

### COMPARISON BETWEEN RECOVERY PROFILE OF REPEATED BOLUS DOSE AND CONTINUOUS INFUSION OF CISATRACURIUM IN PATIENTS UNDERGOING PROLONGED SURGERIES USING TRAIN OF FOUR: A PROSPECTIVE STUDY

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#### Abstract

**Background:** The administration technique plays a key role for rational usage of muscle relaxants. Repeated bolus doses and continuous infusion technique of neuromuscular drug administration each have its own pros and cons. To compare the efficacy of intermittent bolus administration and continuous infusion of cisatracurium in terms of intraoperative dose and postoperative recovery. Sixty patients of ASA I & II class posted for prolonged surgeries (2 to 4 h) randomly assigned into two groups consisting of 30 patients each in this prospective randomized study. **Materials and Methods:** Patients were randomized to receive either 0.02 mg/kg IV repeat bolus doses (Group B) or an infusion of cisatracurium was initiated and titrated to maintain a 90% - 95% neuromuscular blockade (Group C). **Result:** The average drug consumed in Group B and Group C was 22.30 mg and 36.03 mg respectively (P = 0.000). The mean time to train of four (TOF) ratio 0.8 was 33.57 min and 45.50 min in Group B and in Group C respectively (P = 0.000.) **Conclusion:** Our study supports the use of intermittent bolus dose of cisatracurium for prolonged surgeries. This favours lower intraoperative drug dose and shorter recovery time postoperatively.

## INTRODUCTION

Cisatracurium is a newer non-depolarising muscle relaxant. It is a R-cis-R-cis isomer of atracurium, which was primarily developed to overcome the side effects associated with older neuromuscular blocking agents such as histamine release and laudanosine accumulation.<sup>[1]</sup>

Hoffmann elimination is responsible for about three fourth of the whole elimination rate of cisatracurium and it mainly undergoes in the tissue and plasma. Hoffmann clearance is dependent on the pH value and the body temperature. Remaining one third is excreted by an organ-dependent manner. At present, muscle relaxants mostly of non-depolarizing type are administered by repeated bolus dosing technique. The plasma non-specific esterase do not directly hydrolyze drug Cisatracurium, and its metabolic products do not possess neuromuscular blocking properties.<sup>[2]</sup>

The two administration techniques of any drug - repeated bolus dose and continuous infusion

technique have their own pros and cons. In comparison to the conventional intermittent bolus dose, the technique of continuous administration of an intravenous anaesthetic agent provides better control of depth of anaesthesia, and ensures greater haemodynamic control, less drug consumption in total, and hastens the time to recovery which means a prompt discharge.<sup>[3,4]</sup> This is appropriate in favour of hypnotic and opioid drugs.<sup>[4]</sup>

However, the literature reports for muscle relaxants are controversial.<sup>[5]</sup> Previous study on subjects undergoing cardio-thoracic surgery administration of cisatracurium with intermittent bolus technique lead to reduced intraoperative drug dose and quick postoperative recovery. In contrast the total consumption of neuromuscular blocking agent and the recovery time from neuromuscular blockade required using the two techniques differed from the findings of those studies conducted using opioids or induction drugs.<sup>[5]</sup>

In a study by Secuk M *et al*,<sup>[6]</sup> no statistically significant difference for the recovery time between

these two drug delivery method for cisatracurium was found.

Because of its pharmacological characteristics cisatracurium can be delivered by either continuous infusion or intermittent bolus injection method. Cisatracurium given by continuous infusion maintains steady neuromuscular blockade with lesser consumption of drug.<sup>[2]</sup> For prolonged procedures cisatracurium infusion is favoured since prolonged infusion hardly affects recovery.<sup>[7]</sup>

Miller DR *et al*,<sup>[8]</sup> in 2000 compared the cumulation potential of cisatracurium and rocuronium during continuous infusion in surgical procedures lasting for 2–4 hours. They concluded that these drugs do not demonstrate cumulation when given by continuous infusion for upto 3.5 hours.

An administration technique with faster recovery rates and less consumption of the drug should be preferred as it would directly contribute to decreasing the duration of post anaesthesia care unit (PACU) stay leading to timely discharge and decrease the overall cost of anaesthesia. In this study we compared the two administration techniques in terms of postoperative recovery time and total intraoperative consumption of cisatracurium, in prolonged surgeries of two to four hours duration using train of four (TOF) monitoring.

## MATERIALS AND METHODS

Sixty subjects including both the genders and aged between 20 to 60 years belonging to American Society of Anaesthesiologists (ASA) grade I or II scheduled for prolonged surgeries (2 to 4 hours) under general anesthesia were randomly allotted to either of the two groups consisting of 30 patients each by picking the “CHIT IN A BOX” method after obtaining institutional ethical committee’s approval. Group B patients received repeat bolus doses of cisatracurium and Group C patients received continuous infusion of cisatracurium.

Patients with known allergy to concerned drug, severe psychiatric disturbances or with history of drug abuse, with hepatic / renal insufficiency, haemodynamically compromised patients, pregnant and lactating patients, with any cardiac disease, BMI > 30 kg/m<sup>2</sup>, severe anemia and malnutrition, fluid and electrolyte imbalances, neuromuscular disorder and subjects taking medicine which could interfere with neuromuscular blockade, were excluded from the study.

Subjects were interviewed and examined one day before the scheduled surgery. Pre-operative evaluation done and written informed consent was taken.

The following materials were used for this study – Injection cisatracurium, 20 ml syringe for infusion, train of four (TOF) monitor and syringe pump (Infusion pump).

Patients in group B received repeated bolus administration of cisatracurium 0.02 mg/kg IV and in

group C subjects received cisatracurium infusion, titrated to maintain a 90% - 95% neuromuscular blockade.

In the operation theatre, a multiparameter monitor was used to record baseline data like heart rate, blood pressure and arterial oxygen saturation by pulse oximeter (SpO<sub>2</sub>) were recorded and electrocardiograph (ECG) monitoring done. Each subject was premedicated with midazolam 2mg IV, glycopyrrolate 0.2 mg IV and fentanyl 2µg/kg IV. All subjects were given a 70% nitrous oxide in oxygen gas mixture. Propofol 2mg/kg IV was used for induction of anesthesia and isoflurane 0.4%- 0.8% for maintenance of anaesthesia. Cisatracurium 0.2mg/kg IV was given to facilitate tracheal intubation.

The ulnar nerve was stimulated at 15 minutes interval using train of four (TOF) supramaximal stimulation (50mA) to assess neuromuscular blockade.

The subjects in group B were administered intermittent doses of cisatracurium (0.02 mg/kg) as and when required. Subjects in group C were administered continuous infusion of cisatracurium (2µg/kg/min). The level of neuromuscular blockade was assessed at an interval of every 15 min. The target was to maintain one twitch response of TOF. The dose of cisatracurium was increased or decreased as per the level of neuromuscular blockade and the drug infusion was stopped 30 minutes before skin closure.

Post operatively, the spontaneous recovery (from neuromuscular blockade) was assessed every 5 minutes till the appearance of all TOF twitch responses and TOF ratio (T4:T1 ratio) reached to 0.8

Reversal for neuromuscular blockade was achieved with glycopyrrolate (0.008mg/kg IV) and neostigmine (0.05mg/kg IV) and thorough suctioning was done. Patients were extubated after complete recovery. Time (in minutes) to achieve TOF ratio of 0.8 and the total intraoperative consumption of cisatracurium was noted.

The statistical evaluation of data was done using SPSS software. *P*-value < 0.05 was considered significant.

## RESULTS

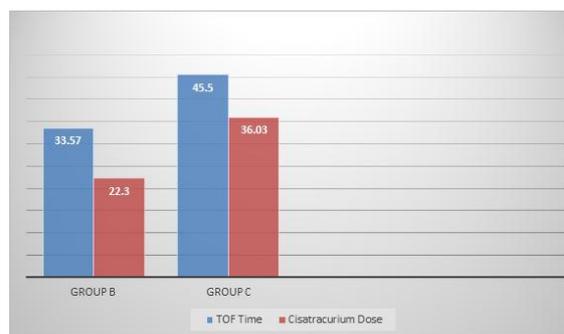
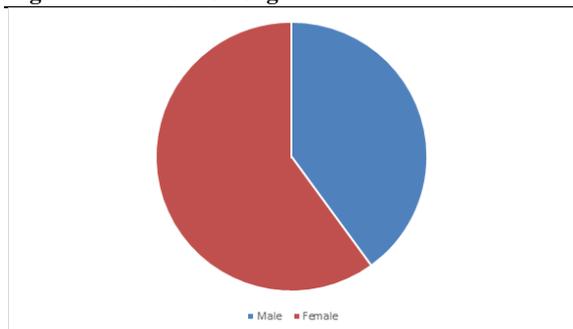
The demographic characteristics and duration of anaesthesia in the two groups were comparable. This difference was not statistically significant; [Table 1]. Distribution of gender in the sample is shown in [Figure 1].

Regarding recovery from neuromuscular blockade in the two groups the mean time to Train of Four ratio 0.8 was 33.57 min in Group B and the same was 45.50 min in Group C. this difference was highly statistically significant. [Table 2]

The mean intraoperative dose of cisatracurium consumed in Group B was 22.30 mg and that in Group C was 36.03 mg with *P*-value 0.000 which is statistically significant [Table 3].

A comparative data of [Table 2 and Table 3] is shown in [Figure 2].

**Figure 1: Distribution of gender.**



**Figure 2: Comparison of Table 2 and Table 3**

**Table 1: Demographic data and duration of anaesthesia**

Data	Group B	Group C	P - value
Age in years	36.10 ± 11.06	40.03 ± 9.64	0.147
BMI (kg/m <sup>2</sup> )	23.43 ± 2.91	23.17 ± 3.36	0.744
Sex (male: female)	13 : 17	11 : 19	0.598
Anesthetic duration (min)	243.77 ± 19.11	245.90 ± 17.00	0.767

**Table 2: Comparison of Time to TOF 0.8**

Data	Group B (mean ±SD)	Group C (mean ±SD)	P - value
Time to TOF 0.8 (min)	33.57 ± 2.66	45.50 ± 2.50	0.000

**Table 3: Comparison of mean intraoperative dose of Cisatracurium**

Data	Group B (mean ±SD)	Group C (mean ±SD)	P - value
Dose of Cisatracurium (mg)	22.30 ± 3.16	36.03 ± 2.25	0.000

## DISCUSSION

The advent of muscle relaxation in anaesthesiology has given a new face to the branch. While using a muscle relaxant, the doses given should strike a balance between adequate muscle relaxation contributing to a quieter operative field and avoidance of overdosage leading to postoperative residual neuromuscular blockade. The administration technique also plays a key role for rational usage of muscle relaxants.<sup>[2]</sup>

A study by Martineau *et al.*,<sup>[9]</sup> revealed that vecuronium and atracurium accumulate during prolonged infusions, and this can be obviously noted by gradual and progressive reduction in infusion requirements. These accumulative characteristics were implicated to increased half-life (elimination) of vecuronium.

Recovery after single bolus dose of neuromuscular blockade may be attributed to redistribution. Recovery becomes totally dependent on elimination during prolonged infusions because the peripheral compartments get saturated over time. Repeated bolus dosing also produces similar results.<sup>[10]</sup>

Neuromuscular monitoring helps in preventing a dramatic fluctuation in the extent of the neuromuscular block as without it administering a muscle relaxant would be dependent on clinical signs like increase in airway pressure, bucking, body movements, capnography changes etc.<sup>[2]</sup> This could again lead to overdosage.

In our study, we used TOF monitoring and maintained TOF response of one throughout the surgery. This aided us in appropriate dosing of the muscle relaxant.

The correct dosing of non-depolarizing muscle relaxant remains important so as to strike a balance between avoidance of overdosage of the drug leading to delayed postoperative recovery and to achieve adequate muscle relaxation with a silent operative field.

T1 recovery to 20 % for starting continuous infusion or giving intermittent bolus injection occurs quickly with the use of 2 ED 95 (0.1 mg/kg) of cisatracurium in anaesthesia induction. The optimal condition for tracheal intubation can be achieved earlier by increasing the intubation dose of cisatracurium to 3 ED 95 - 5 ED 95.<sup>[2]</sup> In this study, we used 0.2 mg/kg IV cisatracurium to facilitate intubation.

Inhalation anaesthetics enhance the non-depolarizing muscle relaxant blockade and prolong the duration of action of non-depolarizing type muscle relaxants. This leads to reduction in the maintenance dose of muscle relaxants. When compared to propofol, the cumulative dose requirements of cisatracurium to maintain a 90% neuromuscular blockade was reduced by 42%, 41 % and 60%, respectively with isoflurane, sevoflurane and desflurane.<sup>[11]</sup>

The anaesthetic technique used was similar in both groups to avoid the effects of using different anaesthetics on prolonging recovery time and thereby

affecting the test results. Factors affecting recovery in this study were made comparable.

The demographic characteristics were comparable in both groups so as to remove gender, BMI, and age effects on drug consumption and recovery profiles.

The lower body temperature can extend the duration of action of muscle relaxant and thereby interfere with the test results. Therefore, the body temperature was maintained constant in all patients throughout the surgery and hypothermia was avoided.

In our study, the duration of anaesthesia in Group B was 243.77 minutes and that in Group C was 245.90 minutes which do not differ significantly and are comparable. The time to spontaneous recovery measured by time to TOF ratio 0.8 was 33.57 minutes in the bolus infusion group (Group B) and 45.50 minutes in the continuous administration group (Group C) with  $P=0.000$ . So the recovery time was significantly less in the bolus group. The average drug consumed in the Group B was 22.30 mg and that in Group C was 36.03 mg with  $P=0.000$ . Thus the average drug consumption was statistically significantly less in the bolus group compared to the continuous infusion group.

Recovery profiles of cisatracurium infusion and bolus dosing technique have varied in various previous studies using different anaesthetic techniques in various surgical settings.

Mirinejad *et al*,<sup>[5]</sup> noted a shorter recovery time with cisatracurium the bolus group compared to the infusion group. The mean intraoperative drug dose of cisatracurium was lesser in intermittent bolus group compared to infusion group. Also the total intraoperative dose in intermittent bolus group was significantly lesser than infusion group. The findings of Mirinejad *et al* are consistent with our study although the recovery times are relatively longer. This could be attributed to the hypothermic cardiopulmonary bypass in their patients.

Dong *et al*,<sup>[2]</sup> reported no significant difference for the duration of neuromuscular blockade in the two groups.

In a study by Secuk M *et al*,<sup>[6]</sup> no significant difference for recovery time after cisatracurium administration using the two methods was observed. This could be due to low study power.

## CONCLUSION

In conclusion, our study supports the use of intermittent bolus dose of cisatracurium for prolonged surgeries. This favours lower intraoperative drug dose and shorter recovery time postoperatively. However more studies with larger sample size and in different population groups are needed to support the findings of this study.

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