Archives of Anesthesiology and Critical Care (Supplementary 2023); 9(5): 380-385.

Available online at http://aacc.tums.ac.ir

Research Article

Comparison of Onset of Action, Intubating Conditions, and Recovery Characteristics of Rocuronium and Cisatracurium in Patients Undergoing Abdominal Surgery under General Anesthesia: A Prospective Randomized Control Trial

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ARTICLE INFO

Article history:
Received 30 September 2022
Revised 22 October 2022
Accepted 07 November 2022

Keywords:
Rocuronium;
Cisatracurium;
Endotracheal intubation;
Neuromuscular blocking drugs;
Train of four count

ABSTRACT

Background: Neuromuscular blocking drugs (NMBD) have paved the way for the conduct of every known surgical procedure. However, the hunt for optimum NMD with appropriate intubating circumstances is continuous. Rocuronium and cisatracurium are amongst the newer NMBDs. We aim to compare the onset of action, intubating conditions, duration of action, and recovery features in a dose twice the ED95 in patients having abdominal surgery.

Methods: A total 60 American Society of Anesthesiology (ASA) I and II adult patients were randomized equally into Group A and Group B. Group A received Inj. Rocuronium 0.6 mg/kg and Group B received Inj. Cisatracurium 0.10 mg/kg. We assessed the intubating conditions after ensuring jaw relaxation using both the clinical criteria and neuromuscular monitoring whereas onset time, duration of action and recovery time were assessed using neuromuscular monitoring only.

Results: In Group A, a significant rapid onset of action of muscle relaxant was seen compared to Group B (2.4±0.30 mins versus 4.0±0.09 mins, p= 0.00). 93% patients had excellent intubating conditions in Group A compared to 73% patients in Group B (p= 0.038). The duration of action in Group A was 36.73±1.05 mins and in Group B was 47.40 ±1.33mins (p=0.00). Similarly, early mean duration of recovery was found in Group A-45.30±1.29mins versus Group B -57.77±1.19 mins, p= 0.00).

Conclusion: Rocuronium provides rapid onset of action with excellent intubating conditions, and shorter duration of action with an early recovery time compared to cisatracurium.

Introduction

In 1926, Lundy coined the phrase "BALANCED ANESTHESIA", which encompasses analgesia, amnesia, muscle relaxation with the abolition of autonomic reflexes, and maintenance of homeostasis [1]. With the development of neuromuscular blocking drugs (NMBDs), the fundamental notion of balanced anesthesia was created.

By facilitating endotracheal intubation and allowing sufficient muscle relaxation to envisage the optimal surgical area, NMBDs revolutionized the practice of anesthesia. As a result, abdominal, cardiothoracic,

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neurological, and organ transplant procedures became conceivable.

The most common muscle relaxant with rapid onset intubating conditions is succinylcholine, a depolarizing NMBD. However, its shorter duration of action and phase II block with repeated administration led to the search for ideal NMBDs which can provide rapid excellent intubating conditions with adequate muscle relaxation, hemodynamic stability, predictable and complete return of skeletal muscle functions [2].

Rocuronium bromide, a mono-quaternary amino steroidal derivative of the 3-hydroxy analog of vecuronium has a rapid onset of action and a short duration of action [3-4]. The adult dose required to depress 95% of twitch response to nerve stimulation i.e., ED95 is 0.3 mg/kg and 2× ED95 i.e., 0.6 mg/kg is routinely used for endotracheal intubation [5]. Cisatracurium is a benzylisoquinoline non-depolarizing muscle relaxant approved for human use by the FDA. It is a purified form of one of isomer of atracurium besylate and constitutes 15% of the commercially available atracurium. Relative to atracurium, it has a lower tendency to release histamine, thereby providing higher autonomic stability and on metabolism produces five times less laudanosine than atracurium. The adult ED95 of cisatracurium is 0.05mg/kg and 2× ED95 (0.1 mg/kg) has been successfully used for routine endotracheal intubation and to provide muscle relaxation during surgery [6].

There is a paucity of literature in comparison of intubating conditions between two muscle relaxants, i.e., rocuronium and cisatracurium. Hence, the present study was undertaken to compare these two-muscle relaxants in a dose of 2 × ED95 with regards to intubating conditions, onset of action, hemodynamic effects, duration of action, and recovery characteristics in patients undergoing abdominal surgery under general anesthesia. The primary objective of the study was to compare the intubating conditions, the onset and duration of action, and the recovery characteristics of these two muscle relaxants. The comparison of hemodynamic parameters and the incidence of side effects was the secondary objective of the study.

Methods

This prospective, comparative, randomized study was conducted in the multispecialty operation theatre of a tertiary care centre i.e., Fortis hospital, Mohali after the approval of protocol by the ethical committee of the institution with Ethical Comittee's number IEC/2019/TH/06 (functions in accordance with ICH GCP, Schedule Y, ICMR guidelines). This study was carried out over a period of six months from June 2019 onwards.

Study participants: This study included ASA grade I and II patients between 18 to 65 years of age with no difficult airway defined as Modified Mallampati grade 1 and 2 for the study who were planned for abdominal surgery. All patients with major cardiovascular, pulmonary, and neuromuscular disease, renal or hepatic dysfunction, known allergy to rocuronium or cisatracurium, or difficult airway including Mallampati grade 3 and 4 were excluded. All patients were informed about the study protocol and written informed consent was obtained.

Randomization and Blinding

Block randomization with a sealed envelope system was used in the study. In this technique, patients were randomized in a series of blocks of ten. Here, the anesthesia investigator involved in the study prepared ten randomly generated treatment allocations within sealed opaque envelopes, assigning Group A and Group B inside 5 envelopes each. Group A label received injection rocuronium 0.6 mg/kg and Group B label received injection cisatracurium 0.10 mg/kg. Once a patient had given consent to enter a trial, an envelope was opened by anesthesia resident not involved in the study, and then he/she prepared drugs into two 20cc syringes with one labelled as bolus muscle relaxant and another labelled as maintenance relaxant. Neither the patient nor the investigator knew which label represented which group, thus making the study double blinded.

Anesthesia Protocol

A day prior to surgery, a detailed clinical history and a thorough physical and systemic examination, including an evaluation of the airway, were carried out. All the patients were instructed to keep nil per oral for 8 hours for solids and 2 hours for clear liquids and a premedication of tablet alprazolam 0.25 mg and tablet ranitidine 150 mg was given before the surgery according to institutional protocol.

In the operation theatre, patients were monitored for baseline parameters such as pulse rate, mean blood pressure and saturation of peripheral oxygen (Spo2). These parameters were recorded for every 5 minutes during the surgery. An intravenous (IV) line was secured with and ringer lactate was administered. Preoxygenation with 100% oxygen was done for 3 minutes. Prior to induction, fentanyl 2 mcg/kg was given. Induction was done using propofol 2-2.5 mg/kg body weight till loss of verbal contact. Neuromuscular monitoring was carried out by train of four (TOF) stimulation to the adductor pollicis muscle. For endotracheal intubation, according to group allocation Group A- injection rocuronium 0.6 mg/kg and Group B- injection cisatracurium 0.10 mg/kg was given. Endotracheal intubation was attempted when jaw relaxation as assessed by the Cooper scoring system was scored as 3 and TOF count 0-1.

After intubation, anesthesia was maintained with oxygen in air (ratio of 50:50), isoflurane to maintain a minimum alveolar concentration (MAC) of 1. An intermittent maintenance dose of muscle relaxant-rocuronium 0.15 mg/kg or cisatracurium 0.03 mg/kg was administered when the TOF count was 2 (TOF stimulation was repeated every 5 min). Intraoperatively,

patients were monitored for normothermia by inserting an oropharyngeal temperature probe and clinically for signs of histamine release in the form of flushing, erythema, wheals, laryngospasm, bronchospasm and treatment with rescue medicines and techniques if required were also noted.

After the completion of surgery, when TOF count was 4 and TOF ratio was 0.9 and looking at clinical parameters, a neuromuscular reversal agent, i.e., neostigmine 0.05 mg/kg and glycopyrrolate 0.08 mg/kg IV was slowly injected and later the trachea was extubated. All patients were shifted to the post anesthesia care unit (PACU) for post-operative monitoring and for post-operative pain, injection paracetamol 1 gram were prescribed to each patient. They were observed for the first two hours after surgery before shifting to their respective wards.

The following parameters were monitored during the study period:

1) Neuromuscular monitoring was carried out using the ORGANON TOF Watch by Acceleromyography method. The first electrode was applied 1 cm distal to the ulnar crease of the wrist, and the other electrode was placed 3-4 cm proximal to the first electrode. The mode of stimulation was train of four (TOF), i.e., 2 Hz every 15 seconds after an injection of Propofol that acted as control. The following parameter were noted-

Onset time – the time required to reach TOF count was zero after NMBD administration.

Duration of action - Time when first top-up dose of muscle relaxant required after TOF count reached 2 following intubating dose of NMBD.

Recovery time - Time from the last top-up dose of muscle relaxant till TOF count - 4 and TOF ratio of 0.9 was attained, is considered as recovery time.

2) Intubating Conditions: According to the cooper scoring system [5], intubating conditions were assessed and categorized. It includes 3 components, and each component was given score of 0-4. Score 0- indicates no jaw relaxation, closed vocal cords and severe cough as response to intubation and Score 4 indicates relaxed jaw, open vocal cords, and no response to intubation. Intubating conditions were scored as: Excellent [8-9], Good [6-9], Fair [3-5], and Poor [0-2].

3) Hemodynamic parameters as Pulse rate, mean blood pressure, SpO2 were documented at different time intervals. Baseline T1- before induction, T2- after induction, T3- after injection of muscle relaxant, T4 - after intubation and after every 5 minutes for 30 minutes.

4) Signs of Histamine Release: Patients were monitored intraoperatively for clinical signs of histamine release in the form of flushing, erythema, wheals, laryngospasm, and bronchospasm. Rescue medicines if required were also noted.

5) Postoperative Side Effects: Nausea, vomiting, shivering, itching, bradycardia or tachycardia, hypotension, prolonged neuromuscular block, and muscle weakness were noted in the PACU for 2 hours, and rescue medicines were given.

Sample Size Calculation

A sample size was estimated based on the difference of clinical duration (25min) for the two groups based on previous studies conducted by Adamus M et al [7] Cisatracurium vs. rocuronium: A prospective, comparative randomized study in adult patients under total intravenous anesthesia). For CIS 0.10 group, mean of clinical duration was 42 and for ROC 0.60 group, was 35 with SD of 9. At a power of 80 % and confidence interval of 95 %, sample size came out of 26 subjects. To account for the possible dropouts, but it was decided to include 30 patients in each group.

Statistical Analysis

The statistical calculations were carried out using SPSS (Statistical Package for the Social Science) SPSS 21 version statistical program for Microsoft Windows. Data were described in terms of range; mean ±standard deviation (± SD), median, frequencies (number of cases) and relative frequencies (percentages) as appropriate. The Normality of quantitative data was checked using measures of Kolmogorov-Smirnov tests. The primary outcome of the intubating conditions assessed by intubation score compared by Chi square ($\chi 2$) test and exact test was used when the expected frequency is less than 5. To test for significance of the difference between the two groups (onset, duration, and recovery time of the muscle relaxants) Mann Whitney U test for independent samples for non-parametric data was performed. Comparison of quantitative variables between the study groups was done using Student t-test for parametric data. A probability value (p value) less than 0.05 was considered statistically significant.

Results

Sixty-six patients were assessed for eligibility, out of which six patients did not meet the inclusion criteria. Hence, 60 patients were randomized to either Group A or Group B. All of them were followed up and included in the final analysis (Figure 1).

Patients in both the groups were comparable with respect to demographic characteristics such as number of participants, age, weight, gender, and ASA physical status ($p>0.05$). The mean duration of surgery (minutes) was similar in both groups (Group A- 91 ±5.48 and Group B 88.33 ±5.31, p-value- 0.06). Both demographic and intraoperative characteristics were shown in (Table 1).

In Group A, a significant rapid onset of action of muscle relaxant was seen compared to Group B (2.4±0.30 mins vs 4.0±0.09 mins, p-value- 0.000). Also, 93% patients had excellent intubating conditions in Group A, while in Group B, 73% patients had excellent intubating conditions, and the difference was significant between the two groups (p value- 0.038). In group A, the duration of action was 36.73±1.05mins and in group B, the duration of action was 47.40 ±1.33mins and the difference between them was significant (p-value-0.000). Similarly, a significant difference in the mean duration of

recovery was found between the two groups (Group A-45.30±1.29mins vs Group B -57.77±1.19 mins, p-value-0.00) (Table 2).

A change in heart rate and blood pressure were also observed during the study period. Both the groups had increase in heart rate and blood pressure following intubation period but statistically significant higher heart rate was seen in Group A compared to Group B (p value=0.000). Five minutes following intubation, heart rate and blood pressure was comparable in both the groups (Figure 2a and Figure 2b). In Group A, 77% of the patients experienced pain at the injection site which was statistically significant (P value= 0.000). There were no post-operative complications in either group of patients.

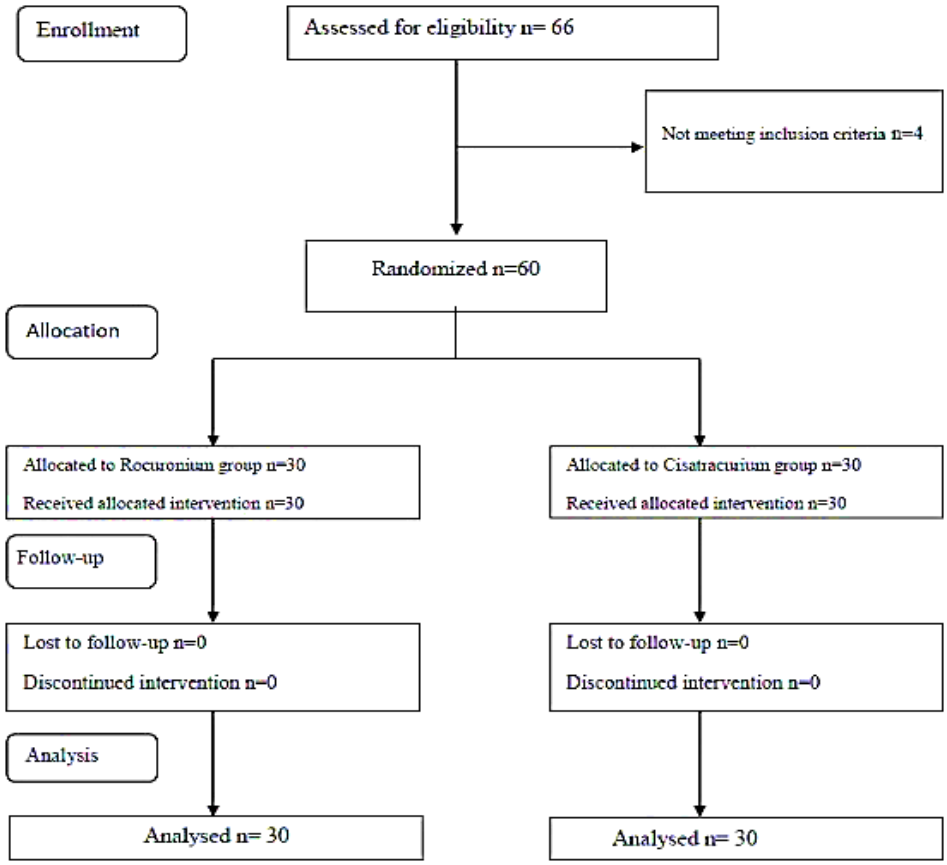

Figure 1- CONSORT Flow diagram

Table 1. Comparison of Demographic and Intraoperative Characteristics

	GROUP A (n=30)	GROUP B (n=30)	P value
Age (years)	49.40±11.20	46.87±11.46	0.390
Sex (M/F)	15/15	13/17	0.605
Weight (Kgs)	68.40±9.66	69.60±9.00	0.620
ASA (I/II)	15/15	13/17	0.605
Duration of surgery (minutes)	91 ±5.48	88.33 ±5.31	0.06

Table 2- Comparison of parameters after Neuromuscular Block Drug Administration

Parameters	GROUP A	GROUP B	P value
Onset of Action (minutes)	2.4 ± 0.30	4.0 ± 0.09	0.000*
Intubation Score (Excellent/ Good)	93%/7%	73%/27%	0.038*
Duration of Action (minutes)	36.73 ± 1.05	47.44 ± 1.33	0.000*
Time of Recovery (minutes)	45.30 ± 1.29	57.77 ± 1.19	0.000*

Values are presented as mean ± SD and number (n)/(percentage)

*p<0.05 is considered statistically significant

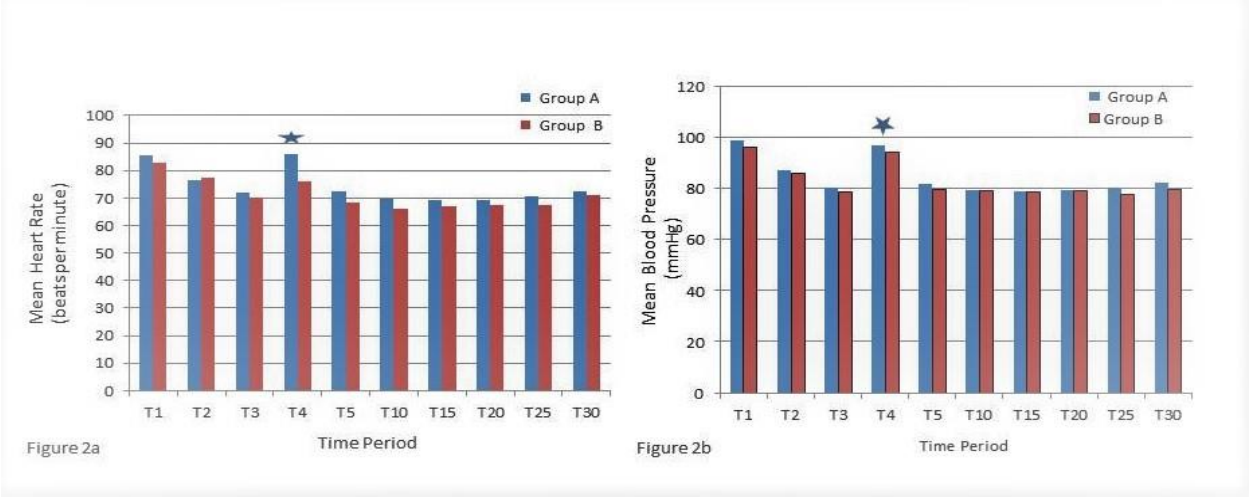

Figure 2- Comparison of hemodynamic parameters among the two groups

Discussion

Endotracheal intubation is an integral part of anesthesia during surgical operations. Not only does it rely on the level of anesthesia, but also on the type of neuromuscular blockers used, and the degree of muscle relaxation provided. In the current study, we found that rocuronium in a dose of 2 × ED95 provided a rapid onset of action (2.4±0.30 min), with excellent intubating conditions (in 93% patients) and an early mean duration of recovery when compared to cisatracurium in equivalent doses.

In order to predict the response of neuromuscular blocking drugs, in our study, we used both clinical criteria by the cooper scoring system and neuromuscular monitoring by the TOF. Both methods are well established in the literature [5,8]

In present study, the mean onset of action of rocuronium was shorter compared to cisatracurium. This is in agreement with the hypothesis that the onset of action is proportional to the potency of the drug. The lower the potency, the shorter will be the onset of action. Rocuronium has the lowest potency, that's why it is found to have a shorter onset time.

The results of the present study were comparable with results from previous studies with respect to the onset of action [9]. However, onset time was not comparable with our study. Lee H et al [10] reported onset time of 102 ± 49 sec and 197 ± 53 sec with rocuronium and cisatracurium respectively. Variable onset time can be explained by the differences in intubating dose used. They reported results with a 3×ED95 dose while we used 2×ED95 dose in current study. Omera M et al [9] mentioned 70.6 ±18.2 sec and 160.4 ±14.3sec with rocuronium and cisatracurium respectively. However, the onset time of both drugs was significantly shorter. Here, difference in experimental design used describe earlier onset of action of both muscle relaxants. Omera M et al recorded onset time using fentanyl, propofol, 60% nitrous oxide in oxygen with 2% isoflurane while we used fentanyl, propofol with oxygen.

In the current study, intubating conditions were either excellent or good following evaluation with the cooper scoring system. Excellent intubating conditions (rocuronium group - 93% and cisatracurium group -73% patients) and good intubating conditions (rocuronium group - 7% and cisatracurium group -27% patients) were seen in our study. Similar results were reported by Suri et al [10]and Mohanty et al [11]. Lee et al [12], on the other hand, reported overall excellent intubating conditions in both cisatracurium and rocuronium, which could be attributed to the higher dose used (3×ED95).

The mean duration of action was calculated by train of four (TOF) count as 2. In our study, it was found to be 36.73±1.05 min with rocuronium and 47.40±1.33 min with cisatracurium. Similar results were also reported in the literature [7,9].

Earlier, clinical parameters such as adequate tidal volume, sustained handgrip, head lift for 5 seconds and protrusion of tongue were used to assess the residual effect of muscle relaxants prior to the extubation of the patients. The clinical assessment requires an awake and cooperative patient [13]. However, in the modern era, the residual effect of muscle relaxants can easily be evaluated using TOF count compared to clinical parameters. In our study, time to recovery using TOF ratio to 90% was significantly prolonged with cisatracurium compared to rocuronium (57.77±1.19 min versus 45.30±1.29 min). Similar results were also described by Caroll M. T et al [14] who compared the train-of-fade response of cisatracurium (0.10 mg/kg) with rocuronium (0.6mg/kg). They found that the median time of spontaneous recovery to a TOF ratio of 0.8 with cisatracurium was 65 mins and with rocuronium was 50 mins.

The 'ideal' neuromuscular blocking drug should provide cardiovascular stability. The hemodynamic

parameters in the current study were comparable with study drugs except for elevated heart rate, which was seen in both the groups after intubation and later reached pre-intubation levels.

In addition, we observed pain at the site of injection in 77% patients as withdrawal movements on the concomitant hand following rocuronium injection. Similarly, Omera et al [9] reported a burning type of pain at the site of injection with rocuronium in more than 50% of patients, and Ruetsch et al [15] reported withdrawal movements. The cause of this pain is unclear, but as mentioned in the previous study by Borgeat et al [16] the acidic pH 4 of rocuronium and the release of local mediators as kininogen cascade probably cause pain. Pre-treatment with magnesium sulphate, lignocaine and sodium bicarbonate was beneficial for rocuronium induced pain [17].

Limitations

There were a few limitations to this study. Firstly, the patients included were only ASA Physical Status I and II patients, and therefore, the results are not applicable to the patients of a higher grade of ASA Physical status. Secondly, the small sample size of 30 in each group. In the future, further studies on a larger and adequately powered sample should be conducted to confirm the results of the present study.

Conclusion

Rocuronium 0.6 mg/kg has shorter onset of action, provide excellent intubating conditions as compared to equipotent dose of cisatracurium 0.1 mg/kg. Both the drugs are similar as far as cardiovascular stability is concerned. Rocuronium has comparatively shorter clinical duration and recovery time when compared to cisatracurium in equipotent dose, hence should be preferred for shorter duration of surgery lasting one to one and a half hour.

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