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Original Article

Anaesthesia Section

Efficacy of Different Doses of Cisatracurium for Intubation during Surgeries under General Anaesthesia- A Randomised Clinical Study

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ABSTRACT

Introduction: Cisatracurium is a new non depolarising, Neuromuscular Blocking Drug (NMBD) with fast onset and short duration of action. It is a stereoisomer of atracurium with a potency of approximately three to four times greater than that of atracurium. As it is devoid of histamine release, it reduces the chances of adverse effects during operative procedures. However, the optimum intubating dosage needs to be established in patients. This warrants the need for studies focusing on the efficacy of different doses of cisatracurium and their outcomes.

Aim: To study the efficacy of three different doses of cisatracurium {2x Effective dose (ED) 95, 4x ED95, and 6x ED95} for the time of onset of action, duration and haemodynamic stability offered for intubation.

Materials and Methods: A double-blind, randomised clinical study was conducted from December 2017 to July 2019 at a tertiary care hospital and research centre, Kolhapur, Maharashtra, India. Total 90 patients, undergoing surgeries under general anaesthesia were allocated into three groups, group A received 0.1 mg/kg, group B received 0.2 mg/kg and group C received 0.3 mg/kg of cisatracurium. Time taken for Train Of Four (TOF) to reach 0 was taken as the onset of action, and appearance of TOF two, three or patient's attempt to breathe was taken as duration of action. Haemodynamic changes were also assessed preoperatively and postintubation immediately after confirmation of placement of ETT.

Results: Mean age 33.23±6.26 years in group A, 37.70±10.80 years in group B, 38.23±8.764 years in group C (p-value=0.06). Least time was required for the TOF to become zero by group C (5.10±1.01 minutes) as compared to groups A and B (9.91±1.39 and 7.48±1.45 minutes) which was statistically significant (p-value <0.001). The duration of action was also more in group C (49.83±5.33) compared to group A (27.23±6.97) and group B (36.17±7.62) (p-value=0.00001). Group C had better haemodynamic stability as the heart rate remained more stable than group A and group B.

Conclusion: Higher dose of cisatracurium provides faster onset, longer duration of action with better cardiovascular stability. This predictable recovery from non depolarising muscle relaxation makes it a good choice of muscle relaxant agent for intubation.

Keywords: Haemodynamic, Histamine release, Muscle relaxant, Stereoisomerism

INTRODUCTION

Muscle relaxants or neuromuscular blocking agents are used during surgery to keep the patient immobile during general anaesthesia. In recent years, muscle relaxation has become an inevitable part of anaesthesia, intensive and emergency care [1,2]. It is routinely being used for procedures like endotracheal intubation and during surgery thereby facilitating immobilisation of patients. When administered in optimal concentrations followed by regular top-ups or continuous infusion, it contributes to the safety of the patients as well [3].

The first neuromuscular blocking agent to be used was called curare. It was used in 1942 by Harold Griffiths and Enid Johnson for relaxation in abdominal surgeries. Following this, many neuromuscular blocking agents such as alcuronium, tubocurarine, and gallamine were discovered, but are no more used due to the adverse effects they produce [4]. Atracurium was the first non depolarising muscle relaxant discovered. The duration of effect is limited by its metabolism by Hofmann's degradation and not dependent on the liver or renal function as is the case with other depolarising agents. However, it is associated with adverse effects like flushing, erythema, bradycardia, bronchospasm, and dyspnoea resulting due to the release of histamine [5].

Cisatracurium is one of the 10 stereoisomers of atracurium, which is devoid of histamine release [6]. It is an intermediate-acting, non depolarising NMBD, with minimal cardiovascular side-effects [3]. It acts as a competitive antagonist to acetylcholine and binds to nicotinic cholinergic receptors at the muscle motor endplate. As acetylcholine cannot bind anymore on these receptors, end-plate potential cannot develop. The neuromuscular blocking potency of cisatracurium is proposed to be almost three times that of atracurium [7]. It undergoes degradation by Hoffmann reaction, and the liver and kidneys play only minor roles in its metabolism and elimination.

Generally, the recommended dose of cisatracurium for induction ranges between 0.1-0.2 mg/kg, although it could vary in patients who are critically ill [8]. Currently, studies comparing different ED of cisatracurium are scarce, and performed for a particular set of surgeries [9,10]. The present study aimed to study the efficacy of three different doses of cisatracurium for intubation during general anaesthesia, in different types of surgeries. The primary outcome was the time required for intubation (onset of action) and secondary outcomes were duration of action and haemodynamic stability.

MATERIALS AND METHODS

A double-blind, randomised clinical study was conducted from December 2017 to July 2019 at a D. Y. Patil Medical College, tertiary care hospital and research centre, Kolhapur, Maharashtra, India. Approval was obtained from the Institutional Ethics Committee (DMCK/129/2017). An informed consent letter was obtained from each patient.

Sample size calculation: The mean pulse rate recorded after one minute of intubation was 102.62 with SD of ±4.06 in group A and 99.57±3.35 and after five minutes 98.02 with SD of ±3.35.

$$\text{Sample size } n=\frac{(Z_{\alpha/2}+Z_{\beta})^2\times 2\times\sigma^2}{d^2}$$

N1=30, so this is sample size of one group. In group A=30, group B=30 and group C=30. Total sample size=90.

$Z_{\alpha/2}=(\alpha/2)^{th}$ quantile of normal distribution

$Z_{\beta}=(\beta)^{th}$ quantile of normal distribution

D=difference in means

σ^2=population variance

Sample size calculated is around 90 at 95% confidence interval. Sample size of 30 was taken in each group, so our total sample size=90 i.e 30 in each group A,B and C respectively.

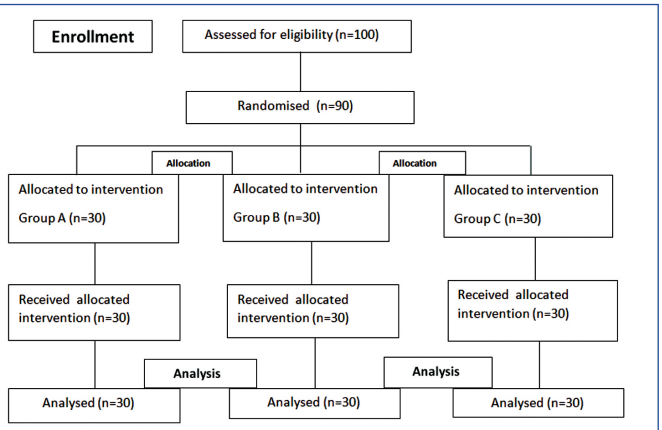
Inclusion criteria: A total of 90 patients between 15-65 years, belonging to American Society of Anesthesiologists (ASA) grade I or II and requiring endotracheal intubation to undergo surgery under general anaesthesia were selected. Patients with Mallampati Class 1 and 2, thyromental distance >6.5 cm, adequate neck mobility were included in the study.

Exclusion criteria: Patients of ASA Grade 3 or more, Mallampati Class 3 or more, thyromental distance <6.5 cm, short neck, restricted neck mobility, and history of allergy were excluded from the study.

Patients were allocated randomly into three groups:

- Group A- 0.1 mg/kg
- Group B- 0.2 mg/kg
- Group C- 0.3 mg/kg

Randomisation was done using a computer-generated randomisation chart. Both the anaesthesiologist and patient were blinded. The preparation of medication according to the allocated group was done by a nurse, who was trained and qualified for such activity. The drug was prepared in 10 mL for all the groups [Table/Fig-1].



[Table/Fig-1]: CONSORT flow diagram.

A day before the surgery, all patients were assessed for their clinical history, detailed clinical examination, and investigation. Clinical history was elicited to rule out symptoms of any cardiovascular, respiratory, hepatic, renal, or metabolic disease. Clinical examination included a general examination, systemic examination, and airway assessment to assess the functional status of the patients.

Study Procedure

All patients were kept nil by mouth for six hours before the surgery, in the operation theatre, intravenous access was secured for all patients. A baseline reading of pulse, blood pressure, and oxygen saturation were noted. Neuromuscular monitoring was carried out along with the use of clinical judgment. The adductor pollicis muscle of either hand was monitored for neuromuscular monitoring. Electrodes were applied on the volar side of the wrist. The distal electrode was placed 1 cm proximal to the point where the proximal flexion crease of the wrist traverses the radial side of the tendon extending towards the flexor carpi ulnaris muscle and the proximal electrode was positioned 3 cm proximal to the distal electrode. All patients received premedications consisting of injection glycopyrrolate -0.004 mg/kg Intravenous (i.v), injection ondansetron 0.1 mg/kg i.v., injection omeprazole 40 mg/kg i.v. in 500 mL Normal Saline (NS) over 30 minutes, injection metoclopramide 10 mg i.v., injection midazolam 0.05 mg/kg i.v. and injection fentanyl 2 mcg/kg i.v..

Anaesthesia was induced with injection propofol 2 mg/kg and after the patients were under anaesthesia as judged by the loss of eyelash reflex and could be ventilated well with, bag and mask ventilation. Inj. cisatracurium (CISATRA, Themis India, 2 mg/mL) was administered in the required dose according to the groups they belonged to group A, group B and group C. The investigator injected the drug prepared by the nurse according to the randomisation schedule and monitored the TOF. Inhalational agent sevoflurane was used to achieve a Minimum Alveolar Concentration (MAC) value of 1.0 until TOF, 0 was achieved, i.e., satisfactory intubating conditions were achieved to maintain the depth of anaesthesia. After 90 seconds of injection of cisatracurium, TOF was observed every 30 seconds until it reached 0 using the TOF watch Inmed device (Inmed Equipments Pvt. Ltd., Vadodara, Gujrat, India).

Once the TOF score reached 0, endotracheal intubation was performed. Laryngoscopy and endotracheal intubation was carried out using MacIntosh laryngoscope blade no. 3 by one of the senior investigators who was not a part of the study. Airway secured by using appropriate size cuffed portex endotracheal tube (males 8-8.5, females- 7-7.5) and secured with tape after confirmation of air entry by chest auscultation as bilaterally equal and end-tidal carbon dioxide monitoring. Vitals are recorded postintubation to assess the intubation response.

Anaesthesia was maintained with oxygen/air/sevoflurane. The TOF was assessed every five minutes after 20 minutes of intubation to find the duration of action of cisatracurium. The clinical duration of action of each patient was noted until the time of attempts to start breathing or a TOF score of 2 or 3 was seen. Patients were monitored clinically for any adverse effects of histamine release. The drug dose was not revealed to the investigator who conducted the intubations to avoid bias in the results.

STATISTICAL ANALYSIS

Descriptive data analysis was performed by R studio with version 1.2.5001 software. The categorical data were compared, and associations were calculated using the R-Studio, v1.2.5001. The p-value ≤0.05 were statistically significant. In the given study total 3 groups are comparatively studied and under each group total of 30 sample size was collected. Analysis of variance (ANOVA) and Kruskal-Wallis test was done for finding the significant mean difference in those three groups. Paired t-test was used to find the statistical difference between pre operative and postintubation vitals.

RESULTS

The three groups A, B, and C had no difference based on the demographic parameters and Body Mass Index (BMI) [Table/Fig-2]. The common surgeries that were performed were tonsillectomy (n=18, 20.00%), cholecystectomy (n=22, 24.44%), laparoscopic appendectomy (n=31, 34.44%) and diagnostic laparoscopy (n=10, 11.12%).

The time required for (onset of action) TOF to become 0 was assessed. Least time was taken by group C with a mean of 5.10±1.01 minutes as compared to group A and B, 9.91±1.39 minutes, and 7.48±1.45 minutes, respectively and was found to be statistically significant (p-value ≤0.05) [Table/Fig-3]. Similarly, the duration of action was also found to be significantly different among groups. Group C had the longest duration of action with a mean of 36.17±7.62 minutes compared to group A with a mean of 27.23±6.97 minutes, and group B with a mean of 36.17±7.62 minutes [Table/Fig-3]. The difference in duration was statistically significant as the p-value <0.001. There was good jaw relaxation and satisfactory intubating conditions in all the groups, irrespective of the dose. The mean heart rate varied significantly in groups A and B between the preoperative period and postintubation, the p-values being p-value <0.001 and p-values <0.001, respectively. No significant differences in heart rate was noted between the preoperative period and postintubation in group C (p-value <0.001 [Table/Fig-4]. The Systolic Blood Pressure (SBP) varied significantly in preoperative and postintubation in all the groups, Diastolic Blood Pressure (DBP), varied significantly in group A and C , but not in group B [Table/Fig-4].

Variable	Group A (0.1 mg/kg)	Group B (0.2 mg/kg)	Group C (0.3 mg/kg)	p-value (Kruskal-Wallis Test)
Gender	17 Female/13 Male	12 Female/18 Male	15 Female/15 Male	-
Body mass index (m/kg^2)	23.3±2.53	24.8±2.107*	24.76±2.22*	**0.19**
Age (year)	33.23±6.26	37.70±10.80	38.23±8.764	0.06

[Table/Fig-2]: Gender, age and Body Mass Index (BMI) distribution of patients (n=90, 30 in each group).
Kruskal-Wallis test used for p-value calculation, p-value <0.05 was considered as statistically significant

Group	Mean±SD (min)	Median (min)	p-value (Kruskal-Wallis Test)
Onset of TOF			
Group A	9.91±1.39	10	**<0.001**
Group B	7.48±1.45	7.15	
Group C	5.10±1.01	5	
Duration of action			
Group A	27.23±6.97	25	**<0.001**
Group B	36.17±7.62	25	
Group C	49.83±5.33	37.5	

[Table/Fig-3]: Comparison of onset (TOF 0) and mean duration of action among groups (n=30 each).
Kruskal-Wallis test used for p-value calculation, p-value <0.05 was considered as statistically significant

Variables	Mean±Standard deviation	p-value
Heart rate (beats/minute)		
Preoperative (ANOVA)		
Group A	86±13.521	**0.0194**
Group B	86.8 3±13.316	
Group C	95.9±17.253	
Postintubation (Kruskal-Wallis Test)		
Group A	109.0 3±8.344	**0.0001**
Group B	103.77±5.998	
Group C	100.57±4.591	
Systolic blood pressure (mmHg)		
Preoperative (ANOVA)		
Group A	128.73±11.8	0.0723
Group B	120.97±11.863	
Group C	122.77±17.464	
Postintubation (Kruskal-Wallis Test)		
Group A	101.23±19.26	**0.0216**
Group B	111.2±10.23	
Group C	106.07±8.07	
Diastolic blood pressure (mmHg)		
Preoperative (Kruskal-Wallis Test)		
Group A	78.7±9.781	0.2840
Group B	74.13±9.627	
Group C	76.6±5.379	
Postintubation (Kruskal-Wallis Test)		
Group A	66.73±9.72	0.0700
Group B	73±10.289	
Group C	70.87±10.234	

[Table/Fig-4]: Comparison of Heart rate, Systolic Blood Pressure (SBP), Diastolic Blood Pressure (DBP) and p-values among groups A, B and C.

By using paired t-test it was found that SBP shows a significant difference between preoperative and postintubation vitals in groups A, B, and C, which is due to the pressor response to intubation. DBP also showed a significant difference between preoperative and postintubation vitals, in groups A and C only but group B showed better stability. HR shows a significant difference between preoperative vitals and postintubation in groups A and B respectively, but group C was more stable [Table/Fig-5]. No adverse response nor other complications were noted in any of the patients, regardless of the dose used.

DISCUSSION

Neuromuscular blocking agents are frequently used for the relaxation of the skeletal muscle during tracheal intubation in patients undergoing surgeries under general anaesthesia. An ideal anaesthetic agent should have a rapid onset, good muscle relaxation, predictable clinical duration of action, better haemodynamic stability, without residual paralysis, and without posing any complications [3,11]. Cisatracurium, a derivative of atracurium, has been proposed to be a molecule of choice and it is devoid of histamine release. Cis atracurium has been used in various types of surgeries like abdominal surgeries [12], laparoscopic surgeries, [13] gynaecological procedures [14], spine surgeries [15], and even in Intensive Care Unit (ICU) as well [8]. This study evaluated three different doses of cisatracurium for the onset of action, duration of action, and haemodynamic stability offered. Three groups were matched regarding age and sex. Higher doses showed faster onset of action with a longer duration. Heart rate remained more stable during intubation with the higher dose of cisatracurium. SBP was increased in all three groups as a stress response to intubation. Group B had stable DBP compared to the other two groups. Overall haemodynamic stability offered was inconclusive.

Polovnikov EV et al., studied 24 women of class III and IV obesity posted for gynaecological procedures divided into two groups receiving 0.15 mg/kg according to real body weight and 0.15 mg/kg, ideal body weight. Patients who received doses related to ideal body weight showed better control [14]. Dose-dependent prolongation of action was seen in patients who received dosing according to real body weight. This new isomer of atracurium has a wide range of intubating doses. The present study evaluated three different intubating doses of cisatracurium 2x ED95, 4x ED95, and 6x ED95.

Atef H et al., compared atracurium and three doses of cisatracurium for abdominal surgeries [12]. They found two ED dose of Atracurium showed faster onset of action (3.24±0.55) than two ED dose of cisatracurium (4.37±0.46), but four ED of cisatracurium dose showed faster onset of action (2.9±1.4) than atracurium (3.24±0.55). In this study, faster onset of action was found with a higher dose of cisatracurium, six ED dose had the fastest onset. Aswani B et al., compared between two doses 0.1 mg/kg (2×ED95) and

Group	Time	SBP Mean±SD (mmHg)	p-value	DBP Mean±SD (mmHg)	p-value	HR Mean±SD (mmHg)	p-value
A	Preoperative	128.73±11.80	**<0.0001**	78.70 (9.78)	**<0.0001**	86.0±13.52	**<0.0001**
	Postintubation when TOF 0	101.23±19.26		66.73 (9.72)		109.03±8.34	
B	Preoperative	120.97±11.86	**<0.0001**	74.50 (9.63)	0.6153	86.83±13.32	**<0.0001**
	Postintubation when TOF 0	111.2±10.23		73.0 (10.29)		103.77±5.99	
C	Preoperative	127.1±17.46	**<0.0001**	76.6 (5.38)	**0.0037**	95.9±17.25	0.155
	Postintubation when TOF 0	106.07±8.07		70.87 (10.23)		100.57±4.59	

[Table/Fig-5]: Comparison of Systolic Blood Pressure (SBP), Diastolic Blood Pressure (DBP), Heart rate in preoperative vitals, postintubation when TOF is 0 by between the groups.
p-value <0.05 was considered as statistically significant, calculated by paired t-test

0.2 mg/kg (4×ED95) of cisatracurium for its intubating conditions, haemodynamic response and any untoward effects; and found that higher dose (4× times the ED95 dose) provides excellent intubating conditions and stable haemodynamic [6].

In the present study, the heart rate varied significantly among groups A, B, and C, corresponding to the different doses of cisatracurium (0.1 mg/kg, 0.2 mg/kg and 0.3 mg/kg). This the difference was more pronounced in postintubation vitals (p-value <0.0001) than the preoperative period. The lowest heart rate and closest to the preoperative value was reported in group C (0.3 mg/kg) suggests better maintenance of heart rate than groups A and B. Better muscle relaxation provided by a higher dose probably results in better heart rate stability. Cao Q et al., used three doses of cis atracurium (low dose- 0.15 mg/kg body weight, medium dose 0.2 mg/kg and high dose 0.3 mg/kg) for radicle resection of lung cancer.They found better haemodynamic stability with the higher dose of cisatracurium, which is concurrent to the present study [10].

A similar trend of the higher dose of cisatracurium to provide a more stable heart rate has also been reported by Atef H et al., as well [12]. It has been well suggested in previous studies that the SBP and DBP varied insignificantly between groups, both in the preoperative period and postintubation. The duration of action (minutes) for group A was 27.23 with an SD of 6.971and for group B was 36.17 with SD of 7.621 (0.1 mg/kg and 0.2 mg/kg, respectively) but increased significantly in group C to 49.83 with an SD of 5.331 (0.3 mg/kg). The duration of action here was however far shorter than in other studies. The reason for this difference may be related to the potency of the drug which is affected by inadequate maintenance in the cold chain during transport and storage of the drug. Likewise, Atef H et al., also reported a prolonged duration of action with increasing cisatracurium concentration [12].

No adverse events were reported in any of the cases, advocating the safety of the doses used for the study, similar to previous studies as cisatracurium is known to induce mast cell activation and pseudo-allergic reactions [5]. Other important factors which are needed to be considered on deciding the cisatracurium dose for intubation is BMI [15], desired time of intubation and the anticipated length of surgery.

The principal advantage of cisatracurium is the lack of histamine release which provides better cardiovascular stability as compared to atracurium and other histamine-releasing NDMR. Also, faster onset, longer duration of action with larger doses of cisatracurium 4xED95 (0.2 mg/kg), which also provides better cardiovascular stability, thus making it a good muscle relaxant agent for endotracheal intubation in clinical practice. This study covers different types of surgeries under general anaesthesia, thereby ruling out surgery-specific deviations in the outcomes.

Limitation(s)

This was a single-centre study. Further studies in a target population with hepatorenal involvement are required to test the efficacy of the drug since this study was carried out among the general population. Authors used TOF for the onset and duration of action. Advanced monitors are available in the market which can give more precise readings.

CONCLUSION(S)

The efficacy of cisatracurium is more at higher doses. It provides cardiovascular stability, predictable recovery from Non depolarising Neuromuscular Blockers, thus making it a good choice for a muscle relaxant agent during endotracheal intubation in clinical practices. It can be used in different types of surgeries in combination with anaesthetics in maintaining haemodynamic parameters.

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