential disappearance of twitch response			

Score	Jaw relaxation	Vocal Cords	Response to intubation
0	Impossible	Closed	Severe Coughing or bucking
1	Opens	Closing	Mild Coughing
2	Moderate	Moving	Slight diaphragmatic movement
3	Easy	Open	No movement
[Table-2] Cooper scoring System103			
excellent (score 8-9), good (score 6-7), fair (3-5) or poor (0-2)			

STATISTICALANALYSIS

Data were statistically analysed using graphpadinstat® 3 statistical software. 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, height and weight. (p>0.05) in the three groups [Table 3]

Profiles	Group A	Group B	Group C	P Value
No of patients	40	40	40	
Mean age	33.25±9.06	32.97±7.68	31.22±9.42	0.53
Height	160.08±10.08	162.88±9.78	159±10.7	0.33
Weight	62.07±11.80	60.70±11.7	60.57±12.03	0.82
ASA class(I/II)	33/7	31/9	32/8	
Sex(M/F)	13/27	20/20	22/18	
[Table 3]: Demographic profile M-Male, F- Female, ASA-American Society of Anaesthesiologist				

The mean and standard deviation of baseline heart rate, systolic blood pressure and diastolic blood pressure, and at different time intervals at 0,1,3,5 mins after intubation among three groups were compared. The results obtained from the analysis shows that there was an increase in heart rate, systolic blood pressure and diastolic blood pressure compared to baseline in all the three groups at 1mins after intubation. They gradually return to baseline at 5mins but this may be due to stress response and there was no statistical significant difference.

In the present study, the mean ± SD time for onset time in Group A was 4.29±0.26, Group B was 3.27±0.38and Group C was 3.38±0.39. On statistical analysis, the p value was found to be <0.0001, which is extremely significant. [Table 4]

Onset Time	Group A	Group B	Group C
Mean±SD	4.29±0.26	3.27±0.38	3.38±0.39
P value	<0.0001		
[Table 4]: Mean Onset time (in mins)			

Intubating conditions were accessed both clinically by cooper's method and correlated with TOF count at 3 mins.

The intubating conditions as assessed clinically were excellent in 16 cases, good in 24 cases in Group A, whereas in Group B excellent in 27 cases and good in 13 cases and in Group C excellent in 30 cases and good in 10 cases. [Table 5]

	Group A	Group B	Group C
Excellent	16	27	30
Good	24	13	10
Fair	0	0	0
Poor	0	0	0
[Table 5]: Intubating conditions assessed clinically P value <0.0001			

Assessment of intubating conditions by TOF response: In Group A no case TOF 0 was achieved, TOF 1,2,3 and 4 were observed in 1 case,16 case,20 cases and 3 cases

TOF Count	Group A	Group B	Group C	
0	0	16	7	Excellent
1	1	19	24	Good
2	16	5	9	Fair
3	20	0	0	Poor
4	3	0	0	Poor
[Table 6] Intubating conditions as assessed by TOF count P Value <0.001				

respectively whereas in Group B, TOF 0,1and 2 were observed in 16 cases, 19 cases and 5 cases respectively and in Group C TOF 0,1 and 2 were observed in 7 cases, 24 cases and 9 cases respectively. [Table 6]

DISCUSSION

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[10].

Cisatracurium possess most of these properties of an “ideal” muscle relaxant. It 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[11,12].Cisatracurium may not yield satisfactory intubating conditions such as those seen with equipotent doses of Atracurium. The recommended intubating dose of Cisatracurium is 3ED95 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 abdominal surgery

In the present study the mean onset time in group A was 4.29±0.26 min, in Group B was 3.27±0.38 and in Group C was 3.38±0.39 mins. The difference in the mean time between the 3 groups was found to be statistically significant. The present study concurs with the findings of the studies of Mellinghoff et al[13], Bluestein et al[14] who have also reported the onset time similar to our present study.

In our study intubating conditions were assessed both clinically and co related with TOF Count at the time of intubation. Intubation time was fixed at 3 mins. We found that 2 ED95 dose of atracurium and 3 ED95 dose of cisatracurium provided superior intubating conditions than 2 ED 95 cisatracurium, which was statistically significant. However intubating conditions of 3 ED95 cisatracurium and 2 ED 95 atracurium were comparable and statistically nonsignificant. El kasaby[15] et al

found excellent Intubating conditions of Cisatracurium in higher doses versus 2ED95 dose of cisatracurium and Atracurium. Our study finding coincides with their results. Our study finding was also similar to finding of Bluestein et al[14]

The changes in heart rate, mean arterial blood pressures at the different time intervals after intubation were also comparable in all the three groups and had no significant difference.

CONCLUSION

From our clinical comparative study, we have observed that the intubating conditions with 3 ED95 Cisatracurium and 2 ED95 Atracurium is comparable and significantly better than 2 ED 95 Cisatracurium at the same time, the onset time in 2 ED 95 Cisatracurium was significantly longer when compared to 3 ED 95 Cisatracurium and 2 ED 95 Atracurium. No significant hemodynamic changes were noted in any of the three groups Thus, it can be concluded that 3 ED95 Cisatracurium and 2 ED95 Atracurium are comparable and better than 2ED 95Cisatracurium to facilitate endotracheal intubation in elective abdominal surgeries with shorter onset time and better intubating conditions

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