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Research Article

AN EVALUATION OF ATRACURIUM, CISATRACURIUM AND ROCURONIUM ON THE INTUBATING CONDITION: A COMPARATIVE STUDY

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A B S T R A C T

Introduction: The present study was undertaken with an aim to compare the intubating conditions, onset time, haemodynamic effects and adverse effects with the use of atracurium, cisatracurium and rocuroniumto develop a non-depolarising muscle relaxant with a speed of onset comparable with succinylcholine but with less adverse effects.

Materials and Methods: A randomized double blinded study was conducted among 75 adult patients according to inclusion and exclusion criteria. They were randomly distributed into three groups (25 patients each). Group I received 0.6mg/kg rocuronium, group II received 0.1mg/kg cisatracurium and group III received 0.5 mg /kg atracurium intravenous injection. To assess the intubating condition and the onset of action of different drugs, a Train of four monitor was used.

Results: The mean onset time of action was fastest in group I(89.28±5.53 seconds with intubating condition score of 8.68) than group II and group III. All three groups had similar or comparable haemodynamic response after intubation. There were no side effects recorded.

Conclusion: From the study, it could be concluded that rocuronium at a dose of 0.6 mg/kg provides better intubating condition than atracurium and cisatracurium.

INTRODUCTION

In the present day practice, smooth, rapid and safe endotracheal intubation is an integral part of administration of anaesthesia, in a patient undergoing surgery. Succinylcholine, a depolarizing muscle relaxant with its rapid onset of action and short duration of action provides an ideal intubating condition.[1,2,3] But it can cause adverse effects like fasciculations, increased intracranial pressure, increased intraocular pressure. Succinylcholine also causes intracellular release of potassium from the myocytes, resulting in transient hyperkalemia which may precipitate dysrhythmias and cardiac arrest. Because of these adverse effects and risks associated with succinylcholine, extensive laboratory work has been done in order to develop a non-depolarizing neuromuscular blocking agent with a speed of onset comparable to succinylcholinebut with less adverse effects. So, when succinylcholineis considered undesirable or contraindicated, the non-depolarizing neuromuscular blocking drugs can be used safely to accelerate the favourable intubating condition.[2,4,5]

Atracurium is an intermediate acting non depolarizing neuromuscular blocking agent which was introduced into clinical anaesthesia in 1980s. Atracurium has four chiral centers in its bis-benzylisoquinolinium structure. Atracurium breaks down spontaneously in the blood stream by "Hofmann Elimination". Atracurium was developed in an attempt to obtain a non depolarizing agent which has more rapid onset of action, shorter duration and with less cardiovascular side effects as compared to the older agents. Although it may release histamine and may be accompanied with a slight fall in arterial pressure.[3,5]

To overcome this, cisatracurium was introduced clinically. Cisatracurium is apurified form of one of the 10 stereoisomers of atracurium, accounting for about 15% of the total mixture. It does not cause histamine release and cardiovascular side effects are significantly less.[1,2,3]

Rocuronium is an aminosteroidal non-depolarizing neuromuscular blocking agent. It is a monoquarternary analogue of vecuronium. It is primarily eliminated via hepatic reuptake and biliary excretion and upto 20% is excreted unchanged in urine. It does not trigger histamine release. It has one metabolic 17-desacetyl rocuronium which has only 5-10% of activity of present compound.[7,8,9,10,11]

In literature, we found there is a paucity of work evaluating the intubating condition of these drugs and no such study has been done in this part of the country. So, we had planned to design a study to evaluate and compare the intubating condition and

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onset of action of these drugs with the help of TOF (train of four) stimulation.

The purpose of present study was to compare the intubating conditions, onset time, haemodynamic effects and adverse effects with the use of atracurium, cisatracurium and rocuronium.

MATERIALS AND METHODS

The study was a prospective, randomized, double-blinded one conducted at Department of Anaesthesiology, Regional Institute of Medical Sciences, Imphal, Manipur, India, over a period of two years from September 2017 to August 2019 after taking institutional research ethics board approval and written informed consent from 75 patients of ASAgrade I & II physical status and aged between 18 to 60 years, scheduled to undergo elective surgery under general anaesthesia, were enrolled in the study. Patient with history of cardiovascular, respiratory and ischemic heart diseases, renal and hepatic dysfunctions, neuromuscular dysfunction, myopathies, with anticipated difficult intubation and patients receiving drugs interfering with neuromuscular action were excluded from the study.

A set of 75 serial numbers were designated to 75 numbers of cases according to their date and time of operation. The serials and subsequently the cases were allotted to 3 different treatment groups by simple randomization technique through a computer based application resulting in allocation of 25 randomly selected cases in each group, either group I, II or III as to receive inj. rocuronium, inj. cisatracurium and inj. atracurium respectively.

Group I (n =25) = Rocuronium 0.6mg/kg body weight.
Group II (n =25) = Cis-atracurium 0.1mg/kg body weight.
Group III (n =25) = Atracurium 0.5mg/kg body weight.
Sample size was calculated based on the study conducted by Mellinghoff H *et al*[6]where we recruited 25 patients in each group considering 5% dropout.

On arrival in the pre-anaesthetic room, intravenous access was secured with 18 G IV cannula and all patients were given crystalloid intravenous infusion at 6-8 ml/kg and pre-medicated with inj. metoclopramide (10mg) IM and inj. glycopyrrolate (0.2mg) IM.

Inside the operation theatre, the patients were connected to the multiparameter monitors for measuring the heart rate (HR), blood pressure (BP), electrocardiogram and peripheral oxygen saturation (SPO_2) and baseline values of these variables were recorded. For neuromuscular monitoring a peripheral nerve stimulator, TOF watch (Organon-infar), Netherland was used. The ulnar nerve was stimulated percutaneously at the wrist joint with a supramaximal stimulus of 0.2ms duration at a frequency of 0.1 Hertz (Hz).

After pre-oxygenation with 100% O_2 for 3 minutes, anaesthesia was induced with IV inj 1% propofol 2mg/kg body weight till the loss of eye lash reflex. Once the control response had been noted the neuromuscular blocking agent or the study drug was injected and endotracheal intubation was carried out and the onset time of muscle relaxants i.e. the time for the appearance of twitch height upto 25% of initial response from the point of injection of study drug was assessed along with intubating condition score suggested by Cooper R *et al*[12] consisting of total nine score in relation to jaw relaxation, vocal cords conditions and response to intubation which were graded as excellent if score was (8-9), good if score was (6-7), fair if score was (3-5) and poor if the score was (0-2).

Table 1 Intubating conditionas per Cooper R et al[12]

Score	Jaw relaxation	Vocal cord	Response to intubation
0	Poor(impossible)	Closed	Severe coughing or bucking
1	Minimal(difficult)	Closed	Mild coughing
2	Moderate(fair)	Moving	Slight diaphragmatic movement
3	Good(easy)	Open	None

The vital parameters of the patient such as pulse rate, and mean arterial pressure were noted before induction, at the time of induction of anaesthesia and then immediately after endotracheal intubation on administration of neuromuscular blocking agents.

The time for the appearance of twitch height upto 25% of initial response from the point of injection of study drug was noted and this represented the optimal intubating condition of the drug. Study end point was determined just after intubation. Anaesthesia was maintained ina balanced technique with nitrous oxide and oxygen in a ratio of 50:50 along with sevoflurane and systemic analgesics. Heart rate, blood pressure and peripheral oxygen saturation were monitored routinely.

At the end of the surgery, residual effect of the muscle relaxant was detected by TOF ratio and was antagonized with inj. neostigmine (50 mcg/kg) and inj. glycopyrrolate (10mcg/kg). Patient was extubated after the return of the airway protective reflex and was kept in post anaesthetic care unit for monitoring.

The parameters and patient data were recorded and entered in Microsoft Excel sheet and results were analyzed as per intention to treat analysis technique. Comparison among three groups were done by using chi-square test for categorical variables, and ANOVA test for continuous variables and students t-test was used for continuous variables in case of intergroup comparison of two groups and $p \leq 0.05$ was considered significant. Statistical Package for Social Sciences (SPSS) for Windows version 21.0 software, Chicago, SPSS Inc. was used for statistical analysis.

RESULTS

Total 75 patients were recruited for the study purpose. The demographic parameters such as age, weight, sex, ASA status were comparable in all the three groups and did not affect the outcome of our present study as shown in table-2

Table 2 Socio-demographic characteristics of the patients in each group (n=25)

Variable	Groups			p-value
	I n=25	II n=25	III n=25	
Age(in yrs) [mean ± SD]	39.84 ± 13.80	41.68 ± 14.21	39.56 ± 12.50	0.84*
Weight(in kg) [mean ± SD]	60.40 ± 7.45	60.48 ± 0.38	60.40 ± 5.29	0.99*
Sex Male:Female	4:21	5:20	6:19	0.78†
ASA I:II	20:5	17:8	22:3	0.22†

*One-way ANOVA; †Chi-square test

It was observed that Group I, who received rocuronium 0.6 mg/kg of body weight had shortest mean onset time of action

i.e. 89.28 seconds, next to it was Group III, who received atracurium 0.5 mg/kg of body weight, where mean onset time of action was 139.48 seconds and finally Group II, who received cisatracurium 0.1 mg /kg of body weight witnessed the longest mean onset time of action i.e. 172.12 seconds. The result was statistically significant (p = 0.000) as shown in table-3

Table 3 Distribution and comparison of onset time of drugs (in seconds) in the three groups (N=75)

Groups	Onset time of drugs(mean ± SD)	p-value*
Group I	89.28 ± 5.53	
Group II	172.12 ± 5.27	0.00
Group III	139.48 ± 4.12	

*One-way ANOVA

In order to evaluate the ideal intubating condition, mean intubating score was calculated and comparison was done among three groups. For statistical analysis ANOVA test was advocated. Table-4 shows that mean intubating score was higher in Group I, followed by Group III and lowest in Group II. Here p-value (0.00) was found to be significant.

Table 4 Distribution and comparison of intubating score in three groups (N=75)

Groups	Intubating score(mean ± SD)	p-value*
Group I	8.68 ± 0.48	0.00
Group II	7.60 ± 0.58	
Group III	8.12 ± 0.60	

*One-way ANOVA

Table-5 highlights that excellent intubating condition was seen in all cases (100%) of group I, where in group III excellent condition was observed in 88% of cases and in group II excellent intubating condition is found in 56% of cases in comparison to other levels of intubating conditions like good and fair. This result was statistically significant (p=0.00).

Table 5 Comparison of intubating condition in all three groups

Intubating score	Groups, n (%)			
	Group I	Group II	Group III	p=value*
Poor	0	0	0	0.00
Fair	0	0	0	
Good	0	11(44%)	3(12%)	
Excellent	25(100%)	14(56%)	22(88%)	

The haemodynamic changes were comparable in all the three study groups without any significant difference. No adverse effect related to study was reported.

DISCUSSION

In the present day anaesthesia technique some of the commonly available non depolarizing muscle relaxants have been tried to facilitate endotracheal intubation. In our study we have compared three non depolarizing muscle relaxants. In group I, patients received rocuronium 0.6 mg/kg, which was 2 times of ED_{95} (0.3mg/kg) dose of rocuronium. In group II, patients received cisatracurium 0.1mg/kg, which was again 2 times of ED_{95} (0.05mg/kg) dose of cisatracurium. Similarly in group III, patients received atracurium 0.5mg/kg, which is approximately 2 times of ED_{95} (0.23 mg/kg) dose of atracurium. So, we had compared all three drugs at a dose $2\times ED_{95}$ as regard to onset of action, intubating conditions, haemodynamic changes and adverse effects.[13,14,15]

In our present study we have found that group I, who received rocuronium 0.6 mg/kg had shortest mean onset time of action i.e. 89.28 seconds followed by group III or atracurium group (0.5 mg/kg), where onset time of action was 139.48 seconds and finally group II, who received cisatracurium 0.1mg/kg witnessed the longest mean onset time of action i.e. 172.12 seconds.

Similar results were obtained by Omera M *et al*[11], where they compared similar doses of rocuronium and cisatracurium in 40 female patients posted for gynaecological surgery under general anaesthesia. There, they found that rocuronium 0.6mg/kg had a significant shorter onset time of action (mean onset time =70.6 seconds) than cisatracurium 0.1mg/kg (mean onset time of action=160.4 seconds)

Carroll MT *et al*[13] also had similar observation in their study where they compared neuromuscular blocking effect of cisatracurium 0.1mg/kg or 0.15mg/kg with atracurium 0.5mg/kg during anaesthesia with propofol, nitrous oxide and isoflurane. They found the median time for onset of action were significantly shorter with atracurium 0.6mg/kg (median onset time=1.5 mins) than both cisatracurium groups. In cisatracurium 0.1mg/kg group they observed median onset time 2.7 mins, which was significantly higher than atracurium. Mellinghoff H *et al*[6]also found similar result in their study where they compared cisatracurium 0.1mg/kg and atracurium 0.5 mg/kg as regard to onset time of action. They observed mean onset time was higher in cisatracurium (3.1 mins) than atracurium (2.3 mins).

Bakhshi RG *et al*[4]in their study, found that mean onset time of action in cisatracurium besylate 0.2mg/kg group was 3.75 minutes which was faster as compared to 4.79 minutes in atracurium besylate. This result is in contrast with our study findings which is probably because they have taken higher dose of cisatracurium ($4\times ED_{95}$ dose) to compare with atracurium($2\times ED_{95}$ dose),whereas we have compared cisatracurium ($2\times ED_{95}$ dose) with atracurium($2\times ED_{95}$ dose).

It was observed that excellent intubating condition was seen in all cases (100%) of group I, where in group III excellent intubating condition was observed in 88% of cases and in group II excellent intubating condition was found in 56% of cases in comparison to other levels of intubating conditions like good and fair.

Similar observation were obtained by Omera M *et al*[11], where they found clinically acceptable intubating conditions were achieved after 60 seconds more frequently with rocuronium (80%) than with cisatracurium (0%).

Limitations of the study are:

1. Failure to incorporate duration of action of neuromuscular blocking agents (study drugs) in our present study as the end point of our study is just after intubation.
2. Further study is needed incorporating higher doses ($3\times ED_{95}$ dose) of the study drugs to compare the intubating condition among all the three drugs.

CONCLUSION

The observations from the present study showed that rocuronium at a dose of 0.6mg/kg had fastest onset time of action followed by atracurium at the dose of 0.5mg/kg and then cisatracurium at the dose of 0.1 mg/kg. Further it may be concluded that rocuronium provided better intubating condition than atracurium and cisatracurium.

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