## Original Article

# Comparison of the Efficacy of Cisatracurium and Atracurium for Neuromuscular Blockade and Recovery Characteristics in Patients undergoing Various Elective Surgeries under General Anesthesia

**Kavita Jain[1], Surendra Kumar Sethi[2], Ravi Sharma[3]**

*[1]Professor and Head, [2]Associate Professor, [3]Resident, Department of Anesthesiology, JLN Medical College and Associated Group of Hospitals, Ajmer, Rajasthan, India*

DOI:10.37821/ruhsjhs.5.2.2020.278

## ABSTRACT

**Introduction:** Atracurium and Cisatracurium are preferable in patients with compromised organ functions because of their non-organ dependent metabolism. Neuromuscular function monitoring during general anesthesia helps in preventing postoperative residual neuromuscular blockade by avoiding excessive dosage or incorrect timing of the maintenance dose of neuromuscular blocking agent (NMBA).

**Methodology:** This prospective randomized study included 100 patients aged between 18-60 years of either sex belonging to American Society of Anesthesiologists (ASA) physical status I or II posted for various elective surgeries under general anesthesia. Patients were randomly allocated into two groups of 50 each. Group A received Atracurium 0.5 mg/kg, 2 times of effective dose ($2\times ED_{95}$) as loading dose and 0.1 mg/kg as maintenance dose while group B received Cisatracurium 0.2 mg/kg ($4\times ED_{95}$) as loading dose and 0.03 mg/kg as maintenance dose using neuromuscular monitoring. The onset and duration of neuromuscular blockade, recovery characteristics, hemodynamic changes, and adverse effects were recorded.

**Results:** The onset of neuromuscular blockade was significantly faster in group B (3.84±1.55 minutes) as compared to group A (5.13±1.38 minutes) ($p<0.05$). The mean duration of neuromuscular blockade was significantly longer in group B (62.65±2.21 minutes) as compared to group A (36.70±4.58 minutes) ($p<0.05$). Mean 25% recovery of neuromuscular blockade in group B (48.62±4.92 minutes) was significantly longer than in group A (31.84±1.99 minutes) ($p<0.05$) while the mean time of recovery in group B (2.22±0.20 minutes) was significantly shorter than in group A (2.63±0.29 minutes) ($p<0.05$). No significant hemodynamic changes and adverse effects were noted in both groups ($p>0.05$).

**Conclusion:** Cisatracurium ($4\times ED_{95}$) can be used as a safe and effective alternative to Atracurium ($2\times ED_{95}$) in clinical anesthesia practice.

**Keywords:** Atracurium, Cisatracurium, Hemodynamics, Neuromuscular blockade.

## INTRODUCTION

Analgesia, amnesia, and areflexia are essential components of balanced anesthesia.[1,2] Neuromuscular blocking agents (NMBA) are extensively used in the operation theatre and intensive care units. The important concern regarding the use of these drugs is the complete recovery of neuromuscular function and complete elimination of drug after reversal of anesthesia without any residual effects.[3]

An ideal NMBA should have rapid onset of action, be providing rapid and good intubating conditions, have intermediate to short duration of action along with rapid and complete recovery, be providing hemodynamic stability, and be devoid of side effects.[4] However, the currently available NMBAs, whether depolarizing or non-depolarizing, have their own disadvantages.

This prompted for an extensive search of an ideal non-depolarizing NMBA. Although both Atracurium and Cisatracurium are commonly used non-depolarizing NMBAs that can be used safely even in elderly as well as in patients with compromised organ functions because of their non-organ dependent metabolism but the major

undesirable side effect associated with Atracurium is histamine release leading to anaphylactic reaction.[5-7]

Neuromuscular function monitoring is a significant advancement with the use of NMBAs as it helps in preventing postoperative residual neuromuscular blockade by avoiding excessive dosage or incorrect timing of the maintenance dose of NMBA.[8-10] It was hypothesized that Cisatracurium, an intermediate acting non-depolarizing NMBA, at 4 times of effective dose ($4\times ED_{95}$), would provide rapid onset of neuromuscular blockade, good intubating conditions, adequate and rapid recovery with better hemodynamic stability and minimal side effects as compared to its lower doses ($2\times ED_{95}$) and Atracurium ($2\times ED_{95}$). Thus, this study was undertaken to compare Cisatracurium and Atracurium for neuromuscular blockade and recovery characteristics in patients undergoing various elective surgeries under general anesthesia. The primary outcome measure of the study was duration of neuromuscular blockade while secondary outcome measures were onset time of neuromuscular blockade, recovery profile, hemodynamic changes, and adverse effects.

## METHODS

This hospital based prospective randomized comparative study was conducted at a government medical college of Rajasthan after approval from local institutional ethics committee. This trial was registered in Clinical Trials Registry of India (CTRI/2019/03/018144).

A total of 100 patients belonging to American Society of Anesthesiologists (ASA) physical status I or II, aged 18 to 60 years of either sex scheduled for various elective surgeries under general anesthesia were included in this study. This has been depicted in consort flow diagram (Figure 1). A written informed consent was taken prior to the study. Patients with ASA physical status III or above, age <18 years or >60 years, predicted difficult intubation

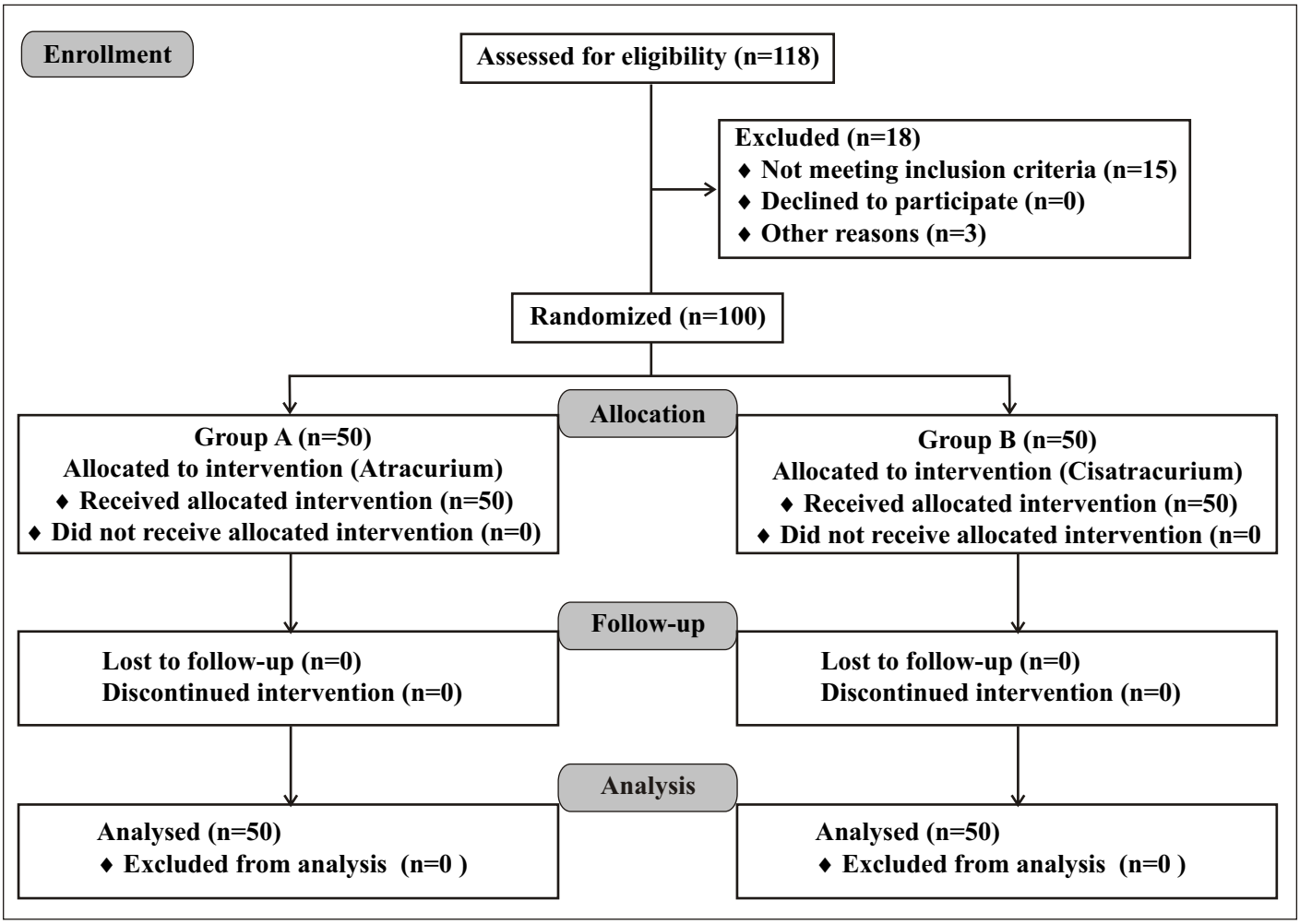


**Figure 1: Consort flow diagram.**

(Mallampati grade >2, pregnant, and obese patients), patients with systemic diseases like diabetes mellitus, hypertension, epilepsy, and patients on medications known to interact with NMBAs like antibiotics, antidepressants, anticonvulsants, anti-arrhythmics, and Magnesium sulphate were excluded from the study.

All the enrolled patients were randomly allocated into two groups with 50 patients in each group using computer generated tables of random numbers. Group A (n=50) received Atracurium 0.5 mg/kg ($2\times ED_{95}$) as loading dose and 0.1 mg/kg as maintenance dose and Group B (n=50) received Cisatracurium 0.2 mg/kg ($4\times ED_{95}$) as loading dose and 0.03 mg/kg as maintenance dose. Study drugs (NMBAs) were prepared by a resident anesthesiologist who was not involved in intraoperative patient monitoring and management. Intubation was done by an anesthesiologist who was unaware of the NMBA used while data collection and analysis during intraoperative period was performed by another anesthesiologist who was unaware of the group distribution.

Thorough preoperative evaluation was done according to the standard protocol and relevant investigations were performed for all the patients before surgery. During preanesthetic examination, patients were explained about the procedure and written informed consent was taken. All the patients were kept nil per oral at least 6 hours prior to the surgery.

On arrival of the patient into operation theatre, an 18 G intravenous (IV) canula was inserted and ringer lactate was started. Standard ASA monitoring was attached to all patients and heart rate (HR), non invasive blood pressure (NIBP), oxygen saturation ($SpO_2$), electrocardiogram (ECG) were observed and baseline values were recorded. A peripheral nerve stimulator (PNS) was attached thereafter for neuromuscular monitoring. After explaining about the nerve stimulation technique, nerve stimulator surface electrodes were applied on the ulnar nerve course above wrist and observation was done on thumb. Patients were preoxygenated with 100% oxygen ($O_2$) for 3-5 minutes. Glycopyrrolate 0.004 mg/kg IV and Fentanyl 2 μg/kg IV were given as premedication. General anesthesia was induced using Propofol 2 mg/kg IV and neuromuscular blockade was achieved using NMBA (Atracurium 0.5 mg/kg IV or Cisatracurium 0.2mg/kg IV) as loading doses for intubation. Neuromuscular monitoring was done using Infinity Trident NMT SmartPod (Drager). Two electrodes were attached on internal aspect of the wrist on the surface of the skin along the course of the ulnar nerve to monitor the response of adductor pollicis (AP) muscle. Acceleration transducer was attached with tape on the internal aspect of the thumb. Hand and wrist were padded with cotton and bandage to avoid hypothermia. After loss of verbal response, baseline supramaximal stimulus of 0.2 ms square wave at 50 mA was given and Train of Four (TOF) response was noted on neuromuscular monitor, after administering loading dose of NMBA to the patients. The ulnar nerve was stimulated at the wrist with a stimulus of 0.2 ms duration in TOF mode at 2 Hz every 12 seconds. Tracheal intubation was performed with appropriate sized endotracheal tube when TOF count of zero was achieved. TOF counts were monitored regularly and maintenance doses were repeated when TOF count of two was achieved. Anesthesia was maintained with Sevoflurane (1-2%) in 100% $O_2$ and controlled ventilation. At the end of surgery, when 25% TOF recovery from the last (maintenance) dose was achieved, reversal was given using combination of Neostigmine 0.05 mg/kg IV and Glycopyrrolate 0.008 mg/kg IV through slow injection. Trachea was extubated when the TOF ratio of 0.9 was achieved. The time of onset and duration of neuromuscular blockade along with recovery profile (mean 25% recovery and mean time of recovery) were noted.

The various hemodynamic parameters including HR, SBP, DBP, MAP, and $SpO_2$ were recorded at baseline, just before induction, just after induction, and after intubation, at 1, 5, 10, 20 30, 40, 50, and 60 minutes, and at every 30 minutes up to 2 hours then every one hour throughout the surgery in two groups. Among adverse effects, signs of histamine release like hypotension (SBP<20% of baseline), tachycardia (HR >100 beats/minutes), skin rash or erythema, and bronchospasm were also observed. Duration of neuromuscular blockade was the time from completion of injection of the loading dose of NMBA till the TOF count two was achieved. Onset time of neuromuscular blockade was defined as the time from completion of the injection of the NMBA till the TOF count was zero. Mean 25% recovery was defined as the time from which 25% recovery occurred after last dose (maintenance dose) of NMBA

during end of the surgery. Mean time of recovery was the time after administering reversal agent upto the time when TOF ratio becomes > 0.9.

**Statistical analysis**

A total sample size of 100 was calculated using power and sample size calculator (PS version 3.0.0.34), α-error of 0.05 and power of 80%.[11] Statistical analysis was done using SPSS, version 20. Before statistical analysis, the collected data was checked for normality using ShapiroWilk test. Descriptive data were expressed as number or percentage and Mean±SD (Standard deviation). Standard qualitative and quantitative tests were used to compare the data (e.g. paired or unpaired student t-test, ANOVA, Chi-Square test). p value ≤0.05 was considered to be significant.

## RESULTS

A total of 100 patients were enrolled for this study. Both groups were comparable with respect to demographic profile including mean age, sex, weight, ASA PS classification and duration of surgery (p>0.05) (Table 1).

The time of onset of neuromuscular blockade in group A and group B was 5.13±1.38 minutes and 3.84±1.55 minutes, respectively which showed that the onset of neuromuscular blockade was significantly faster in group B as compared to group A (p=0.001). Similarly, duration of neuromuscular blockade was significantly prolonged in group B (62.65±2.21 minutes) as compared to group A (36.70±4.58 minutes) (p=0.001) (Table 2).

The mean 25% recovery of neuromuscular blockade was significantly longer in group B as compared to group A (p=0.001). Mean time of recovery of neuromuscular blockade was significantly shorter in group B as compared to group A (p=0.001) (Table 2).

The mean HR at different time intervals i.e. at baseline, just before induction, just after induction, 1 minute after intubation, 5, 10, 20 30, 40, 50, 60 minutes, and at every 30 minutes, thereafter showed that HR was comparable in both groups (p>0.05) (Figure 2). Similarly, mean SBP, DBP, and MAP at different time intervals i.e. at baseline, just before induction, just after induction, and after intubation at 1, 5, 10, 20 30, 40, 50, and 60 minutes, and at every 30 minutes, thereafter showed that these hemodynamic parameters were comparable in both groups at all time intervals (p>0.05) (Figures 3, 4, and 5).

The mean $SpO_2$was also comparable in both groups at all time intervals (p>0.05). No signs of histamine release (hypotension, tachycardia, skin rash or erythema, and bronchospasm) and no other significant side effects were observed in both groups (p >0.05).

## DISCUSSION

In the present study, the dosage of NMBA chosen was based on the $ED_{95}$ value. $ED_{95}$ is the dose of NMBA needed

**Table 1: Demographic profile of the study groups**

| Parameters | Group A (n= 50) | Group B (n= 50) |
|---|---|---|
| **Age (years)** | 40.62±14.03 | 37.24±10.42 |
| **Weight (kgs)** | 62.12±9.47 | 56.74±10.18 |
| **Gender (M/F)** | 16/34 | 11/39 |
| **ASA PS I/II (n)** | 40/10 | 43/7 |

**Table 2: Comparison of neuromuscular blockade and recovery characteristics in the study groups**

| Parameters | Group A (n=50) | Group B (n=50) | p value |
|---|---|---|---|
| **Onset of NMB (minutes)** | 5.13±1.38 | 3.84±1.55 | 0.001* |
| **Duration of NMB (minutes)** | 36.70±4.58 | 62.65±2.21 | 0.001* |
| **Mean 25% recovery (minutes)** | 31.84±1.99 | 48.62±4.92 | 0.001* |
| **Mean time of recovery (minutes)** | 2.63±0.29 | 2.22±0.20 | 0.001* |

NMB; Neuromuscular Blockade, * significant (p<0.05)

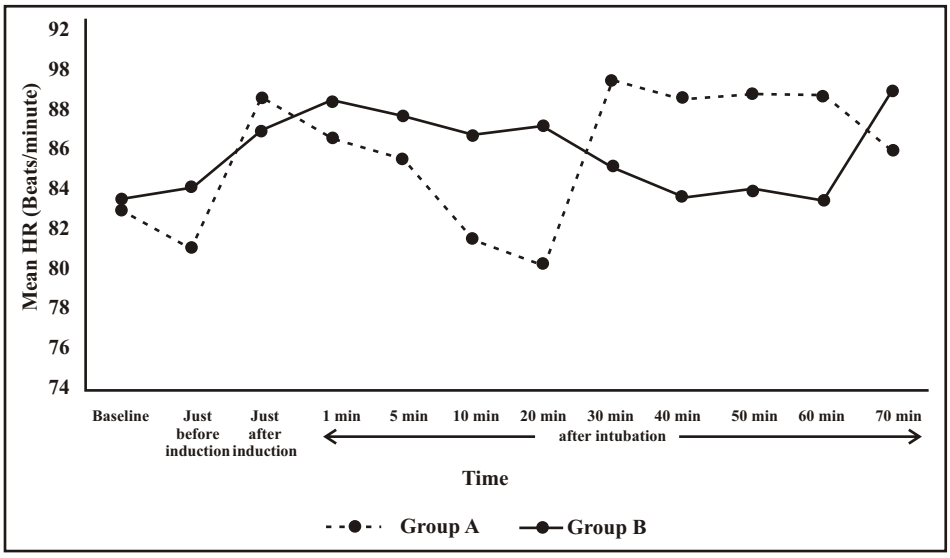


**Figure 2: Comparison of mean heart rate in the study groups.**

to produce 95% suppression of the single twitch response. The dose of NMBA needed for endotracheal intubation is usually more and is used in multiples of $ED_{95}$ dose. Two times the $ED_{95}$ ($2\times ED_{95}$) dose (0.5 mg/kg) of Atracurium has been used for intubation in the present study while four times the $ED_{95}$($4\times ED_{95}$) dose (0.2 mg/kg) of Cisatracurium has been used to obtain intubating conditions.[12,13]

In the present study, the mean time of onset of neuromuscular blockade was found to be significantly faster in group B (Cisatracurium group) as compared to group A (Atracurium group). El-Kasaby et al[14] compared Atracurium ($2\times ED_{95}$) and different doses of Cisatracurium ($2\times ED_{95}$, $4\times ED_{95}$, and $6\times ED_{95}$) and they found that higher doses of Cisatracurium ($4\times ED_{95}$ and $6\times ED_{95}$) showed significantly faster onset time than with Atracurium ($2\times ED_{95}$) which coincides with the present study. A study demonstrated that mean time of onset in Cisatracurium group (3.75 minutes) was faster as compared to that in

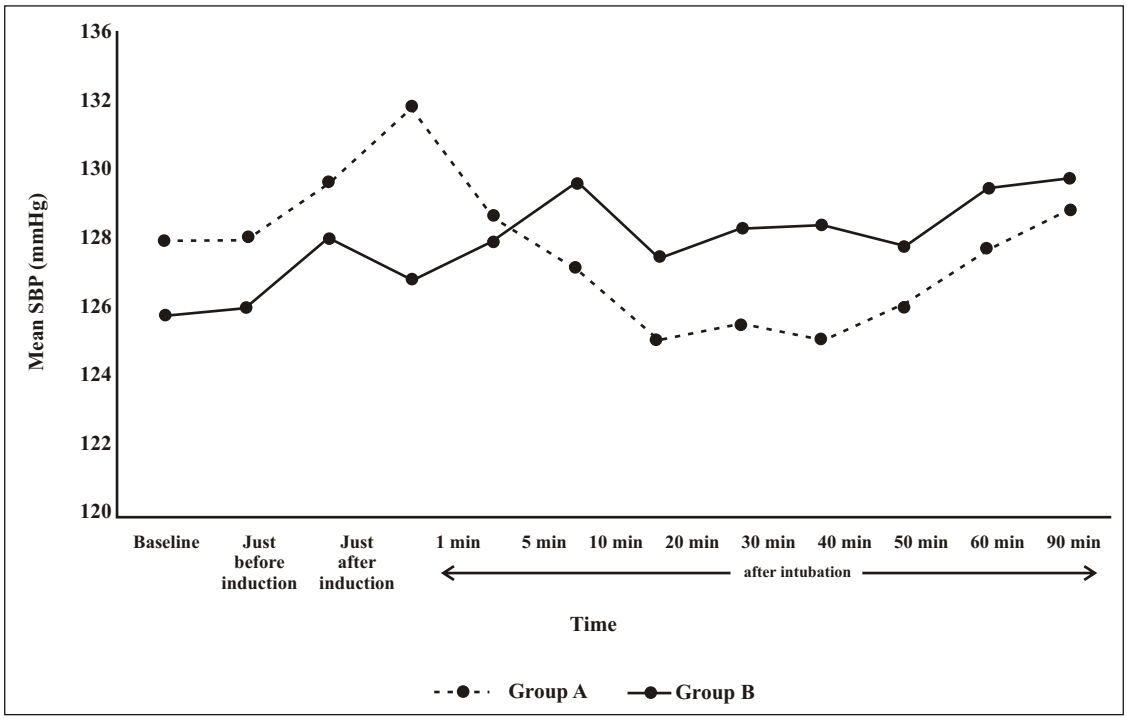


**Figure 3: Comparison of mean systolic blood pressure in the study groups.**

Atracurium group (4.79 minutes) but it was statistically insignificant.[11] Our results are similar to this study in terms of faster onset of neuromuscular blockade. Bluestein et al[15] reported that with increasing dose of Cistracurium from 0.1 to 0.15 and 0.2 mg/kg, the mean time of onset has decreased from 4.6 to 3.4 and 2.8 minutes, respectively and this was in concordance to our results.

Cisatracurium is one of the ten stereoisomers of Atracurium which is approximately three times more potent than atracurium.[16] At equipotent doses, the slower onset of action of Cisatracurium as compared to Atracurium is probably due to its greater potency, a mechanism that has been proposed for other NMBAs. So the more potent non-depolarizing NMBA has a slower onset.[17] The results obtained in the present study with respect to onset time of Atracurium and Cisatracurium might be due to use of non equipotent doses of both NMBAs which showed that 4 or more than 4 times of $ED_{95}$ dose is required for faster onset of Cisatracurium but at the cost of increased duration of neuromuscular blockade.

In the present study, the mean duration of neuromuscular blockade in Cisatracurium group (62.65±2.21 minutes) was significantly longer as compared to Atracurium group (36.71±4.58 minutes). A study reported that mean duration of action of first dose in Cisatracurium group (61.50 minutes) was significantly longer as compared to that in Atracurium group (38.57 minutes).[11] Studies have reported that the mean time of clinically effective duration of neuromuscular blockade with Cistracurium (0.2 mg/kg) was 61 minutes which was also almost similar to our results.[15,16] Similarly, EI-Kasaby et al[14] reported that mean clinical duration of action of Cisatracurium 0.2 mg/kg (65.5±10.5 minutes) was significantly longer than Atracurium 0.5 mg/kg (44.4±4.13 minutes).

After administration of appropriate $ED_{95}$ dose of different non-depolarizing NMBAs, a significant direct relationship has been found between potency of the NMBAs and duration of neuromuscular blockade which explains the prolonged duration of action of Cisatracurium as compared with Atracurium.

The time of mean 25% recovery from the last maintenance dose in Cisatracurium group was significantly prolonged as compared to Atracurium group. Bakhshi et al[11] demonstrated that 25% recovery from the last supplemental dose in Cisatracurium group (48.73 minutes) was significantly longer as compared to Atracurium group (33.63 minutes) (p=0.001). Similarly, Carroll et al[16] also observed that the time from drug administration to 25% recovery with Cisatracurium 0.15 mg/kg (51-59 minutes) was longer as compared with Atracurium 0.5 mg/kg (47-48 minutes) but

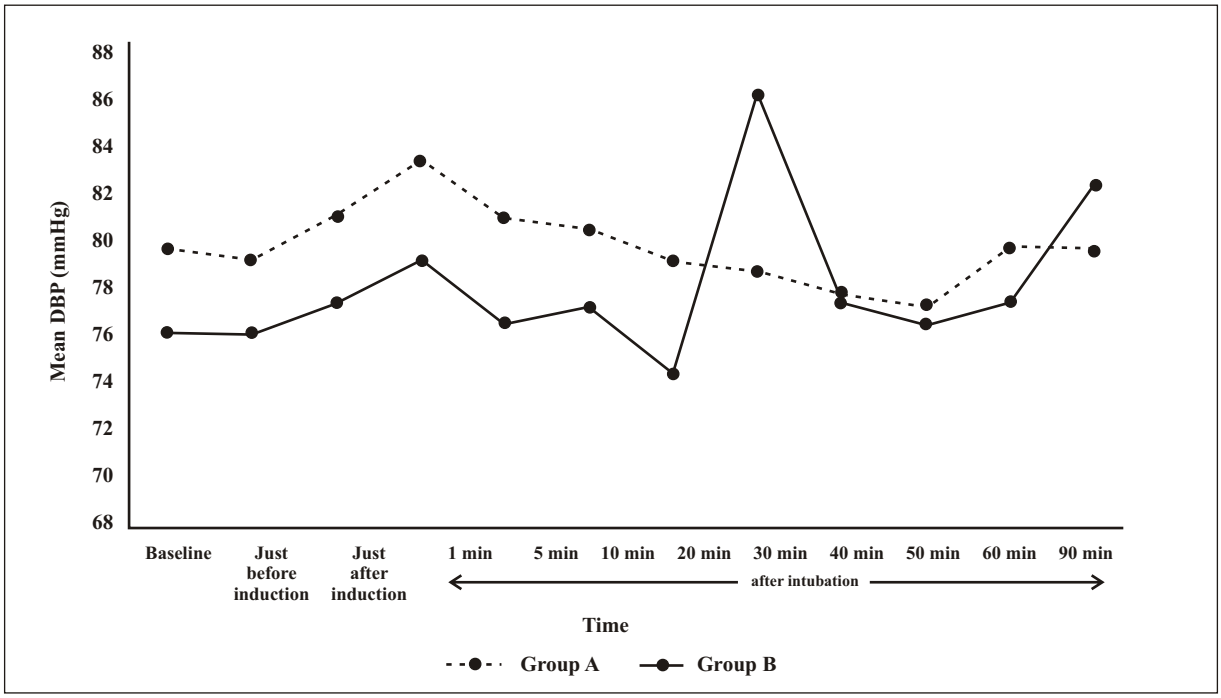


**Figure 4: Comparison of mean diastolic blood pressure in the study groups.**

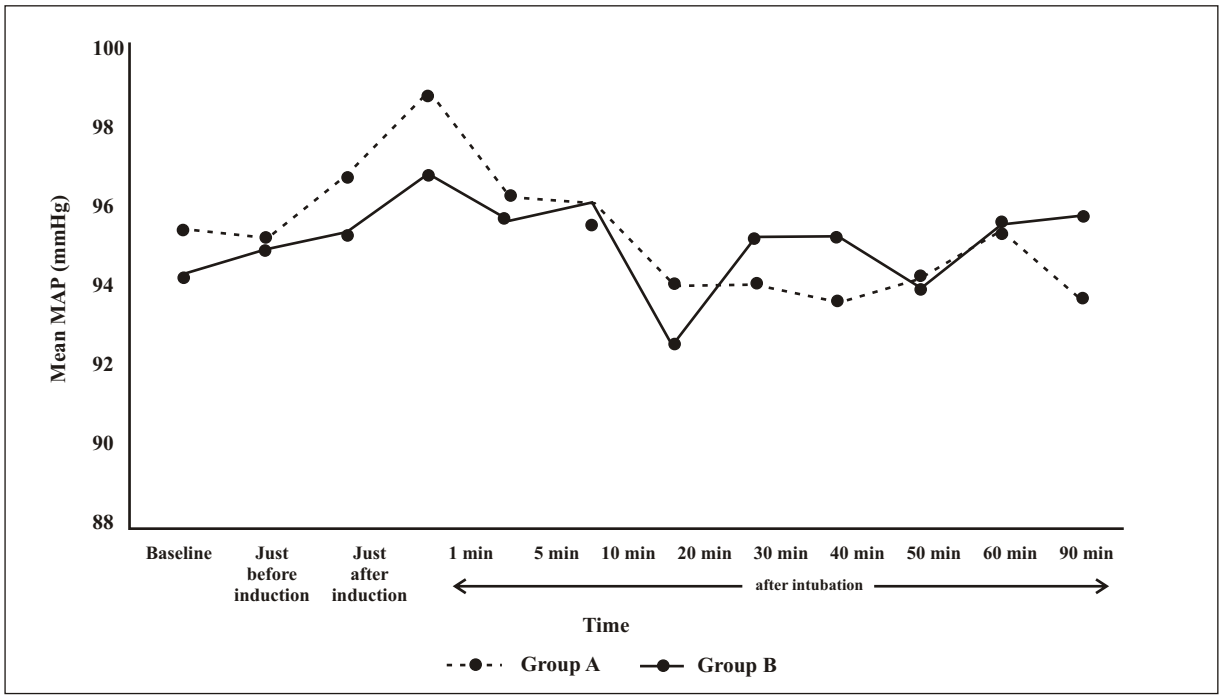


**Figure 5: Comparison of mean MAP in the study groups.**

the difference was not statistically significant (p>0.05). Although the results were insignificant but the 25% recovery from last supplemental dose was prolonged with Cisatracurium.

The recovery of neuromuscular function depends primarily on the drug (NMBA) distribution that takes place when the plasma concentration of NMBA declines. However, the recovery from neuromuscular blockade is more dependent on drug elimination than distribution (i.e. 25% to 75% or greater).[18]

The mean time of recovery after giving Neostigmine (reversal agent) in Cisatracurium group was significantly shorter as compared to Atracurium group (p=0.001). Bakhshi et al[11] found that the mean time of recovery from reversal in Cisatracurium group was 2.30 minutes which was shorter as compared to 2.40 minutes in Atracurium group but both the groups were comparable in terms of mean time of recovery. In our study, although the mean time of recovery after giving reversal agent was significantly shorter in Cisatracurium group but this seems to be clinically insignificant and overall mean time of recovery after last supplemental dose of Cisatracurium was found to be longer as compared to Atracurium.

The various hemodynamic parameters (HR, SBP, DBP, MAP, and $SpO_2$) were observed at different time intervals but no significant hemodynamic changes were noted in any of the two groups. Studies have reported that hemodynamic stability for both heart rate and mean arterial blood pressure were more evident even with higher doses of Cisatracurium.[14,19]

Atracurium tends to cause histamine release which may lead to facial flushing and hemodynamic instability. The usual cardiovascular side effects noted as a result of histamine release are hypotension and tachycardia. These adverse effects observed are usually transient and are related to both the dose of NMBA and time course over which it has been administered. Cisatracurium is devoid of histamine-releasing effects, so that cardiovascular changes do not accompany the rapid IV administration of even large doses ($8\times ED_{95}$) of Cisatracurium because of its stereo-specific property and so no significant hemodynamic changes occurred as depicted in the study done by Shang Guan et al.[20]

In the present study, patients were monitored for any adverse effects like signs of histamine release clinically through skin changes graded as flush (if redness lasted >120 seconds), erythema, or wheals and presence of any hemodynamic changes or bronchospasm. We observed that

none of the patients in any group had adverse effects of histamine release. This histamine release may be prevented or minimised by administering the NMBA slowly over a period of 30-60 seconds. Results of the present study are supported by study by Kaur et al.[2] As far as limitations of the present study are concerned, plasma histamine levels were not measured. Apart from this, the stress response after endotracheal intubation was not adequately addressed. The study drugs were used in selected group of patients (ASA I or II) posted for elective surgery but for critically ill patients in intensive care units, these drugs may have altered pharmacokinetics and pharmacodynamics because of deranged organ functions, acid base disturbances, or dyselectrolytemias in these patients. Cost effectiveness might be the limitation with the use of Cisatracurium in comparison to Atracurium.

## CONCLUSION

Cisatracurium ($4\times ED_{95}$) leads to more rapid onset and longer duration of neuromuscular blockade as compared to Atracurium ($2\times ED_{95}$). The overall mean time of recovery was prolonged with Cisatracurium with stable hemodynamics and no clinical signs of histamine release. Cisatracurium ($4\times ED_{95}$) was found to be a safe and effective non-depolarizing NMBA which can be used as an alternative to Atracurium ($2\times ED_{95}$) in clinical anesthesia practice.

## REFERENCES


1. Foldes FF, McNall PG, Borrego-Hinojosa JM. Succinyl choline: A new appraoch to muscular relaxation in anesthesiology. *N Engl J Med*.1952;247:596-600.
2. Kaur H, Attri JP, Chatrath V, Kaur H, Kaur J. Recovery profile of Atracurium versus Cisatracurium. *J Clin Dia Res*. 2018;12:9-12.
3. Mertes PM, Laxenaire MC, Alla F. Anaphylactic and anaphylactoid reactions occurring during anesthesia in France in 1999-2000. *Anesthesiology*. 2003; 99:536-45.
4. Mohanty AK, Sarangi CR, Routray SS, Pattnaik A. Cisatracurium in different doses versus atracurium during general anesthesia for thyroid surgery: A comparative study. *JMed Sci Clin Res.* 2018;4:97-103.
5. Kisor DF, Schmith VD,Wargin WA, Lien CA, Ornstein E, Cook DR. Importance of the organ-independent elimination of Cisatracurium. *Anesth Analg*. 1996; 83:1065-71.
6. Elbradie S. Neuromuscular efficacy and histamine-release hemodynamic changes produced by rocuronium versus atracurium: A comparative study. *J Egypt Natl Canc Inst*. 2004; 16:107-13.
7. Ghorbanlo M, Mohaghegh MR, Yazdanian F, Mesbah M, Totonchi Z. A comparison between the hemodynamic effects of Cisatracurium and Atracurium in patient with low function of left ventricle who are candidate for open heart surgery. *Medical Archives*. 2016; 70:265-268.
8. Padmaja D, Mantha S. Monitoring of neuromuscular junction. *Indian J Anaesth*. 2002; 46:279-88.
9. Cammu G, de Baerdemaeker L, den Blauwen N, de Mey JC, Struys M, Mortier E. Postoperative residual curarization with cisatracurium and rocuronium infusions. *Eur J Anesthesiol*. 2002;19:129-34.
10. Beaussier M, Boughaba MA. Residual neuromuscular blockade. *Ann Fr Anesth Reanim.* 2005; 24:1266-74.
11. Bakhshi RG, Nagaria A, Mohite SN, Ahluwalia G. Comparison of neuromuscular blockade and recovery characterstics of cisatracurium besylate versus atracurium besylate in adult surgical patients. *J Med Sci Clin Res.* 2016; 4:14613-21.
12. Basta SJ, Ali HH, Savarese JJ, Sunder N, Gionfriddo M, Cloutier G et al. Clinical pharmacology of atracurium besylate (BW 33A): A new non-depolarizing muscle relaxant. *Anesth Analg*.1982; 61:723-29.
13. Belmont MR, Lien CA, Quessy S, Abou-Donia MM, Abalos A, Eppich L et al. The clinical neuromuscular pharmacology of 51W89 in patients receiving nitrous oxide/opioid/barbiturate anesthesia. *Anesthesiology*.1995; 82:1139-45.
14. El-Kasaby AM, Atef HM, Helmy AM, El-Nasr MA. Cisatracurium in different doses versus atracurium during general anesthesia for abdominal surgery. *Saudi J Anaesth*. 2010;4:152-57.
15. Bluestein LS, Stinson LW, Lennon RL, Quessy SN, Wilson RM. Evaluation of cisatracurium, a new neuromuscular blocking agent, for tracheal intubation. *Can J Anaesth*. 1996; 43:925-31.
16. Carroll MT, Mirakhur RK, Lowry D, Glover P, Kerr CJ. A comparison of the neuromuscular blocking effects and reversibility of cisatracurium and atracurium. *Anesthesia*. 1998; 53:744-48.
17. Donati F, Meistelman C. A kinetic-dynamic model to explain the relationship between high potency and slow onset time for neuromuscular blocking drugs. *J Pharmacokinet Biopharm*.1991;19:537-52.

18. Wright PM, Hart P, Lau M, Sharma ML, Gruenke L, Fisher DM. Cumulative characteristics of atracurium and vecuronium. A simultaneous clinical and pharmacokinetic study. *Anesthesiology*.1994; 81:59-68.
19. Yazdanian F, Ghandi I, Toutounchi Z. Comparison of hemodynamic effects of atracurium and Cisatracurium in patients undergoing coronary artery bypass grafting. *Journal of Iranian Society of Anesthesiology and Intensive Care*. 2008; 30:56-66.
20. ShangGuan W, Lian Q, Li J, Gao F. Clinical pharmacology of cisatracurium during nitrous oxide-propofol anesthesia in children. *J Clin Anesth*.2008; 20:411-14.

## Corresponding Author

Dr Surendra Kumar Sethi, Flat no. 202, Shiv Enclave, Civil Lines, Ajmer, Rajasthan, India, Pincode-305001.

email: drsurendrasethi80@gmail.com