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Original Article

Compare Onset Time of Cisatracurium for Tracheal Intubation with and without Priming Dose of Rocuronium

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Abstract

Background: Priming is one of those techniques in which a small dose of non-depolarizing muscle relaxants is administered followed by a large intubating dose. Cisatracurium is the newly introduced drug with Hoffman elimination. The problem with its use is delayed onset of action. The present study was conducted to compare the onset of cisatracurium for tracheal intubation with and without priming dose of rocuronium.

Materials and Methods: A total of 60 American Society of Anesthesiologist physical Status I and II patients undergoing surgery under general anesthesia were included in the study. Patients were divided into two groups of 30 each. Patients in Group R received priming dose of rocuronium 0.06 mg/kg before intubating dose of cisatracurium (0.14 mg/kg). Group C patients did not get any priming, only normal saline was given before intubating dose of cisatracurium (0.15 mg/kg).

Results: Time gap between administration of the cisatracurium and complete loss of T_1 was recorded as intubation time. The intubation time was significantly less in Group R, i.e., 130 ± 11.02 s as compared to Group C, i.e., 230.33 ± 12.82 s. The intubating conditions were similar in both the groups. The hemodynamic changes were statistically insignificant. The time to 25% recovery of the T_1 response is defined as the clinically effective duration of neuromuscular block. The rate of recovery is described by the recovery index, which is defined as the time from 25% to 75% T_1 recovery.

Conclusion: Priming with rocuronium decreased the onset time without increasing the clinical duration of action or recovery index.

Key words: Non-depolarizing muscle relaxants, Priming, Cisatracurium, Rocuronium

INTRODUCTION

Endotracheal intubation is one of the important components of general anesthesia. The non-depolarizing muscle relaxants (NDMRs) act by competitively binding at the neuromuscular junction to provide muscle paralysis.[1] Cisatracurium besylate is a newly NDMR, an isomer of atracurium.[2] The problem with cisatracurium is its delayed onset of action. Priming is the technique in which a small dose of NDMR is administered which is followed by a large intubating dose of same or different NDMR. This produces rapid and profound blockade.[3] The present study was conducted to compare the onset of cisatracurium for tracheal intubation with and without priming dose of rocuronium.

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MATERIALS AND METHODS

A randomized prospective double-blind study was conducted in the Department of Anesthesia, Government Medical College, Amritsar, Punjab, India. The randomization was done using the computer generated software. A total of 60 American Society of Anesthesiologist (ASA) Grade I and II between the age of 18 and 65 years with Mallampati grading 1 and 2

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requiring elective surgery under general anesthesia were included in the study. After approval from the institutional ethical committee, an informed written consent was taken. Patients who were <18 years or >65 years, pregnant patients, emergency cases, those allergic to drugs, anticipated difficult airway, morbidly obese, and ASA more than II had a history of neuromuscular disease and who refused to give consent were excluded from the study. A thorough pre-operative checkup was done. A detailed history was taken. The complete general physical and systemic examination including airway assessment was done. Relevant investigations were done. Demographic data including age, sex, and ASA status were collected. Patients were randomly divided into two groups of 30 each. Patients in Group R received priming dose of rocuronium 0.06 mg/kg before intubating dose of cisatracurium (0.14 mg/kg). Patients in Group C received no priming, only normal saline was given before intubating dose of cisatracurium (0.15 mg/kg). Routine fasting guidelines were followed.

In the operating room, multipara monitor was attached. Two stimulating electrodes were placed over the ulnar nerve at the wrist and acceleration transducer attached to the thumb with adhesive tape. Baseline heart rate, blood pressure (BP), and oxygen saturation were recorded. Intravenous line was set on the hand opposite to the electrodes and fluid started. All patients were premedicated with inj. midazolam 0.04 mg/kg, inj. glycopyrrolate 0.2 mg, and inj. butorphanol 40 μg/kg. After preoxygenation with 100% oxygen, anesthesia was induced with inj. propofol 2 mg/kg. After loss of eyelash reflex, O_2-N_2O in the ratio of 4:6 and isoflurane 1% started for the maintenance of anesthesia using closed circuit. Supramaximal stimulus was given (2 Hz for 2 s) through nerve stimulator. Baseline train of four (TOF) was recorded. T_4/T_1 percentage, i.e., the percentage between the fourth and first twitch recorded. Priming dose of rocuronium (0.06 mg/kg IV diluted to 1 ml with 0.9% normal saline) is given in Group R patients. Group C patients received 1 ml of 0.9% of normal saline. After 3 min of priming interval, intubating dose of cisatracurium 0.14 mg/kg was given to patients of priming group (Group R) and 0.15 mg/kg to patients of non-priming group (Group C) over 5 s. The intravenous line was flushed by rapid flow of fluid for 15 s. TOF was recorded every 10 s till complete loss of T_1. At this point, intubation was attempted by the senior anesthesiologist. Time gap between administration of the NDMR and complete loss of T_1 was recorded as the intubation time. The time of onset of the neuromuscular block is defined as the time to maximum suppression of the T_1 response.

Variable	Excellent	Good	Poor
Laryngoscopy	Easy	Fair	Difficult
Vocal cord position	Abducted	Intermediate/ moving	Closed
Reaction to insertion of the tracheal tube and cuff inflation (diaphragmatic movement/coughing)	None	Slight (1–2-week contractions or movement for <5 s)	Vigorous/sustained (More than two contractions and/or movement for longer than 5 s)

Assessment of intubating conditions (According to Fuchs-Buder *et al.*)[4]

Type of Laryngoscopy

- Easy: Jaw relaxed, no resistance to blade insertion,
- Fair: Jaw not fully relaxed slight resistance to blade insertion,
- Difficult: Poor jaw relaxation, active resistance of the patient to laryngoscopy.

From above-mentioned Intubating Conditions

- Excellent: All qualities are excellent,
- Good: All qualities are either excellent or good,
- Poor: The presence of single quality listed under "poor."

Clinically acceptable are excellent and good conditions. Poor conditions were those who were not clinically acceptable.

After checking position of endotracheal tube and securing it, anesthesia and monitoring continued with total fresh gas flow with O_2-N_2O in 4:6 ratio with isoflurane 1% using closed circuit. Hemodynamics were recorded every 5 min during surgery. The inhalational anesthetic vaporizer switched off 6–8 min before the end of surgery. Neostigmine 0.05 mg/kg and glycopyrrolate 0.01 mg/kg IV were administered after the T_4/T_1 percentage became 75%. The trachea extubated once T_4/T_1 percentage became 90% of baseline.

The time to 25% recovery of the T_1 response is defined as the clinically effective duration of neuromuscular block. The rate of recovery is described by the recovery index, which is defined as the time from 25% to 75% T_1 recovery. The recovery profile was maintained using Aldrete scoring system. The patient was monitored for 24 h for any side effects and complications.

Statistical Analysis

Sample size was calculated keeping in view at most 5% risk, with minimum 85% power and 5% significance level (significant at 95% confidence interval). Raw data were recorded in a Microsoft Excel spreadsheet and analyzed using the Statistical Package for the Social Sciences (SPSS version 23.00). The continuous data were presented as mean with standard deviation (mean ± SD). Number of patients

and/or percentage of cases expressed discrete categorical data. Categorical variables were analyzed using Chi-square test. Normally distributed continuous variables were analyzed using independent sample *t*-test. *P* value was determined finally to evaluate the levels of significance. $P > 0.05$ was considered statistically non-significant; $P = 0.01$ to 0.05 was considered statistically significant and $P < 0.01$ was considered highly statistically significant. The results were then analyzed and compared to previous studies.

RESULTS

As shown in Table 1, the demographic data of both the study groups including age,sex, and ASA grade were comparable as $P > 0.05$ and statistically insignificant.

The time gap between administration of the NDMR and complete loss of T_1 was recorded as intubation time. The intubation time was recorded and compared in both the groups. In Table 2, the two groups are compared in terms of the onset/intubation time, intubation conditions, duration of action and recovery index. The difference in intubation time is highly significant as in Group R, the intubation time was 130.67 ± 11.02 s as compared to Group C where it was 230.33 ± 12.82 s showing that priming with rocuronium decreases the onset time of cisatracurium ($P > 0.01$).

In Group R, 28 (93.3%) of 30 patients had excellent intubating conditions and two (6.67) patients had good intubating conditions. The intubating conditions were rated excellent in 27 (90%) patients and good in three (10%) patients in Group C. The difference between the two groups was statistically insignificant ($P > 0.05$).

The time to 25% recovery of the T_1 response is defined as the clinically effective duration of neuromuscular block. The mean duration of the action of cisatracurium in Group R was 55.17 ± 2.16 min and Group C was 53.77 ± 2.14 min. The mean duration of the action of cisatracurium was comparable in both the groups as the difference among them being statistically insignificant ($P > 0.05$).

The recovery index is defined as the time from 25% to 75% T_1 recovery. The mean recovery index of cisatracurium in Group R was 15 ± 0.83 min and Group C was 14.27 ± 1.11 min. The two groups were comparable in terms of recovery index as the difference is statistically insignificant ($P > 0.05$).

The hemodynamic profile (heart rate, systolic BP, diastolic BP, and mean arterial pressure) of both the groups was observed and recorded. It was found to be comparable with no statistically significant difference as $P > 0.05$.

Table 1: Demographic profile

Variables	Group R	Group C	*P* value
Age (years)	40.30±10.65	39.20±11.3	0.724
Sex (M/F)	17/13	14/16	0.438
ASA (I/II)	22/8	21/9	0.77

P>0.05 (non-significant), mean±SD. ASA: American Society of Anesthesiologist

DISCUSSION

Many NDMRs have been studied till today. However, the problem with NDMR is their delay in onset of action. Various techniques have been studies to decrease the onset time of various NDMRs. Some of them are - priming principle, timing principle, administering large doses, and combining different neuromuscular blocking agents.

Priming principle is the technique in which a small dose of NDMR is administered followed by a large intubating dose. This produces rapid and profound neuromuscular block for suitable intubating conditions.

The studies conducted by Gergis *et al.*[5] and Hutton *et al.*[6] reported that the onset of neuromuscular block could be hastened by administering small dose before the intubating dose. The term priming dose was coined by Foldes.[7] After that, several studies were conducted based on the priming principle.

The mechanism underlying the shortening of the time interval between intubating dose and achieving intubating conditions by priming can be explained by two theories. The first theory proposed that the priming dose occupies a proportion of post-synaptic nicotinic receptors necessary for clinical paralysis. According to this theory, the priming dose is of more importance as compared to the priming interval as it has to occupy critical mass of receptors. The other theory suggests that the priming dose blocks the

Table 2: Onset, intubation conditions, duration of action, and recovery index

Variables	Group R	Group C	*P* value	Statistical significance
Onset/intubation time (s)	130.67±11.02	230.33±12.82	0.001	Significant
Intubation conditions (excellent/good/poor)	28/2/0	27/3/0	0.640	Insignificant
Duration of action (min)	48.18±0.66	47.93±0.37	0.075	Insignificant
Recovery index (min)	15.00±0.83	14.27±1.11	0.093	Insignificant

P>0.05 (non-significant), mean±SD

presynaptic nicotinic receptors, reducing the mobilization and release of acetylcholine so that paralysis is produced rapidly using the intubating dose.[8] Cisatracurium is an NDMR having potency almost 4 times more than atracurium. It has no histamine release and is cardio stable. It is metabolized by Hoffmann elimination so can be used in patients with decreased hepatic or renal function. The problem with this NDMR is the delayed onset of action. Several studies have been conducted to establish the method for decreasing the onset time of cisatracurium.

The combinations of NDMR with different structures are considered to have synergistic effects. The synergism is said to be maximized if two molecules have different roles in prejunctional and postjunctional effect. There are different binding sites at presynaptic and postsynaptic receptors and different binding affinities of 2-alpha subunits of the acetylcholine receptor.[9,10] There occurs potentiation of the neuromuscular block due to synergism of combined NDMRs and different binding affinities.

The synergism has been found for pairs of cisatracurium and rocuronium.[11] A study conducted by England suggested that rocuronium has higher affinity for the presynaptic sites than other NDMR.[12] Furthermore, rocuronium has fast onset and short duration of action. As the combinations of rocuronium and cisatracurium have synergistic effects, so rocuronium may be used as priming agent to decrease the onset time of cisatracurium.[13]

Thus, the present study was designed to compare the onset time of cisatracurium for tracheal intubation with and without priming dose of rocuronium.

We observed that the intubation time in Group R was 130.67 ± 11.02 s and Group C was 230.33 ± 12.82 s which was statistically significant. Hence, the intubation time in priming group was less than the non-priming group. This shows that the priming with rocuronium decreases the onset time of the cisatracurium. The studies conducted by Lin *et al.*[14] and Jung *et al.*[15] showed similar results, i.e., the priming decreases the onset time of cisatracurium.

In our study, to assess the intubating conditions, three parameters, laryngoscopy, vocal cord position, and response to insertion of tracheal tube and cuff inflation, were studied and results compiled to note intubating conditions in both groups. Laryngoscopy was easy in 29 patients of 30 in Group R and 28 patients in Group C. There was one case in Group R and two cases in Group C in which laryngoscopy was fair in grading. There was no statistically significant difference in both the groups.

Vocal cord position was noted, i.e., whether abducted, intermediate or closed, and also on the movement of vocal cords during intubation. In all intubations of Group R, the vocal cords were abducted, and in 29 intubations of Group C, the vocal cords were abducted. Only in one intubation of Group C, the vocal cords were moving. However, statistically no significant difference in both the groups was found.

Response to intubation was noted on the basis of the movements of limbs and coughing in response to insertion of tracheal tube or cuff inflation. 29 patients in Group R and 28 patients in Group C had no response to intubation. One patient in Group R and two patients in Group C had slight coughing in response to cuff inflation.

Hence, our study showed that the intubating conditions were similar in both the groups, i.e., with or without priming with rocuronium. Johann *et al.*[16] and Deepika *et al.*[17] showed similar results that the intubating conditions were similar in priming and non-priming group.

The duration of action and recovery index in Group R 48.18 ± 0.66 and 15.00 ± 0.83 and Group C were 47.93 ± 0.37 and 14.27 ± 1.11, respectively. Both were comparable in both priming and non-priming groups. Hence, priming of cisatracurium with rocuronium will not result in any prolonging of the action of cisatracurium.

We observed that the heart rate, systolic BP, diastolic BP, and mean BP readings were comparable in both the groups. Hence, both rocuronium and cisatracurium are hemodynamically stable drugs.

Both the groups had similar recovery profile of cisatracurium when compared in terms of duration of action and recovery index.

CONCLUSION

From our study, we concluded that the onset time of cisatracurium for tracheal intubation decreases when priming is done with rocuronium. The intubating conditions were excellent or good with cisatracurium alone or after priming with rocuronium. The priming dose of rocuronium does not prolong the duration of action and recovery index of cisatracurium. Both cisatracurium and rocuronium are hemodynamically stable drugs and produce no complications in the intraoperative or post-operative period.

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