ORIGINAL RESEARCH

A comparative study of different doses of Cisatracurium versus Atracurium during general anaesthesia for oncosurgery

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ABSTRACT

Aim: Cisatracurium is an intermediate duration non-depolarising neuromuscular blocking drug and is devoid of histamine release. However, 2× ED95 dose of cisatracurium does not provide satisfactory intubating condition. The objective of this study was to evaluate and compare onset of action, hemodynamic effects and any adverse effects for different doses of cisatracurium. **Method:** The study designed as randomized controlled clinical trial to compare between atracurium (2×ED(95) and different doses of cisatracurium (2×ED(95), 3×ED(95) regarding onset time, duration of action, condition of intubation, hemodynamic effects, and sings of histamine release clinically. Sixty four patients were randomly assigned to one of three groups, the first group (group 1) received 2×ED(95) dose of atracurium, group 2 received 2×ED(95) dose of cisatracurium, group 3 received 4×ED(95) dose of cisatracurium, while group 4 received 6×ED(95) dose of cisatracurium. The Datex relaxograph (Type NMT-100-23-01, S/N: 37541) for neuromuscular monitoring was used. **Results:** Onset time was found to be significantly lower with 2×ED(95) dose of atracurium than with the same dose of cisatracurium. At the same time, higher doses of cisatracurium (4×ED(95) and 6×ED(95)) showed onset time and longer duration of action that was significantly lower than with atracurium and with lower dose of cisatracurium (2×ED(95)). **Conclusion:** The same dose (2×ED(95) dose) atracurium is more effective neuromuscular blocking agent than cisatracurium, while higher doses of cisatracurium 4×ED(95) and 6×ED(95) provide more effective, more rapid neuromuscular blocking with longer duration of action, stable hemodynamic status, and no associated signs of histamine release clinically.

Keywords: Cisatracurium, ED 95 doses, Hemodynamic stability, Histamine release

INTRODUCTION

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.[1-2] Rapid and safe endotracheal intubation is an integral part of administration of anaesthesia during surgical procedures which depends upon type and degree of muscle relaxation, depth of anaesthesia and skill of anaesthesiologist.[3-5] 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.[6-8] Atracurium is a benzyl isoquinolinium structure and Vecuronium is a mono-quaternary analogue of steroid relaxant pancuronium. Atracurium is an intermediate acting NDMR ,mixture of 10 optical isomers. It is metabolized by Hoffmann elimination and nonspecific ester hydrolysis.It is associated with histamine release leading to hypotension, anaphylaxis. The pharmacokinetics and duration of nts alternative to succinylcholine with the same or similar parameters like neuromuscular block produced by Atracurium is

not altered by renal failure, liver failure. Cisatracurium is a new NDMR, intermediate acting benzylisoquinolinium ,1Rcis-1'Rcis stereoisomer of Atracurium.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 and is cardiovascular stable in both healthy patients and those with coronary artery disease.[9] On metabolism 5 times less laudanosine is produced. The clinically effective duration of action and rate of spontaneous recovery from equipotent doses of Cisatracurium and Atracurium besylate are similar. Although Cisatracurium is more potent than the parent mixture (ED_{95}) 0.05mg/kg vs 0.2mg/kg its pharmacodynamics profile is similar to that of Atracurium except for a slower onset. $2ED_{95}$doses of Cisatracurium (100µg/kg) do not yield satisfactory intubating conditions such as those seen with equipotent doses of Atracurium .The recommended intubating dose of Cisatracurium is $3ED_{95}$.[10-12] Hence keeping in view of the above facts a study under heading "Cisatracurium in different doses versus Atracurium during general anaesthesia for abdominal surgery: a comparative study, has been taken by me to compare onset time,condition of intubation ,duration of action ,degree of neuromuscular blockade, hemodynamic effects, signs of histamine release between the two drugs.

METHOD

The present clinical study was performed in a tertiary care Hospital, Cuttack during the period from November 2021 to October 2022. The admitted patients in the surgery wards scheduled for various types of elective abdominal surgical procedures were included in this study.

Inclusion criteria-Pts. with ASA physical status class-I and II,

Age-18-60 years

Pts posted for elective abdominal surgery

Exclusion criteria

Hepatic, renal or neuromuscular disease

Asthma, COPD, smoker

Cardiovascular disease, hypertensive patients

H/O or Anticipated difficult intubation(e.g. obesity, Pregnancy, mallampati III or IV and thyromental distance < 6 cm)H/o known allergy to drugs under study. Those taking anticonvulsants, amino glycosides or any Other medications which may affect action of NDMRs.

60 Patients of either sex aged 18-60 years of ASA physical status I &II were selected for the purpose of study.

Gr-A :-(20 patients):-Intubating dose of atracurium 0.5mg/kg IV.

Gr-C1 :- (20 patients):-Intubating dose of cisatracurium 0.10mg/kg IV.

Gr-C2 :- (20 patients):-Intubating dose of cisatracurium 0.15mg/kg IV

The purpose and 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 20patients each to receive an intubating dose of one of the drug chosen for study. Randomization was done by lottery basis. All the cases underwent a thorough clinical examination preoperatively and were scrutinized for exclusion of any underlying disease. Routine investigations such as blood haemogram, total leukocyte count, differential leukocyte count, stool examination, urine analysis, serum urea and creatinine levels, blood sugar, serum electrolytes, liver function tests, X-ray chest PA view, an ECG and a cardiological evaluation was done. Any abnormality detected preoperatively was optimized before surgery. On arrival into the operating room non-invasive monitors like Electrocardiogram (ECG), Non-invasive BP, and pulseoximetry were connected to the patient. Intravenous access was done with an 18G cannula and infusion of crystalloid solution was started. Ryle's tube aspiration was done in all cases.

Pre-medication:-midazolam(0.04 mg/kg IV), Paracetamol (15 mg/kg iv infusion) Glycopyrrolate (0.005 mg/kg iv), nalbuphine(0.5mg/kg iv) Ranitidine (100 mg iv), ondansetron (4 mg iv) Half an hours prior to surgery. All the patients were fasting for 6 hours before surgery. The patients were preoxygenated with 100% oxygen for 3 minutes. Muscle relaxants were given prior to induction with thiopentone sodium. Then induction was done with thiopentone sodium (2.5%) 5mg/kg till the loss of eyelash reflex. The TOF stimulus was given prior to the injection of muscle relaxants. The small silver surface 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 visually.

Muscle relaxants were given according to the following schedule.

Intubating dose- atracurium(0.5mg/kg iv)

cisatracurium (0.10mg/kg iv)

cisatracurium(0.15mg/kg iv)

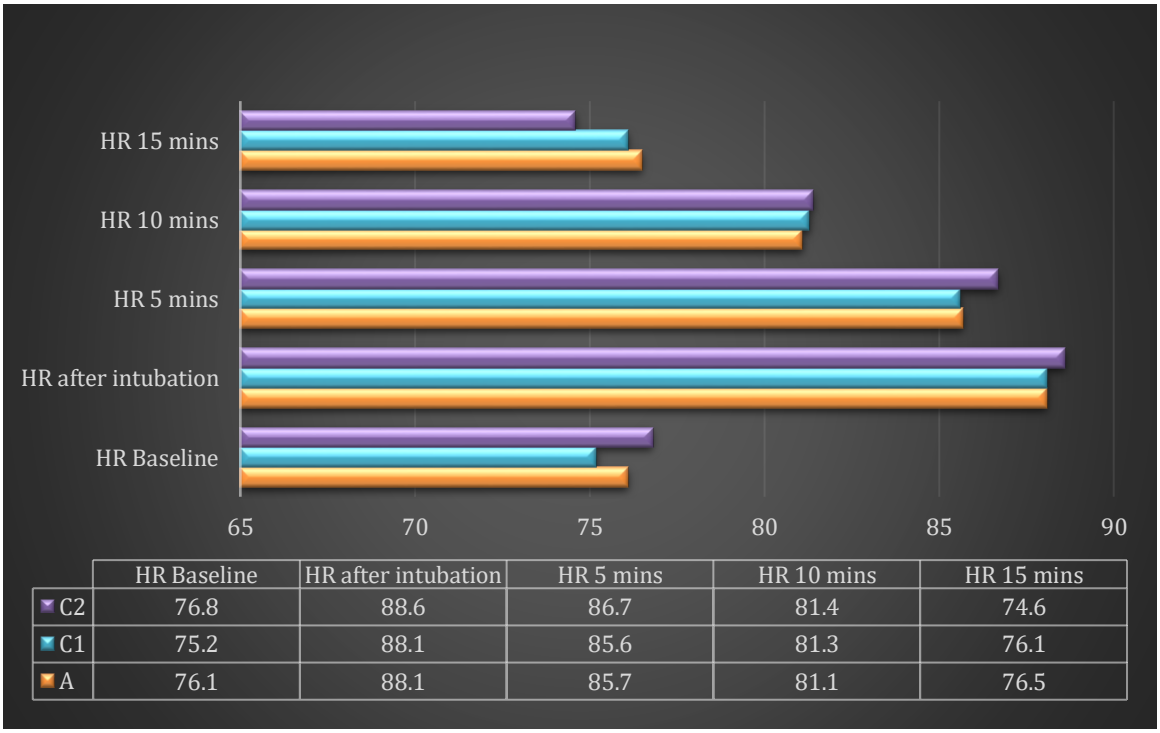
The onset time of the muscle relaxant was determined by measuring the time from injection of muscle relaxant to abolition of all four responses to train of four stimulus. Endotracheal intubation was carried out once maximum block achieved (ie all four responses are ablated) and mechanical intermittent positive pressure ventilation instituted with N2O:O2 (2:1). Intubation conditions were assessed using the train of four stimuli, of the four stimuli; fade in all stimuli was adequate for an effective tracheal intubation. Intubating conditions were categorized as excellent, good, poor and not possible. 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. So haemodynamic parameters like mean arterial pressure and pulse rate were recorded at base line during pre-oxygenation (pre-op),after intubation, at 5 min, 10min and 15 minutes after intubation. Anaesthesia was maintained with N2O:O2 (2:1) and isoflurane as anaesthetic agent. Top up doses of desired muscle relaxant (Atracurium or Cisatracurium) were given to maintain muscle relaxation. After tracheal intubation, 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 (0.05 mg/kg) and inj. Glycopyrrolate (0.008 mg/kg) IV after appearance of all the four twitches of TOF. Extubation was done after proper suctioning of throat secretion and noting consciousness of the patient. 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..A probability value(P-value)<0.05 was considered statistically significant

RESULTS

The mean and standard deviation of age, weight and sex among three groups were compared. ANOVA was done to determine whether there is a significant difference in the age, weight and sex of patients among the three groups A, C1, C2. The results obtained from the analysis shows that there are no statistical differences with respect to age, weight and sex (p>0.05) and the three groups are comparable.

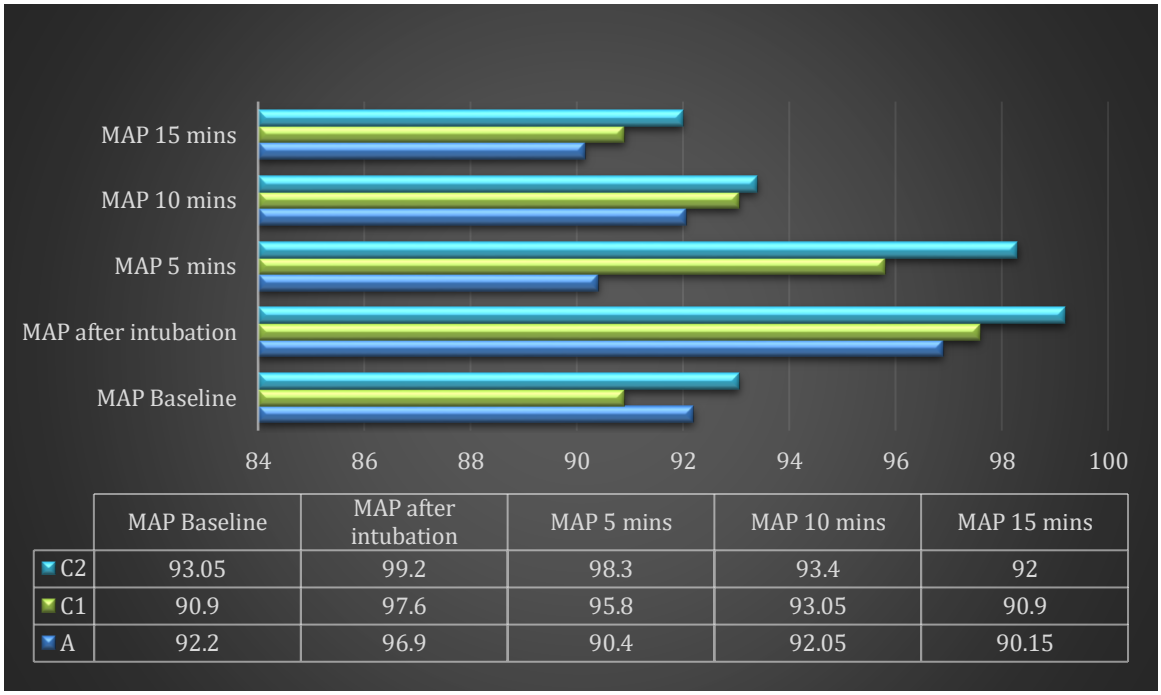
FIG 1:-HEART RATE CHANGES BEFORE AND AFTER ADMINISTRATION OF ATRACURIUM AND CISATRACURIUM



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

The mean and Standard deviation of baseline heart rate, heart rate after intubation and at different time intervals at 5,10,15 mins among three groups were compared. ANOVA was done to determine whether there is a significant difference in the three grps A, C1, C2. The results obtained from the analysis shows that there was an increase in heart rate compared to baseline in all the three groups after intubation and at 5 mins and gradually returns to baseline at 15mins but this may be due to stress response and there was no statistical significant difference. Baseline HR, HR after intubation, HR at 5,10,15 mins are presented as mean ± S.D. Test done was ANOVA.

FIG 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
C2	93.05	99.2	98.3	93.4	92
C1	90.9	97.6	95.8	93.05	90.9
A	92.2	96.9	90.4	92.05	90.15

The mean and Standard deviation of baseline MAP, MAP after intubation and at different time intervals at 5,10,15 mins among three groups were compared. ANOVA was done to determine whether there is a significant difference in the three grps A, C1, C2. 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. The results obtained from the analysis shows that there is no statistically significant difference with MAP changes ($p>0.05$).

FIG 3: ONSET OF ACTION

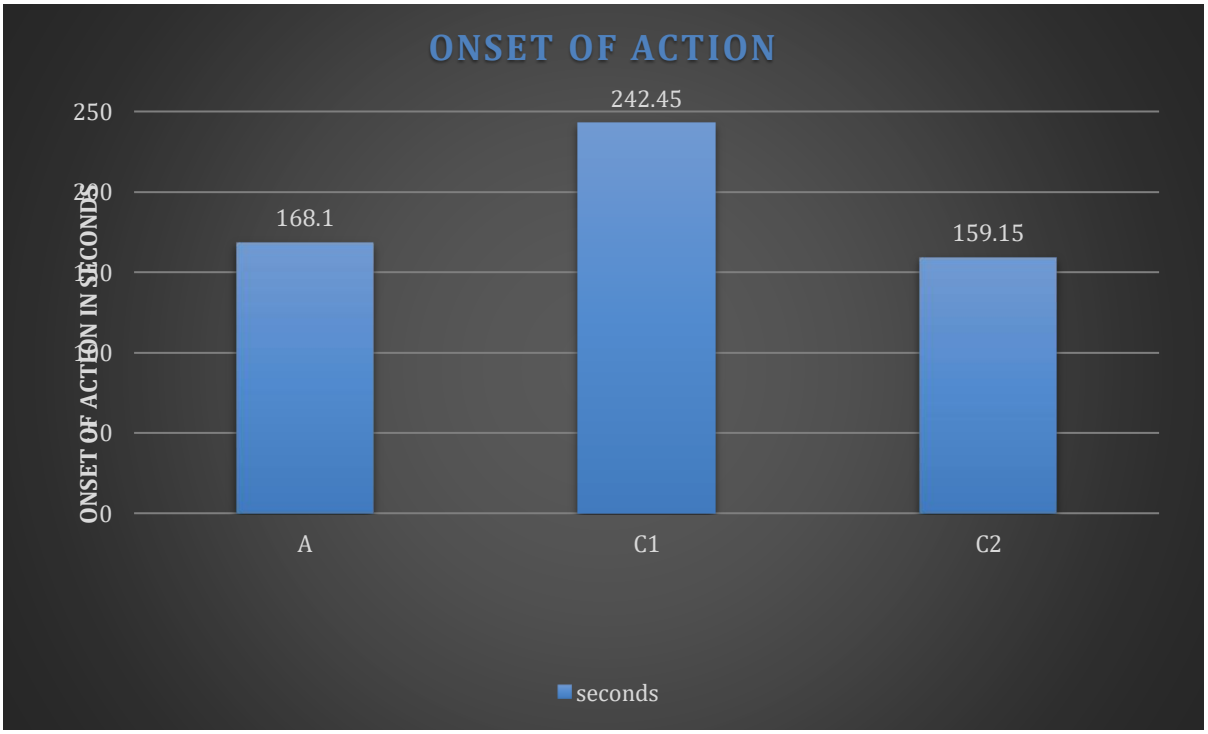


TABLE 1: INTUBATING CONDITIONS

	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

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. 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 grp A and good in 40% cases, while in grp C1 65% had excellent intubating conditions and 35% had good intubating conditions. In grp C2 70% had excellent intubating conditions and 30% had good intubating conditions.

TABLE 2: SIGNS OF HISTAMINE RELEASE

	NO OF PATIENTS
GRP A	2
GRP C1	0
GRP C2	0

Only 2 pts out of 20 who were administered Atracurium showed signs of histamine release i.e facial flushing. While there was no such findings in pts 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 .[13-14] So, its introduction is considered an added advantage over Atracurium. Signs of histamine release were shown in one patient in this study in the form of transient facial flushing after the administration of atracurium; however, this patient did not experience hypotension or tachycardia.[15]So the present study was undertaken to study the neuromuscular properties of Atracurium and to compare it with different doses of Cisatracurium, There have been studies conducted with various doses of these two muscle relaxants for comparison.[16-20] 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. All patients were assessed for hemodynamic state (heart rate, blood pressure), onset time, duration of action, and signs of histamine release clinically, condition of intubations. In our study we used neuromuscular monitoring by Train of four because the response of neuromuscular blocking drugs is not predictable in all patients so the monitoring of neuromuscular function provides more predictable and rational approach to the use of muscle relaxants and better and faster recovery of the patients by optimizing the doses, hence provide better patient care. Among all pattern of stimuli in neuromuscular monitoring , train-of-four is more convenient and popular method for assessment of neuromuscular transmission as it not only causes significantly less discomfort to the patient than tetanic stimuli but in addition has more sensitive index of receptor blockade compared to single twitch stimuli. Due to its relatively lower frequency, it allows response to be evaluated manually or visibly. In our study adequate abdominal relaxation was required which was better with adductor pollicis monitoring. The ulnar nerve at the wrist (as most commonly used site for nerve stimulation) and the response at the adductor pollicis was observed and recorded in my study because adductorpollicis muscle has been promoted as the most useful clinical tool andis the gold standard because of its easy accessibility for visual and tactile assessment. The adductor pollicis muscle exhibits different sensitivity and time course from the laryngeal muscles. But according to Suresh S.N. and Singh NG[21](2010), 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. We, in our study assessed the neuromuscular blockade visually because it is non invasive and more relevant in clinical practice. Although mechanomyography, Electromyography has been used in some of the studies conducted in the past but these equipments are bulky, difficult to operate and feasibility to accommodate them in O.T set up is `nil. In the present study the onset of action was considered as the time taken from Injection of muscle relaxant to abolition of all four responses to train of four stimuli. 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[22] et al,

Bluestein et al 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 were either excellent or good in all the groups in our study. 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 35% patients and in (grp 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 found excellent Intubating conditionsof Cisatracurium in higher doses versus $2ED_{95}$ dose of cisatracurium and Atracurium. There was not any case of not possible intubation among the three studied groups. Our study finding coincides with their results. A study by Bluestein[23] et alwere consistent with our results. They reported that intubation conditions were good or excellent in over 90%of patients in all treatment groups (2 min after approximately 2ED95 doses of cisatracurium or Atracurium and 1.5 min after 3ED95 and 4ED95 doses of cisatracurium).The duration of action of the intubating dose in our study was considered as the time from injection of muscle relaxant to the recovery of the first twitch in the train-of four and maintenance doses were supplemented at the recovery of the first twitch in the train-of-four. The mean ±SD duration of action of Intubating dose in grp A(Atracurium) was 43.0$\pm$2.27 min, grp C1(Cisatracurium) was 43.2$\pm$2.72 min and in grpC2(Cisatracurium) was 64.6±4.83 min. The duration of action was found to be more prolonged in grpC2 with a p-value of 0.000 which is statistically significant. Our study concurs with study by El kasaby[24] et al in which higher doses of Cisatracurium were found to be statistically significant ,more rapid onset of action and longer duration of action than 2ED95 dose of Atracurium and Cisatracurium. Bluestein[25] et al also reported that increasing the initial dose of Cisatracurium(from 0.1 to 0.15 and 0.2 mg/kg) decreased the mean time of onset (from 4.6 to 3.4 and 2.8min, respectively) and increased the mean time of clinically effective duration (45 to 55 and 61 min, respectively).These results were similar to our study results. In our study the mean ±SD pre-op heart rate was 76.10±6.63 per minute in grp A(Atracurium) , 75.2±5.28 per minute in grpC1(Cisatracurium) and 76.8±5.16 per minute in grp C2 respectively which was statistically not significant. 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.

CONCLUSION

It may be concluded that $3ED_{95}$ dose of Cisatracurium. Is more effective neuromuscular blocking agent than$2ED_{95}$ dose of Cisatracurium and Atracurium. It has faster onset of action and longer duration of action. It is hemodynamically more stable. It has no signs of histamine release clinically. Like previous several studies, our study shows that Cisatracurium even with higher dose is safe and more efficacious as compared to Atracurium. Use of the Train of four as means to know onset and completion of muscular paralysis and its duration as well, is also proved to be the method of choice.

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