

Comparison of Neuromuscular Blockade, Intubation Condition and Reversal between Cisatracurium and Rocuronium with 3×Ed95 Doses.

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Abstract

Background: Optimum relaxation done via non depolarising muscle relaxants (NDMR) is expected to be associated with hemodynamic stabilisation, shorter action and proper reversibility. Cisatracurium and rocuronium are newer NDMR belonging to aminosteroid and benzyliisoquinolinium groups respectively with different elimination pathway. Limited studies are available to assess difference of 3×ED95 doses.

Aim: The primary objective of the present study is to assess difference in the onset time and intubation condition with 3×ED95 with both the drugs whereas the secondary objective is to assess the duration of action and reversal conditions.

Materials and methods: 60 patients posted for the general anesthesia were randomly divided into two groups. Group C received cisatracurium and group R received rocuronium. Train of four (TOF) was used via accelerometer. Time to intubate, duration of action and reversibility were noted. Also intubation condition was recorded. ANOVA and Student's unpaired t-test was used for means of quantitative data and Fisher's chi square tests was used for qualitative data.

Results: Onset of action was significantly shorter with rocuronium compared to cisatracurium with excellent intubation condition with both the drugs. Also there was no significant difference between the duration of action, duration between first TOF response and head lift for 5 seconds and to extubate.

Conclusion: In this comparative study, for 3×ED95 doses of cisatracurium and rocuronium, the onset of action is faster with rocuronium and both the drugs having good intubation condition. The duration of action and reversal condition were same with both the drugs.

Keywords: Cisatracurium, Intubation, Neuromuscular blockade, Reversal, Rocuronium.

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Introduction

General anesthesia is a type of anesthesia wherein patients are deeply sedated to be unaware of surgical pain with intravenous (IV) or inhalational drugs. Neuromuscular blockers (NMB) which causes muscle relaxation especially non depolarising muscle relaxants (NDMR) are used to avoid spasm which can hinder the surgical procedure. Hence NMB have a dominant role in anesthesia. [1] Ideally NMB are expected to have short onset time, provide adequate relaxation during intubation and intraoperatively, maintain stable hemodynamic and return of skeletal muscle function which can be easily estimated. [2, 3] As the development of newer NMB pursued, the anesthesiologists are presently provided with drugs with minimal systemic side effects and efficiently used in rapid sequence induction (RSI) of anaesthesia. [2, 3] RSI is done with NMB having shorter onset of action of 60 to 90 seconds, for which succinyl choline which is a depolarising muscle relaxant is often used. This is done to shorten the duration of bag and mask ventilation before intubation, in patients with high risk of aspiration due to delayed gastric emptying like pregnancy or polytrauma.

There are two classes of NDMR: benzyliisoquinolinium and aminosteroid. Cisatracurium besylate is a newer benzyliisoquinolinium NDMR with intermediate duration of action. [4, 5] It was introduced in 1995. It is approximately 4-5 times more potent than atracurium with slower onset of action. [5] It is eliminated mainly by Hoffmann's degradation. It has minimal laudonosine production and no histamine release even at doses of upto 0.3 mg.kg⁻¹ (6xED95) unlike atracurium. [6]

Rocuronium which is a newer aminosteroidal NDMR, introduced to clinical use in 1992 has a rapid onset with intermediate duration of action. [3, 7] Being monoquaternary analogue of vecuronium, it is mainly eliminated via hepatic reuptake and biliary excretion and up to 20% is excreted unchanged in the urine. [8] It has shorter onset time, intermediate duration of action and rapid recovery characteristics along with cardiovascular stability.⁸ Studies suggests that rocuronium at a dose of 0.9-1.2 mg.kg⁻¹ has an onset of action similar to succinyl choline making it suitable alternative for RSI. [8]

Acceleromyography is a simple method of analysing neuromuscular function. [9] Train-of-four (TOF) at the first dorsal interosseus muscle is the evoked potential in muscle recorded after four continuous stimulus at the peripheral nerve.[10]

ED95 is the dose of NMB that is expected to produce 95% block at the adductor pollicis. Two to three times of ED95 doses are needed for intubation. ED95 dose of cisatracurium is 0.05 mg.kg⁻¹. ED95 dose of rocuronium is 0.3 mg.kg⁻¹.

Carroll MT et al. showed that 2xED95 dose of cisatracurium had longer onset time compared to rocuronium and intubating conditions were comparable between both of them. [11] In Lee H et al. study 3xED95 dose of cisatracurium had slower onset of action but provided good intubating conditions compared to rocuronium.[3] The results obtained in both the above studies are different. Also there are very few studies to compare the intraoperative muscle relaxation effect of 3xED95 doses of these two NDMR.

With respect to reversibility and extubation post operatively, even in present days the dilemma exists between clinical criteria and TOF ratio (ratio of fourth to first evoked potential). Naquib et al. meta-analysis could not derive the conclusion that the residual curarisation could be decreased via TOF monitoring. [12] In contrast Hermmerring et al. review showed acceleromyographic monitoring gives the precision and applicability to various muscles and also TOF ratio more than 0.9 suggest adequate period to extubate. [13] There are limited studies to differentiate the reversal effect of 3xED95 doses of cisatracurium and rocuronium both either clinically or via TOF monitoring.

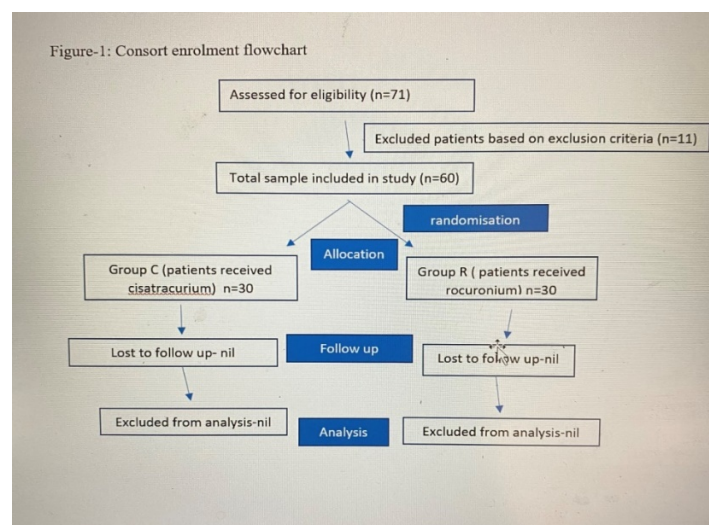
Hence the present study was done to compare 3xED95 doses of cisatracurium and rocuronium for onset and maintenance of relaxation intraoperatively and its reversibility effect during extubation as both these drugs belong to two different categories with different elimination pathway.

Primary objectives are to compare onset of action and intubating conditions. Secondary objectives is to compare duration of action and reversibility using neostigmine with 3xED95 doses of cisatracurium and rocuronium.

Materials and methods:

This is a prospective, randomised, double blinded comparative study conducted between April 2021 to September 2021. 60 patients belonging to American society of anesthesiologists (ASA) grade I and II, who were posted for elective surgeries under general anesthesia lasting for less than three hours were included in the study after ethical committee clearance (ECR/134/Inst/KA/2013/RR-19).

Exclusion criteria were ASA grade above III, age under 18 and over 60 years, obesity with body mass index (BMI) over 30 kg.m⁻², patients receiving medication interfering with NDMR (anticonvulsants, aminoglycosides or polypeptide antibiotics), patients with anticipated difficult intubation and with muscular disorders. After taking informed written consent, the study population were randomly selected among both the groups. Randomisation was done by computer generated tables column. Allotment concealment was done by a person unaware of enrolment. All patients were preoperatively evaluated for the presence of inclusion and exclusion criteria. The patients were assigned into two equal groups with 30 patients in each group depending on the NDMR they received (figure-1).



Group C : received 0.15 mg.kg⁻¹ of cisatracurium. Group R: received 0.9 mg.kg⁻¹ of rocuronium.

Figure 1: Consort enrolment flowchart

After the arrival of the patient to operating room; IV crystalloid was started. Pulse rate (PR), oxygen saturation, surface temperature, ECG, non-invasive blood pressure (NIBP) and end tidal carbon-dioxide were monitored.

After recording the baseline readings, patient were premedicated with IV midazolam 0.05mg.kg^{-1} , IV ondansetron 4mg and IV fentanyl $2\mu\text{g.kg}^{-1}$. Electrode was attached at the radial side on the wrist. Ulnar nerve was stimulated and the impulse was recorded via accelerometer placed on the volar side of the distal phalynx of the thumb which corresponds to adductor pollicis muscle response. Unnecessary arm movements was avoided. With single twitch stimulation, the maximal stimulus was noted. 10% to 15% above this stimulus, supramaximal TOF stimulus was planned to be used after injecting anesthetic agents.

After preoxygenation, IV propofol 2mg.kg^{-1} was injected. IV NDMR was injected depending on the group as mentioned above. The senior anesthesiologist injecting the drug was blinded as the drug is prepared by another anesthesiologist. Every 20 seconds the evoked response to supramaximal TOF electrical stimulation was monitored. Patient was bag and mask ventilated with 40% oxygen, 60% nitrous oxide and isoflurane 0.2% to 2%. Intubation was performed by the same anesthetist who was blinded to give NDMR once TOF is 0. Intubating conditions was assessed using the score described by Goldberg et al. [14]

1. Excellent: Easy passage of the tube without coughing. Vocal cords relaxed and abducted.
2. Good: Slight coughing and/or bucking while passing tube. Vocal cords relaxed and abducted.
3. Poor: Passage of tubes with moderate coughing and/or bucking vocal cords moderately adducted.

4. Not possible: Vocal cords not relaxed, tightly adducted.

If the score was 3 or 4, plan was made to attempt intubation after 30 seconds.

The onset time (interval from the end of muscle relaxant injection till the suppression of first TOF response) was noted. Anesthesia was maintained with a mixture of 40% oxygen, 60% nitrous oxide and isoflourane between 0.2% to 2%.

The duration of action (interval from the end of muscle relaxant injection to the appearance of first TOF response was noted). With the appearance of first response to TOF, maintenance dose of cisatracurium 0.025 mg.kg^{-1} and rocuronium 0.15 mg.kg^{-1} was given.

At the end of surgery, first TOF response appears, reversal was given with IV 0.05mg.kg^{-1} neostigmine and IV 0.01 mg.kg^{-1} glycopyrrolate. Once TOF ratio was greater than 0.9, patient was extubated. The duration between first TOF response and sustained head lift for 3 seconds was recorded. Also duration between first TOF response and TOF ratio > 0.9 was recorded. Intraoperatively analgesia was by IV fentanyl every hourly $1\mu\text{g.kg}^{-1}$. Post operatively the patients were observed for any side effects. Data was collected in the preformed proforma.

Sample size and sampling technique: sample size was 60 patients (30 in each group). The sample size was based on article Lee H et al with 95% confidence interval and 80% power. [3] $n_1 = (\sigma_1^2 + \sigma_2^2 / \kappa) (z_{1-\alpha/2} + z_{1-\beta})^2 / \Delta^2$ and $n_2 = (\kappa * \sigma_1^2 + \sigma_2^2) (z_{1-\alpha/2} + z_{1-\beta})^2 / \Delta^2$. n_1 and n_2 are sample size of group C and R respectively. σ_1 and σ_2 are standard deviation of group C and R respectively. Δ is difference in group means and $\kappa = n_1 / n_2$. Data were entered using MS excel software and analysed using statistical package for social sciences (SPSS) 18 software for determining the statistical significance.

Statistical analysis: frequencies and percentages were calculated for qualitative variables. Range, means and standard deviations were calculated for quantitative variables. Significance of mean of various parameters were assessed with analysis of variance between the two groups. Student's unpaired 't' test was used to test the significance of difference between

quantitative variables and Fisher's chi square tests for qualitative variables. p-value less than 0.05 was considered as significant relationship.

Results:

Both the groups were comparable with respect to age, sex, ASA grades, BMI and duration of surgeries (table-1).

Table 1: Demographic characteristics and duration of surgery.

Parameters		Group-C	Group-R	p-value
Age (mean \pm *S.D.)		37.2 \pm 14.76	37.86 \pm 15.28	0.297
Sex	Males	11 (37%)	16 (53%)	0.194
	Females	19 (63%)	14 (47%)	
**ASA grade	I	15 (50%)	14 (47%)	0.796
	II	15 (50%)	16 (53%)	
Body Mass Index (mean \pm S.D.)		23.82 \pm 2.12	24.70 \pm 1.19	0.053
Duration of surgeries (hours) (mean \pm S.D.)		2.12 \pm 0.54	2.04 \pm 0.55	0.555

* S.D.- Standard Deviation

** ASA- American Society of Anesthesiologist

Onset of action was significantly longer with cisatracurium than rocuronium. Duration of action, though longer with cisatracurium than rocuronium, the difference was not statistically significant. Difference in duration between TOF first response and sustained head lift for 5 seconds after neostigmine injection was not significant. Similarly the difference in

duration between TOF first response and TOF ratio to be more than 0.9 after neostigmine injection was not significant among the two drugs (table-2). The time required to attend the sustained head lift after first TOF response was shorter with both the drugs than the time duration between first TOF response and TOF ratio to be more than 0.9.

Table 2: Onset, duration of relaxation and reversibility

Sl.no	Parameters	Group-C (mean \pm *S.D.)	Group-R (mean \pm S.D.)	p-value
1.	Onset of action (seconds)	194.4 \pm 16.28	139.70 \pm 12.26	<0.0001
2.	Duration of action (minutes)	46.16 \pm 5.97	44.6 \pm 4.9	0.271
3.	Duration between first **TOF response and head lift for 5 seconds after neostigmine (minutes)	2.76 \pm 0.56	3 \pm 4.9 \pm 0.78	0.193
4.	Duration between first TOF response and TOF>0.9 after neostigmine (minutes)	5.3 \pm 0.7	5.53 \pm 0.73	0.212

*S.D.- Standard Deviation

**TOF – Train of Four

The difference in the intubation score between both the groups were not significant with maximum had excellent intubation condition (table-3 and figure-2).

Table 3: Goldberg’s intubation score in both the groups during intubation.

Intubation score	Number of cases	
	Group - C	Group- R
Excellent	26 (87%)	25 (83%)
Good	4 (13%)	5 (17%)
Poor	-	-
Can’t intubate	-	-

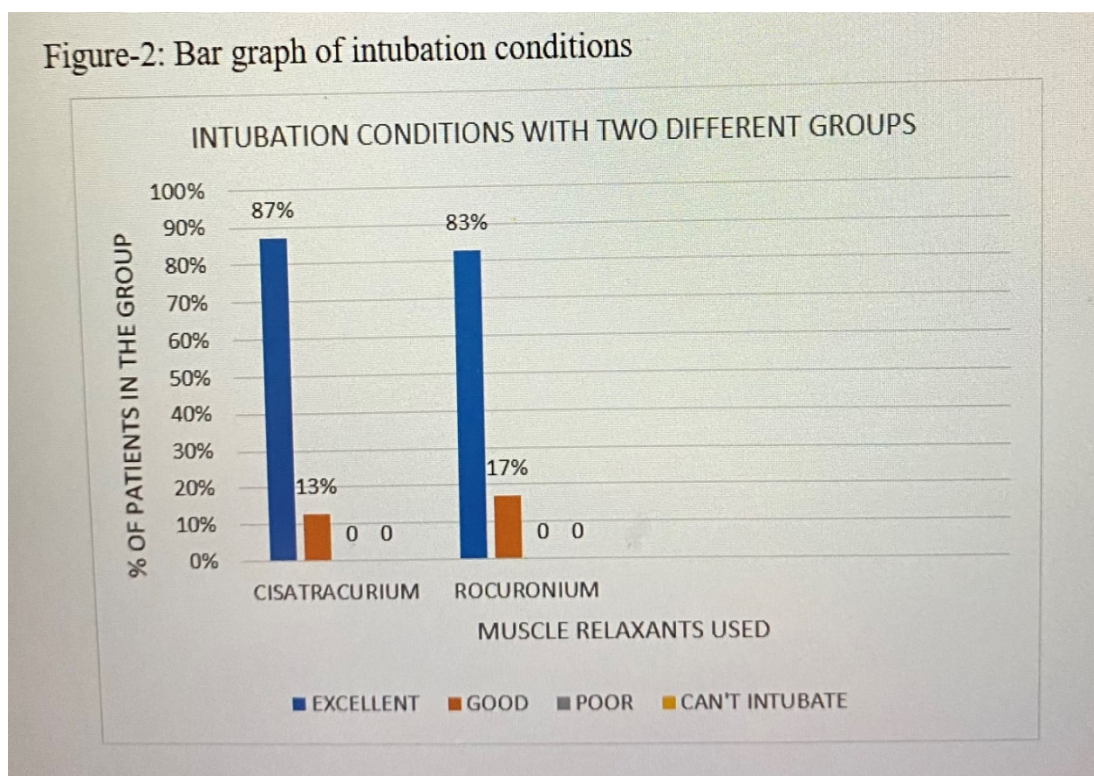


Figure 2: Bar graph of intubation conditions

Discussion:

NMB are very important adjuvant to general anaesthesia. In our study, we tried to assess and compare the effects of 3×ED95 doses of cisatracurium an aminosteroid and rocuronium a benzylalkalonium. The onset of action for the complete suppression of first TOF response was shorter with rocuronium compared to cisatracurium (table-2). Onset time in our study matched with the study of Lee et al. [3], Xiabo et al. and Adamus

et al. [6, 15] In all of these studies 3×ED95 doses of cisatracurium and rocuronium were compared.

Lee et al. compared the onset of action using 3×ED95 doses of rocuronium and cisatracurium using propofol 2mg.kg⁻¹ and ramifentanyl 0.5µg.kg⁻¹. [3] It was statistical significantly shorter with rocuronium 102 ± 49 seconds than with cisatracurium 197 ± 53 seconds. [3]

Xiabo et al. compared $3 \times ED_{95}$ of both these NDMR in adults and elderly patients receiving total intravenous anesthesia (TIVA) with propofol and remifentanyl infusion. [6] Onset of the effect of cisatracurium was 249.30 ± 93.25 seconds and rocuronium was 115.90 ± 37.01 seconds in adult groups whereas it was 261.00 ± 64.56 seconds with cisatracurium and 104.25 ± 33.75 seconds with rocuronium in elderly patients. [6] The difference in onset time of cisatracurium between ours and this study might be because of inhalational agents which we used causing slightly lower onset of time unlike Xiabo et al. study who used TIVA. Muscle relaxation property of inhalational agent perhaps the possible cause.

Onset time of cisatracurium was delayed by three times as compared to rocuronium according to Adamus et al. study with $3 \times ED_{95}$ doses.[15] Here patients were posted for general anesthesia surgery with TIVA maintained with propofol and sufentanil.

Omera et al. and Carroll et al. studies shows that even $2 \times ED_{95}$ of rocuronium has early onset of action compared to cisatracurium. [1, 11]

We assessed the intubation condition once the TOF response completely disappears using the score described by Goldberg et al (table-3 and figure-2). [14] In our study maximum of our patients in both the group had excellent intubation conditions once the TOF response was absent, and the difference was not significant. In Omera et al. study, where $2 \times ED_{95}$ dose was used, clinically acceptable intubation condition was achieved at short time of 60 seconds with rocuronium compared with cisatracurium which was 120 seconds and these times corresponded to the complete absence of TOF responses.¹

In our study the difference in duration of action of both the NDMR were not significant (table-2) and hence the duration of action was almost the same which is

also seen in Adamus et al. and Xiabo et al. study. [6, 15] In Adamus et al. the $3 \times ED_{95}$ doses duration of action of cisatracurium was 52 ± 7 minutes and of rocuronium was 52 ± 12 minutes.¹⁵ Xiabo et al. study had the duration of cisatracurium and rocuronium as 49.50 ± 9.15 minutes and 48.30 ± 13.97 minutes respectively whereas in elderly it was 50.45 ± 4.66 minutes and 70.75 ± 27.31 minutes respectively.[6] The elderly patients had significantly longer duration of action with rocuronium than in adults compared to cisatracurium which might be because of slow metabolism and elimination. [6]

We studied the reversal property of NDMR via two methods: clinically followed by TOF monitoring, after the injection of neostigmine and glycopyrrolate, both given once there was first TOF response. Thus we assessed and compared the induced recovery with $3 \times ED_{95}$ dose of both NDMR.

In our study both, the duration from first TOF response to head lift for 5 seconds and from first TOF response to TOF ratio greater than 0.9, were though longer with rocuronium compared to cisatracurium (table-2), the difference was not statistically significant. Sagir et al. assessed induced recovery. In their study, they compared reversibility of cisatracurium and rocuronium using 4%-6% of desflurane and 50% of N₂O in oxygen whereas we used isoflurane 1% - 2% and 40% of N₂O during intraoperative maintenance. Both of our studies used inhalational agents intraoperatively and not TIVA.¹⁶ In Sagir et al. study, the difference in time duration between reversal of NDMR and clinical tests like occurrence of visual disturbances, head lift, sustained leg lift and hand grip test were not significant with both the drugs.[16] Also the duration to attend the TOF ratio more than 0.9 was similar with both the drugs. [16] But they used $2 \times ED_{95}$ dose to study induced recovery along with

inhalational agents. We obtained similar result with 3×ED95 doses of both the drugs.

Reversal index (RI) is also used to assess the recovery of muscle relaxants and compare the NDMR reversibility. It is the duration between the increase of single twitch response from 25% to 75%. [10] There are several studies with RI to assess reversibility. We compared the result of RI of some studies which used cisatracurium and rocuronium with ours. The difference in RI was not significant in Xiabo et al. study who used 3×ED95 doses and Park et al. study who used 2×ED95 doses of study drugs. [6,17] These studies assessed the spontaneous recovery without anticholinesterase, which were similar with both the drugs. In our study the duration of induced recovery with anticholinesterase was similar with both the drugs.

In Jellish et al. study, TOF recovery time was prolonged significantly with rocuronium compared to cisatracurium. [18] This is contradicting to our study. But here prolonged infusion of both these NDMR were used in neurosurgical patients unlike intermittent bolus dose as in our study. The prolonged infusion can alter the pharmacokinetics of drugs and hence longer recovery time of rocuronium which is mainly eliminated by liver whereas cisatracurium has organ independent Hoffmann's elimination hence perhaps shorter recovery time. [19]

There were some limitations with our study. We did not use RI and also we did not compare the spontaneous recovery because we wanted to assess the pattern of induced recovery among both the drugs as very limited study have done it. Drug pharmacokinetics and pharmacodynamics could have been affected with the inhalational agents but as the inhalational agents were used in both the groups the results are comparable. Post tetanic count could also have been recorded to know the deeper intensity of blockade but we

focussed on TOF responses as it is more widely used. We used post tetanic response to predict first TOF response because as the count decreases from 9 to 4-5, it indicates the shortly appearance of first TOF response.

Conclusion:

In this study of comparison of 3×ED95 doses of an aminosteroid NDMR cisatracurium and benzylisoquinolinium NDMR rocuronium, there is significant faster onset of action for intubation with rocuronium than cisatracurium. Both drugs have excellent intubation conditions after complete disappearance of TOF responses and similar duration of action. The induced reversibility of both the drugs either clinically or once the TOF ratio is greater than 0.9 is also similar.

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