A Prospective Randomised Study Comparing Neuromuscular Blockade And Recovery Characteristics Of Two Different Doses Of Cis - Atracurium Versus Atracurium In Elective Surgeries

Suman K*, Medha V, Surendra B***, Tanya M******

*Senior Resident, Department Of Anaesthesiology, SMS Medical College, Jaipur, 302004, India, **Post Graduate, Department Of Anaesthesiology And Critical Care, Dr. S.N. Medical College, Jodhpur, 342003, India, ***Senior Resident, Department Of General Surgery, J.N.U. Institute For Medical Sciences And Research Centre, Jaipur, 302017, India, ****Senior Resident, Department Of Anaesthesiology, R.U.H.S College Of Medical Sciences, Jaipur, 302033, India

Abstract: Background: Cisatracurium is the stereoisomer of atracurium but has considerably higher neuromuscular blocking potency, better hemodynamic profile and no association with dose-dependent histamine release, as compared with the parent compound(1)(2,3). On the other hand, 2 ED95 doses of cis-atracurium (100 µ g/kg) do not create satisfactory intubating conditions such as those seen with equipotent doses of atracurium. There are limited studies which provide us the clarity of a better neuromuscular blocker in terms of intubation and maintainence amongst the two with the most optimum dose. Material And Methods: The study designed as randomised controlled trial, recruited 150 patients into three groups: Group A-atracurium 0.5 mg/kg(2×ED95), Group B and C- cis-atracurium 0.2 mg/kg (4×ED95) and 0.4 mg/kg (8×ED95) respectively and compared them on the basis of onset, duration of action, recovery time, haemodynamic effect and signs of histamine release clinically. Result: Patients in Group C had significantly shorter onset time of block when compared with group A & B. Mean duration of block after loading dose was significantly shorter in Group A than group B & C. Group B had a shorter duration of block than C. Recovery time of block in group A was significantly shorter than group B & C. Conclusion: Cis-atracurium in dose of 0.2 mg/kg seems to be better alternative to atracurium 0.5 mg/kg and cis-atracurium 0.4 mg/kg in providing faster onset, intermediate duration of action with fast recovery and it can be used for intubation as well as maintenance. [K S Natl J Integr Res Med, 2021; 12(6): 26-31]

Key Words: Endotracheal intubation, Atracurium, Cis-atracurium

Author for correspondence: Dr. Tanya Mishra, Senior Resident, House No: 65, Gayatri Nagar-B, Durgapura, Jaipur, Rajasthan, 302018, India. E-Mail: mishratanya15738@gmail.com Mobile: 9887867791

Introduction: Rapid and safe endotracheal intubation is of utmost importance in the practice of general anaesthesia. The time interval between suppression of the protective reflexes by induction of anaesthesia and the development of satisfactory intubating conditions is considered a critical period. It is desirable that this period should remain as short as possible. Neuromuscular blocking agents are used for facilitating endotracheal intubation and providing muscle relaxation during general anaesthesia as they interrupt transmission of nerve impulse at neuromuscular junction[4]. The ideal neuromuscular blocking agent for intubation needs to have a rapid onset, brief duration of action, free from hemodynamic changes, devoid of residual paralysis and provide excellent intubating conditions like fully relaxed jaw, widely open vocal cord and absence of intubation-response[5]. Atracurium and Cis-atracurium are intermediate acting non-depolarising neuromuscular blocking agents which belong to benzylisoquinolone compounds[6]. Cisatracurium is 1Rcis-1'Rcis stereoisomer of atracurium. It is a purified form of one of the 10 stereoisomers of atracurium which, unlike the parent compound, is not associated with dose dependent histamine release in humans[2,3,7].Despite the higher potency, cis-atracurium is associated with more stable hemodynamics than atracurium and does not cause histamine release. In same dose ($2\times ED_{95}$) of both, atracurium is more effective neuromuscular blocking agent than cis-atracurium. Atracurium releases histamine and causes histamine related side effects like hypotension, tachycardia, flushing, erythema and bronchospasm. Cis-atracurium is a stereoisomer of atracurium which does not release histamine and thus does not cause histamine related side effects[8,9].There are many studies available which have compared between ($2\times ED_{95}$), ($3\times ED_{95}$), ($4\times ED_{95}$) and ($6\times ED_{95}$) of cis-atracurium in term of neuromuscular block characteristics. But there are limited studies which compared block characteristics between atracurium ($2\times ED_{95}$) with ($4\times ED_{95}$) and ($8\times ED_{95}$) of

cis-atracurium. So, we planned to carry out a study to compare between atracurium (2×ED95) and different doses of cis-atracurium (4×ED95) and (8×ED95) in terms of onset, duration and recovery from neuromuscular blockade, haemodynamic parameters and side effects.

Material & Methods: After approval from institutional ethical committee (no: RNT/STAT/ IEC/2018/1836), a prospective randomised double-blind study was carried out on patients of age group 18-65 years who were undergoing surgical procedures with an anticipated duration of at least one hour under general anaesthesia in Maharana Bhupal Government Hospital, RNT Medical college, Udaipur. Patients of ASA grade I and II, undergoing surgery under general anaesthesia were included in the study. Patients with anticipated difficult intubation and those on medication, known to interact with neuromuscular blocking drugs e.g., antibiotics (amino-glycosides and tetracycline), antidepressants, anticonvulsants, anti-arrhythmic (calcium channel blocker and quinidine) and magnesium sulphate were excluded from the study.

A total of hundred and fifty patients were included in the study and using computer generated randomization were randomly allocated by chits into three groups (fifty in each group). Group A received Inj. atracurium with initial dose of 0.5 mg/kg followed by maintenance dose of 0.1 mg/kg. Group B received Inj. cis-atracurium with initial dose of 0.2 mg/kg followed by maintenance dose of 0.04 mg/kg and Group C received Inj. cis-atracurium with initial dose of 0.4 mg/kg followed by maintenance dose of 0.08 mg/kg. After complete preoperative assessment and taking written informed consent, patients were taken in operation theatre. Along with routine monitoring (ECG, NIBP, SpO2), bispectral index monitoring and peripheral nerve stimulator (Mindray A7 with integrated NMT module) for neuromuscular monitoring were applied. An 18-gauge intravenous line was secured and intravenous fluid were started. Patients were premedicated with Inj. Glycopyrrolate 0.004 mg/kg, Inj. Midazolam 0.02 mg/kg, Inj. Fentanyl 2 µg/kg.

After recording baseline hemodynamic parameters, the control values for neuromuscular monitoring were obtained by supra-maximal stimulus (50 mA, 2Hz). After pre-oxygenation with 100% oxygen for 3 minutes, patients were induced with Inj. Propofol (2mg/kg) intravenously. NMBA (atracurium 0.5mg/kg, cis-atracurium 0.2 mg/kg or cis-atracurium 0.4 mg/kg) were administered to the patients as per group allocation. Neuromuscular monitoring was carried out at every 15 sec through the stimulation of ulnar nerve via surface electrode.

At "TOF score 0" condition of intubation was assessed and endotracheal intubation was done using proper sized cuffed endotracheal tube. After intubation EtCO2 was also recorded by connecting EtCO2 sensor to the endotracheal tube.

The onset time was determined as the interval from the end of muscle relaxant injection to achieving "TOF score 0" on neuromuscular monitoring.

Anaesthesia was maintained with mixture of 50% N2O in O2 and isoflurane (0.8%-1%) inhalation to maintain BIS index 40-60. Muscle relaxation was maintained with intermittent bolus dose of muscle relaxant atracurium 0.1mg/kg, cis-atracurium 0.04mg/kg or cis-atracurium 0.08mg/kg as per group allocation. Any sign of histamine release was observed and recorded by monitoring skin changes like erythema, wheals and hemodynamic changes like hypotension or bronchospasm. Patients were ventilated by volume-controlled ventilation intraoperatively with maintaining normocapnia.

Intraoperative hemodynamic changes were monitored continuously including: heart rate, systolic and diastolic blood pressure, MAP, oxygen saturation and end tidal CO2. Duration from the last dose of NMBA to 25% recovery of TOF was recorded. At the end of surgery when T1 was 25% from the last dose, muscle blockade was reversed by administration of Inj. Neostigmine (0.07mg/kg) and Inj. Glycopyrrolate (1/5th of Neostigmine) mixture through slow intravenous injection. TOF ratio >0.9 was considered as point for safe extubation. After extubation, patients were shifted to recovery room for post-operative monitoring of hemodynamic parameters for 2 hours.

Statistical Analysis: Open Epi version 3.01 software was used to calculate the sample size. Data were entered in MS EXCEL and statistically analysed using SPSS version 20. Quantitative data

were expressed as Mean±SD. ANOVA test was used to test significance. P value <0.05 was considered statistically significant. Qualitative data were expressed as number and percentages and compared with chi-square test.

Results: All study groups were comparable with regard to the demographic characteristics and the duration of surgeries (Table:1).

Table 1: Distribution Of Patients According To Age, Weight And Duration Of Surgeries

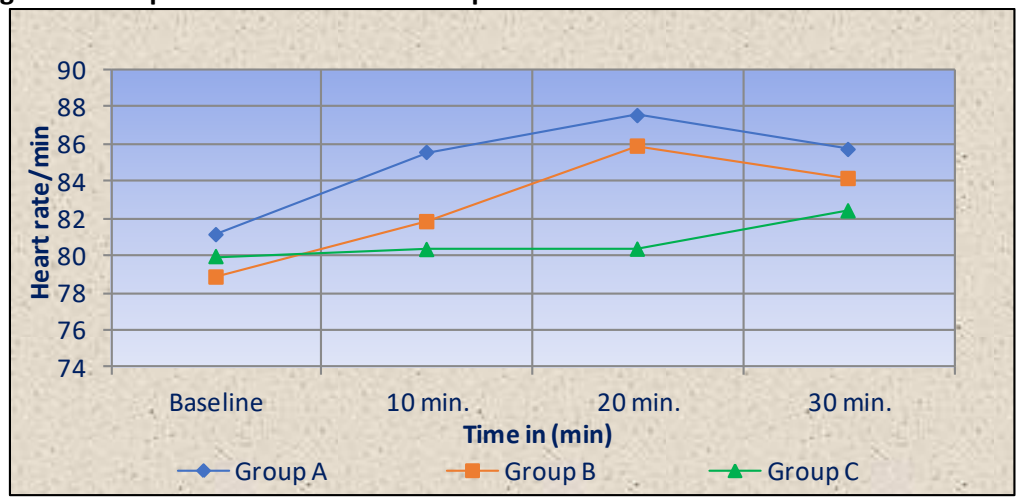
	Group A (N=50)	Group B (N=50)	Group C (N=50)	P Value
Age (Years) Mean±SD	31.50±11.52	34.22±12.24	33.20±11.32	.503
Gender-F/M (%)	40/60	50/50	58/42	0.567
Weight (Kg) (Mean±SD)	63.56±9.34	66.36±9.01	63.50±8.94	0.202
Duration Of Surgery (In Min) (Mean±SD)	110.12±48.12	104.00±48.57	122.66 ± 57.12	0.185

The onset time of block in group A was significantly longer than the other groups and shortest in group C (p=0.000, Annova test, Table:2). On the other hand, the duration of block and recovery time of block were seen to be shortest in group A, followed by group B and longest in group C (p=0.000, Annova test, Table:2).

Table 2: Distribution Of Patients According To Onset, Duration And Recovery Of Block

	Group A (N=50)	Group B (N=50)	Group C (N=50)	P Value
Onset Of Block (In Min.) (Mean ±SD)	5.00±0.77	4.11±0.62	2.52±0.42	0.000*
Duration Of Block (In Min.) (Mean±SD)	30.34±3.95	46.60±6.61	72.10±12.93	0.000*
Recovery Time Of Block (In Min.) (Mean±SD)	25.72±4.01	44.04±10.74	60.88±18.64	0.000*

Figure 1: Comparison Of The Three Groups Based On Heart Rate At Various Time Points



Two patients in group A were reported to experience an episode of hypotension, though overall three of the groups were comparable in terms of systolic, diastolic and mean arterial pressures. Mean heart rate was observed to be statistically higher at 10 and 20 minutes in group A as compared to the other two groups (p 10^{th} =0.049; p 20^{th}=0.003, Annova, fig:1).

In terms of other signs of histamine release (flush, erythema, wheal), no significant difference was seen.

Discussion: While selecting neuromuscular agent for tracheal intubation or skeletal muscle relaxation, main aim of an anaesthesiologist is to select an agent with rapid onset, better hemodynamic stability, long clinical duration of action, and better recovery with less side effects.

Previous studies compared between two intermediate-acting benzylisoquinolone muscle relaxants, atracurium besylate and cis-atracurium besylate with intubating dose $2\times ED_{95}$ (0.5mg/kg)[4,5,7,8] of atracurium, $3\times ED_{95}$

(0.15mg/kg) and 4×ED_{95} (0.2 mg/kg)[4,7,8] of cis-atracurium but limited studies are available on comparison of higher dose of cis-atracurium 8×ED_{95} (0.4mg/kg) with 4×ED_{95} (0.2 mg/kg) cis-atracurium and atracurium 2×ED_{95} (0.5mg/kg).

So, we planned present study to compare higher dose of cis-atracurium 8×ED_{95} (0.4mg/kg) for its block and recovery characteristics along with hemodynamic stability and adverse effects with 4×ED_{95} (0.2 mg/kg) cis-atracurium and atracurium 2×ED_{95} (0.5mg/kg).

The above non-equipotent doses of the drugs were selected because previous clinical studies have shown that cis-atracurium carries the property of stable hemodynamics without any apparent histamine release[2,3,8]. According to Suresh et al[10], monitoring of neuromuscular activity of the Adductor Pollicis using Train of Four in determination of appropriate tracheal intubation time and condition is clinically more relevant than monitoring the Orbicularis Oculi muscle.

The mean onset time of block was significantly shorter for cis-atracurium 0.4 mg/kg (2.52±0.42 min) as compared to cis-atracurium 0.2 mg/kg (4.11±0.62 min) and atracurium 0.5 mg/kg (5.00±0.77 min) ($p<0.05$), which was similar to other studies[11,12]. Bluestein LS et al[11] showed that, on increasing the initial dose of cis-atracurium (from 0.1 to 0.15 and 0.2mg/kg), the mean time of onset decreased (from 4.6 to 3.4 and 2.8 min) respectively. Cisatracurium is on a molar basis, 3-4 times more potent than atracurium[3,7]. The decreased onset of time of cis-atracurium as compared to atracurium at equipotent doses is probably attributable to its greater potency.

In our present study, duration of block of muscle relaxant was observed as the time from injection of loading dose of the drug to return of TOFR = 25%.

The mean duration of block was longer in group C (72.10±12.93 min.) as compared to group B (46.60±6.61 min.) and group A (30.34±3.95 min.). The difference was statistically significant between the three groups ($p<0.05$) which were similar to other studies[11-13]. Lepage et al[3] observed that time to 25% recovery of T1% (duration of action) of atracurium (0.5mg/kg) and cis-atracurium (0.1, 0.2, 0.25mg/kg) was 42, 33, 55 and 79 min respectively which concluded that increasing the dose of cis-atracurium prolongs the duration of action, whereas at equipotent doses, cis-atracurium has a shorter duration of action compared to atracurium. Similar results were obtained by Kasaby et al[8].

In contrast to our study Smith et al[14] did not find any difference in duration of action of atracurium 0.5 mg/kg and cis-atracurium 0.1 mg/kg because they used lesser dose of cis-atracurium (0.1 mg/kg) as compared to our study (0.2 mg/kg). A significant direct relationship has been found between duration of action and potency of the drug after administration of appropriate ED_{95} dose of different non- depolarizing neuromuscular blocking drugs which explains the prolonged duration of action of cis-atracurium as compared with atracurium.

In our study, mean recovery time was longer in group C (60.88±18.64 min.) as compared to group B (44.04±10.74 min.) and group A (25.72±4.01 min.). The difference was statistically significant between the three groups ($p<0.05$). Recovery of neuromuscular function takes place as the plasma concentration declines and greater part of this decrease occurs primarily (up to initial 25%) because of distribution. In the later part, recovery comes to relies more on drug elimination rather than distribution (i.e., from 25% to 75% or greater).

Shyamlal Thakral et al in their study compared atracurium to cis-atracurium and found a better recovery profile and rapid onset with Cis-atracurium especially in a dosage of 0.2mg/kg which resonates with our study. MT Carroll et al[12] observed the time from drug administration to 25% recovery with cis-atracurium 0.15 mg.kg−1 (51–59 min) was longer compared with both cis-atracurium 0.1 mg.kg−1 (45–48 min) and atracurium 0.5mg/kg (47–48 min) but the difference was not statistically significant because they did not antagonize the block from very profound levels (i.e., no response to TOF) or when a much greater spontaneous recovery had taken place (i.e., T_1>50%).

Bisbenzylquinolinium compounds, in general tend to cause histamine release, which can often result in facial flushing and hemodynamic variations. The cardiovascular effects normally observed secondary to histamine release are a decrease in mean arterial pressure and a

compensatory increase in heart rate. These responses normally are transient and related to both dose and time of the relaxant administration. Cis-atracurium is devoid of histamine-releasing effects so that cardiovascular changes do not accompany the rapid IV administration of even large doses ($4\times ED_{95}$) of cis-atracurium because of its stereospecific property and thus no significant hemodynamic changes occur[15].

In our study, two patients who received atracurium showed signs of histamine release in the form of transient hypotension, difference being statistically insignificant. But, at time intervals 10 and 20 min. the mean heart rate was observed to be significantly higher in group A than groups B and C. The slight instability of hemodynamic profile in group A could have been merely a chance finding, attributable to a variety of other factors or could possibly be a consequence of histamine release.

Except for the transient perturbations in the atracurium group in terms of hemodynamics, none of the patients in any of these groups showed any signs of histamine release like erythema, flushing or bronchospasm.

Kasaby et al[8] also observed no signs of histamine release in different doses of cis-atracurium (2, 4 or $6\times ED_{95}$) while it was observed with atracurium ($2\times ED_{95}$ dose)- two cases: one case had flushing and other had erythema. Bluestein LS et al[11] reported similar findings.

Conclusion: The present study concludes cis-atracurium in a dose of 0.2 mg/kg seems to be better alternative to atracurium 0.5 mg/kg and cis-atracurium 0.4 mg/kg in providing faster onset, intermediate duration of action, good intraoperative hemodynamic parameters with faster recovery and better safety profile and it can be used for intubation as well maintenance.

References:

1. Taivainen T, Meakin GH, Meretoja OA, Wirtavuori K, Perkins RJ, Murphy AK, Fisher GR, Waiter MR. The safety and efficacy of cisatracurium 0.15 mg. kg− 1 during nitrous oxide–opioid anaesthesia in infants and children. Anaesthesia. 2000 Nov;55(11):1047-5.
2. Lien CA, Belmont MR, Abalos A, Eppich L, Quessy S, Abou-Donia MM, Savarese JJ. The cardiovascular effects and histamine-releasing properties of 51W89 in patients receiving nitrous oxide/opioid/barbiturate anesthesia. The Journal of the American Society of Anesthesiologists. 1995 May 1;82(5):1131-8.
3. Lepage JY, Malinovsky JM, Malinge M, Lechevalier T, Dupuch C, Cozian A, Pinaud M, Souron R. Pharmacodynamic dose-response and safety study of cisatracurium (51W89) in adult surgical patients during N2 O-O2-opioid anesthesia. Anesthesia & Analgesia. 1996 Oct 1;83(4):823-9.
4. 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. differences. 2016 Dec;1(2):3.
5. Mohanty AR, Sarangi CR, Routray SS, Pattnaik A. Cis-atracurium in different doses versus Atracurium during general anaesthesia for thyroid surgery. Journal of medical science and clinical research. 2018 Jul;06:97–103.
6. Naguib M, Brull SJ. Pharmacology of Neuromuscular Blockers. Oxford University Press, London, UK; 2011 Oct 5
7. Belmont MR, Lien CA, Quessy S, Abou-Donia MM, Abalos A, Eppich L, Savarese JJ. The clinical neuromuscular pharmacology of 51W89 in patients receiving nitrous oxide/opioid/barbiturate anesthesia. The Journal of the American Society of Anesthesiologists. 1995 May 1;82(5):1139-45.
8. El-Kasaby AM, Atef HM, Helmy AM, El-Nasr MA. Cisatracurium in different doses versus atracurium during general anesthesia for abdominal surgery. Saudi journal of anaesthesia. 2010 Sep;4(3):152.
9. Jirasiritham S, Tantivitayatan K. A comparison of the efficacy of cisatracurium and atracurium in kidney transplantation operation. Journal of the Medical Association of Thailand. 2004 Jan;87(1):73–9.
10. Suresh SN, Singh NG. Comparison between Adductor Pollicis and Orbicularis Oculi as Indicators of Adequacy of Muscle Relaxation for Tracheal Intubation Following Rocuronium Induced Neuromuscular Block: Randomized Comparative Clinical Trial. Recent Research in Science and Technology. 2010 Dec 1;2(5).
11. Bluestein LS, Stinson LW, Lennon RL, Quessy SN, Wilson RM. Evaluation of cisatracurium, a new neuromuscular blocking agent, for tracheal intubation. Canadian journal of anaesthesia. 1996 Sep;43(9):925-31.

12. Carroll MT, Mirakhur RK, Lowry D, Glover P, Kerr CJ. A comparison of the neuromuscular blocking effects and reversibility of cisatracurium and atracurium. Anaesthesia. 1998 Aug;53(8):744-8.
13. Basta SJ, Ali HH, Savarese JJ, Sunder N, Gionfriddo M, Cloutier G, Lineberry C, Cato AE. Clinical pharmacology of atracurium besylate (BW 33A): a new non-depolarizing muscle relaxant. Anesthesia and Analgesia. 1982 Sep 1;61(9):723-9.
14. Smith CE, Van Miert MM, Parker CJ, Hunter JM. A comparison of the infusion pharmacokinetics and pharmacodynamics of cisatracurium, the 1R-cis 1' R-cis isomer of atracurium, with atracurium besylate in healthy patients. Anaesthesia. 1997 Sep;52(9):833-41.
15. ShangGuan W, Lian Q, Li J, Gao F. Clinical pharmacology of cisatracurium during nitrous oxide-propofol anesthesia in children. Journal of clinical anesthesia. 2008 Sep 1;20(6):411-4.

Conflict of interest: None

Funding: None

Cite this Article as: KS, VM, BS, MT. A Prospective Randomised Study Comparing Neuromuscular Blockade And Recovery Characteristics Of Two Different Doses Of Cis - Atracurium Versus Atracurium In Elective Surgeries. Natl J Integr Res Med 2021; Vol.12(6): 26-31