www.jmscr.igmpublication.org
Impact Factor 5.244
Index Copernicus Value: 83.27
ISSN (e)-2347-176x ISSN (p) 2455-0450
crossref DOI: https://dx.doi.org/10.18535/jmscr/v4i12.52

IGM Publication
Journal Of Medical Science And Clinical Research
An Official Publication Of IGM Publication

Comparison of Neuromuscular Blockade and Recovery Characterstics of Cisatracurium Besylate versus Atracurium Besylate in Adult Surgical Patients

Authors
Dr Rochana G Bakhshi[1], Dr Anisha Nagaria[2], Dr Shubha N Mohite[3], Dr Gurlyn Ahluwalia[4]
[1]Ex –Professor, Dr D Y Patil Medical College, Consultant Anesthesiologist, Apollo Group of Hospitals, Belapur, Navi Mumbai
[2,4]Third year Resident, Dr D Y Patil Medical College, Navi Mumbai
[3]Professor, Dr D Y Patil Medical College, Navi Mumbai
Corresponding Author
Dr Rochana G Bakhshi
Devneeti, Plot no.61, Sector-7, Behind D Mart, Koper Khairane, Navi Mumbai-400709, Maharashtra, India
Email: *drrochana_b@apollohospitals.com, Mobile no: +91-9323272151*

ABSTRACT
Aims: *To compare neuromuscular blockade and recovery characteristics of cisatracurium and atracurium in adult patients.*
Methodology: *60 patients, 18-65 years, ASA class I &II for surgery under general anesthesia were randomly allocated to cis-atracurium and atracurium group. After induction agent, dose of neuromuscular blocking drug (NMBA) atracurium 0.5mg/kg loading and maintenance dose of 0.1mg/kg or cisatracurium ,0.2mg/kg and maintenance dose of 0.03mg/kg was given to the patients.*
The onset time was determined as the interval from the end of muscle relaxant injection until "Train of four (TOF) score 0". Neuromuscular monitoring was carried out at every 15s to stimulate the ulnar nerve via surface electrodes. Duration from the last dose of NMBA to 25% recovery of TOF was recorded.
Results: *Mean Duration of action (DOA) of 1ST dose in Cisatracurium group was 61.50 minute which was significantly more as compared to 38.57 minute in Atracurium group. Recovery from last dose in Cisatracurium group was 48.73 minutes, 33.63 minutes in Atracurium group and difference was statistically significant.*
Conclusion: *Intubating conditions were achieved faster & duration of action was longer with loading dose cisatracurium than atracurium. Between neostigmine administration and attaining a TOF ratio of 80%, time duration was shorter with cisatracurium than atracurium, when administered at TOF 25%.*
Keywords: *cis-atracurium, atracurium, neuromuscular monitoring.*

INTRODUCTION

The introduction of neuromuscular blocking agents was an important development in world of anesthesia in 1942. Neuromuscular blocking drugs interrupt transmission of nerve impulses at neuromuscular junction (NMJ), aid endotracheal intubation and prevent patient movement to facilitate surgery.

Non-depolarizing neuromuscular blocking agents [NMBA] competitively inhibit acetylcholine, differ in the onset & duration of action, metabolic route, potency, adverse effects and cost. An anaesthesiologist is able to choose NMBAs according to these similarities and differences.[1,2,3]

Atracurium and Cisatracurium are non-depolarizing NMBs, intermediate acting, benzylisoquinolone compounds.[4] Cisatracurium is 1Rcis-1'Rcis stereoisomer of atracurium. Cisatracurium 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. [5,6,7,8]

Neuromuscular monitoring is required in an anaesthetised patient to assure complete recovery from a neuromuscular blockade. The main objective of this study was to compare neuromuscular blockade and recovery characteristics between the two non-depolarizing neuromuscular blocking drugs; Cisatracurium besylate and atracurium besylate in adult patients undergoing diagnostic and surgical procedures with general anaesthesia.

AIMS AND OBJECTIVES

AIM

The aim was to study the difference between cisatracurium besylate and atracurium besylate in terms of onset, duration of action of first loading dose, 25% recovery from last supplemental dose and neostigmine reversal after assessing clinical parameters and recovery from TOF ratio.

OBJECTIVE

1. To compare the onset and duration of action and recovery index of atracurium besylate and cisatracurium besylate.
2. To record the systolic blood pressure (SBP), diastolic blood pressure (DBP) and pulse rate; vital parameters in first 10 minutes after administration of loading dose.
3. To evaluate the safety and efficacy of cisatracurium besylate as compared to atracurium besylate for neuromuscular blockade in adult patients during diagnostic/ therapeutic procedures.
4. Neuromuscular monitoring using TOF parameters.

MATERIAL AND METHODS

A prospective randomised double blind study was carried out on patients of age group 18-65years who underwent elective diagnostic and surgical procedures under general anaesthesia in a tertiary care Hospital. Patients of ASA I & II class, undergoing procedure under general anaesthesia were included in the study. Non consenting patients, anticipated difficult intubation and ASA grade III and more were excluded from the study.

Total sample size was 60, each group having 30 patients selected as per random allocation software.[9] Two investigators participated in the study, first investigator prepared the drugs and second investigator was responsible for monitoring and data collection and was blinded to the study.

Group A: Atracurium with initial dose of 0.5 mg/kg , maintenance dose of 0.1mg/kg

Group B: Cisatracurium with initial dose of 0.2 mg/kg maintenance dose of 0.03mg/kg

The patients were assessed preoperatively. Written informed consent was taken.

In the O.T. along with routine monitors such as ECG, NIBP, SpO2, a peripheral nerve stimulator (PNS) for neuromuscular monitoring was also attached.

Intravenous line was secured. Patients were pre-oxygenated with 100% oxygen for 3 min.

General anaesthesia was induced with midazolam 1mg, fentanyl (1-2 µg/kg), propofol (2 mg/kg) intravenously. Trachea was intubated with appropriate size endotracheal tube.

Anaesthesia was maintained with a mixture of 50% N_2O in O_2 and isoflurane (0.8%-1%) and assisted ventilation. After a stable baseline reading of hemodynamic parameters NMBA (atracurium

0.5mg/kg / cisatracurium 0.2mg/kg) was given for patients according to the previously mentioned doses for each group and injected intravenously.

Neuromuscular monitoring was carried out after obtaining the control values by supramaximal stimulus (50 mA, 2 Hz) at every 15s to stimulate the ulnar nerve via surface electrodes. From the time of injection of NMBA, patient's blood pressure and pulse rate was monitored each minute for next 10minutes and then every 10 minutes throughout the surgery.

The onset time was determined as the interval from the end of muscle relaxant injection until "TOF score 0".At "TOF score 0" endotracheal intubation was done using proper size tube. Anaesthesia was maintained with a mixture of 50% N_2O in O_2, isoflurane (0.8-1%), boluses of the muscle relaxant (with the maintenance dose of atracurium 0.1mg/kg and cisatracurium 0.03mg/kg) was given at TOF score 2. Patients were monitored for any signs of histamine release clinically by observing skin changes graded as flush (if redness lasted> 120 s), erythema, or wheals and presence of any hemodynamic changes or bronchospasm. Intraoperatively patient was on volume controlled ventilation and normocapnia maintained.

Intra-operative hemodynamic changes were continuously displayed on the monitor including: heart rate (HR), systolic and diastolic blood pressure every 1 minute from the time of injection of drug and then every 10 minutes, oxygen saturation (SpO_2), and end tidal CO_2.

Duration from the last dose of NMBA to 25% recovery of TOF was recorded.

At the end of surgery when TOF recovery was 25% from the last dose, reversal was achieved by administration of neostigmine and glycopyrrolate mixture (0.05 mg/kg neostigmine and 8µk/kg glycopyrrolate) through slow IV injection.

Patient was then shifted to the recovery room for post -operative monitoring.

RESULTS AND ANALYSIS

Demographically both the groups were comparable. Systolic and diastolic blood pressures and pulse rate were comparable and no statistical difference was seen between the two groups.

Mean onset of action in Cisatracurium besylate group was 3.75 minutes which was faster as compared to 4.79 minutes in Atracurium besylate group but difference was not statistically significant. (student t test, p value: 0.123,not significant)(fig 1)

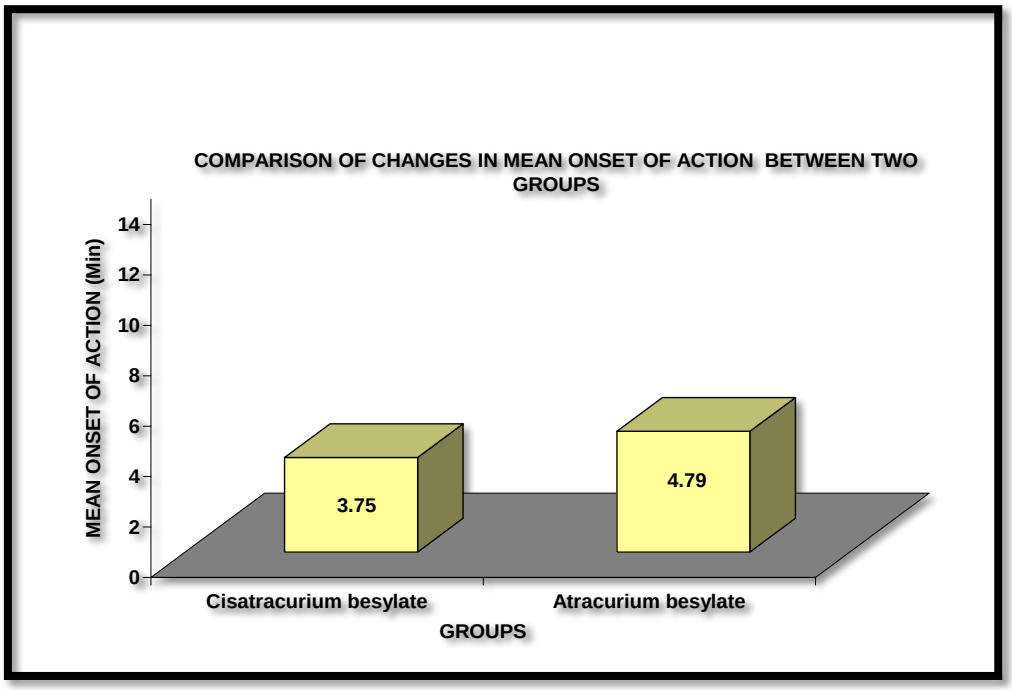

Figure 1

Mean duration of action (DOA) of 1ST dose in Cisatracurium besylate group was 61.50 minute which was significantly more as compared to 38.57minute in Atracurium besylate group. (student t test, p value: 0.001) (figure 2)

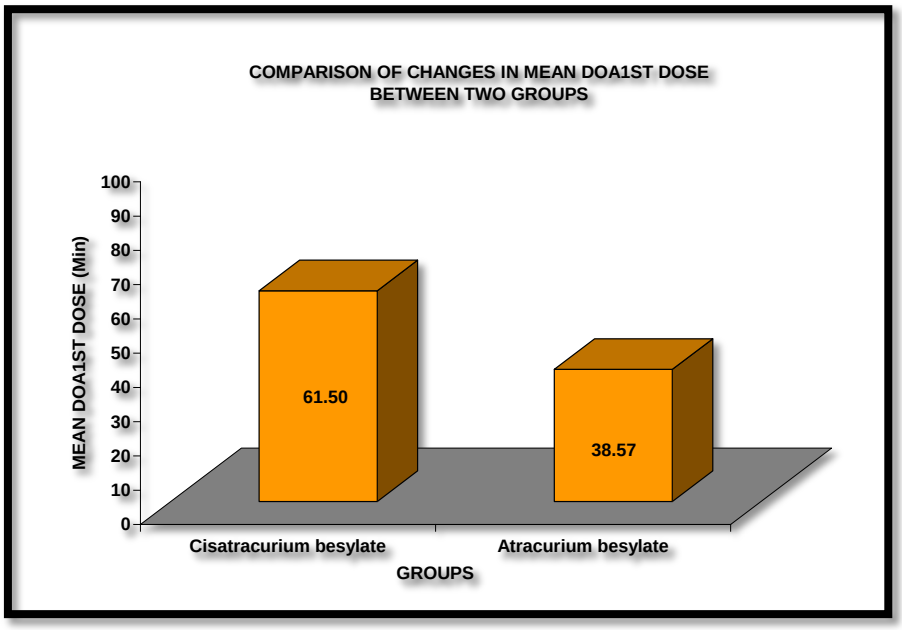

Figure 2

The mean 25% recovery in Cisatracurium besylate group was 48.73 minutes which was more as compared to 33.63 minutes in Atracurium besylate group and difference was statistically significant. (Student "t" Test*P = 0.001, significant)(figure 3)

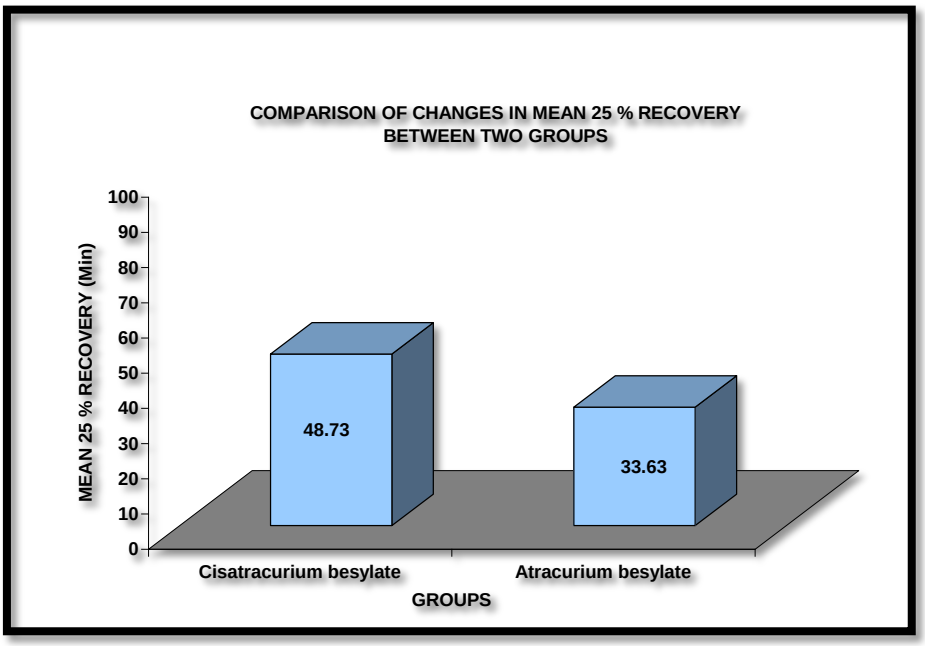

Figure 3

The mean time of recovery from reversal in both the groups was comparable and statistically significant. (sample t- test *P-Value is 0.000 significant) (figure 4)

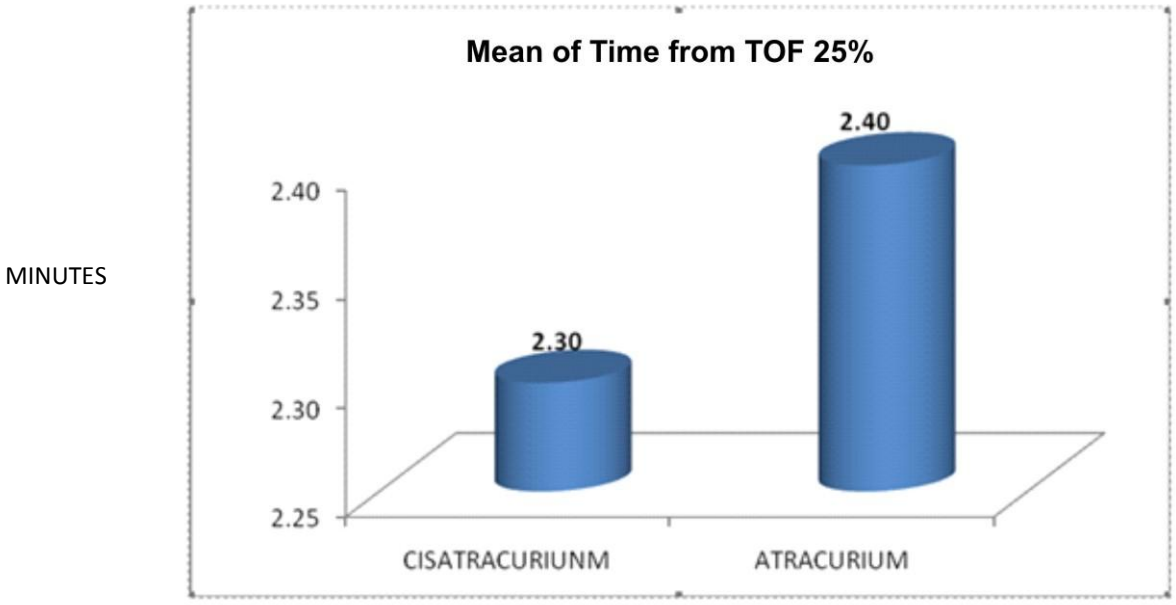

Figure 4

DISCUSSION

Two non-depolarising muscle relaxants of intermediate duration of action , Atracurium and Cisatracurim besylate were compared in this study in terms of onset of action, duration of action of first dose and recovery time from last dose TOF 25%. Hemodynamic parameters including systolic blood pressure, diastolic blood pressure and heart rate were monitored for 10 minutes after administration of the first dose and then every 10 minutes throughout the surgery.

The speed of onset is inversely proportional to the potency of non-depolarizing neuromuscular blocking agents [4]. It has been reported earlier that atracurium $2\times ED_{95}$ dose has a faster onset of action as compared to cisatracurium $4\times ED_{95}$ dose. Presumably cisatracurium has greater potency than atracurium resulting in fewer molecules being administered even with the higher doses. [4] So cisatracurium with higher doses has faster onset of action as compared to atracurium.

In our study mean onset of action in cisatracurium ($4\times ED_{95}$ dose) group was 3.75 minutes and atracurium ($2\times ED_{95}$ dose) group was 4.79 minutes which was not statistically significant.

Similar results were obtained by El –kasaby et al in his study while comparing 3 groups of cisatracurium in different doses($2\times ED_{95}$, $4\times ED_{95}$, $6\times ED_{95}$ dose) with 1 group of atracurium ($2\times ED_{95}$ dose). They observed that with the higher doses of cisatracurium ($4\times ED_{95}$ and $6\times ED_{95}$) onset of action was significantly faster than with atracurium.[10]

M.T. Carroll et al, also had similar observations in their study. [11]

Bluestein and colleagues also compared 3different doses of cisatracurium ($2\times ED_{95}$, $3\times ED_{95}$, $4\times ED_{95}$ dose) with 1 group of atracurium ($2\times ED_{95}$) and had similar results regarding mean time of onset of action. [12]

Neuromuscular block was continuously measured by acceleromyography (TOF every 15 s) for the dose–response effects of both the drugs for comparing the time to maximum depression of twitch height(onset of action) and time to spontaneous recovery of the TOF score 2 and then 25% recovery from the last supplemental dose.

Maximum duration of action of atracurium is suggested to be 25-30 minutes and cisatracurium to be 30-35 minutes with their equipotent doses. In our study mean duration of action of 1st dose in Cisatracurium group was 61.50 minutes with a dose of 0.2mg/kg which was more and statistically significant (P = 0.001)as compared to 38.57

minutes in Atracurium group with dose of 0.5mg/kg.

Similar results were observed by El –kasaby et al. [10]

Bluestein and colleagues in their study observed that increasing the dose of cisatracurium (from 0.1 to 0.15 and 0.2 mg/kg) increases the mean time of clinically effective duration (45 to 55 and 61 min, respectively).[12]

Also C.E. Smith, compared duration of action of cisatracurium 0.1mg/kg and atracurium 0.5mg/kg and found no statistical significance.[13]

Recovery of neuromuscular function takes place as the plasma concentration declines and greater part of this decrease occurs primarily because of distribution. Recovery comes to rely more on drug elimination than distribution (i.e. 25% to 75% or greater). [14]

In our study 25% recovery from the last supplemental dose in Cisatracurium group was 48.73 minutes which was more as compared to 33.63 minutes in Atracurium group and difference was statistically significant(P = 0.001)

M. T. Carroll in his study observed the time from drug administration to 25% recovery with cisatracurium 0.15 $mg.kg^{-1}$ (51–59 min) was longer compared with both cisatracurium 0.1 $mg.kg^{-1}$ (45–48 min) and atracurium 0.5mg/kg (47–48 min) but the difference was not statistically significant. The time between neostigmine administration and attaining a TOF ratio of 0.8 were shorter when it was administered at T_1 = 25%.[15]

Anticholinesterase administration contributes to recovery of neuromuscular function by antagonism of anticholinesterase at NMJ. Secondly, natural process of decrease of plasma concentration of neuromuscular blocker.[4]

Neostigmine being an effective antagonist of neuromuscular blockade helps shorten total duration of block by approximately 40%, whether it was administered at the time of 1%, 10% or 25% of spontaneous when compared to the groups not receiving neostigmine.[11] This was demonstrated by a significantly shorter recovery index in the groups receiving neostigmine. Antagonism of neuromuscular blockade should be initiated preferably when two to four TOF responses are observed.

M.T.Carroll et al in his study, compared median time taken to attain TOF ratio 80% after injecting 0.15mg/kg cisatracurium and 0.5mg/kg atracurium. They found that with cisatracurium group, it took 74minutes to attain TOF 80% without neostigmine and 48 and 50 minutes when neostigmine was administered at TOF 10% and 25% respectively. With atracurium group it took 75 minutes without neostigmine and 56 and 54 minutes when reversal given at TOF 10% and 25% respectively. They concluded that between neostigmine administration and attaining a TOF ratio of 80% time duration was shorter when administered at TOF 25%. [11]

In our study all the patients received neostigmine reversal after assessing clinical parameters) and TOF ratio of at least 25%, till then the patient was allowed to recover spontaneously. In cisatracurium group reversal was given at a mean TOF of 44.90% along with assessment of clinical parameters. This TOF was 2.30minutes from TOF 25%. In atracurium group reversal was initiated at mean TOF of 42.07% after assessing clinical parameters which was 2.40 minutes TOF ratio 25%.

Reversal was achieved with neostigmine and results were comparable and statistically significant. (P=0.000)

Adequate reversal was assessed by sustained head lift, leg lift, hand grip for 5 seconds, eye opening, protrusion of tongue, arm lift to opposite shoulder, normal tidal volume, sustained tongue depressor test and maximum inspiratory pressure 40-50cmH2O or greater [16] was confirmed and patient was shifted.

Similarly Mellinghoff, Hermann MD et al conducted study in which continuous infusion for a constant neuromuscular block was given at the rate of 1.5 +/- 0.4 (range, 1-3) mg $kg^{-1}min^{-1}$and 6.6 +/- 1.7 (range, 3-11) mg kg^{-1} min^{-1} for cisatracurium and atracurium, respectively. They

reported that after continuous infusion of NMBA, recovery appears to be almost identical between atracurium and cisatracurium 16.5 and 15.4 minutes respectively. [17]

Bergeron et al in his study while comparing 3 different doses of cisatracurium 0.05mg/kg, 0.15mg/kg and 0.3 mg/kg; observed that onset time was not significantly different between the doses in adults, but recovery time increased, 23 and 24 minutes respectively.[18]

ShangGuan in his study, reported that with the increasing doses of NMBA, the duration of clinical action was prolonged and risk of postoperative residual block increases. So , proper selection of dose can ensure the desired effect without excessive over dosage. [19]

Cisatracurium is four times more potent as compared to atracurium and does not cause histamine release which indicates that the phenomenon of histamine release is stereospecific.

El –kasaby et al in his study reported that hemodynamic stability for both heart rate and mean arterial blood pressure were more evident even with higher doses of cisatracurium.[10]

Similarly in our study we found that, both groups had comparable hemodynamic stability. Two patients in atracurium group had skin rashes . In these patients fall in blood pressure by approximately 20% of the baseline value at the end of 1 and 2 minute but then came back to base line values at the end of 3 minutes after giving intravenous fluid.

Yazdanian F et al had comparable hemodynamic effects in atracurium and cisatracurium patients but cost benefit was observed with atracurium [20]

With the use of muscle relaxants common adverse reactions can be any cardiovascular effects, allergic reactions and inadequate reversal to normal neuromuscular function as a safety issues. Laudanosine is one of the major metabolite of atracurium metabolism. Peak plasma concentr-ation of laudanosine occur 2minutes after i.v. injection of atracurium and 75% peak occurs at nearly 15 minutes of injection. It depends on liver and kidney for its elimination. Plasma concentration of laudanosine after single dose of atracurium 0.5mg/kg are higher in patient with renal failure compared with the normal patients. So patients with liver disease and those who receive atracurium for long time in ICU are found to have elevated concentration of laudanosine, as high as 5-6µg/ml. It has CNS stimulating property and cardiovascular effects, can cause bradycardia and hypotension [4,21].

Cisatracurium is 1Rcis-1R' cis isomer of atracurium it is five times more potent then atracurium and about five times less laudanosine is produced and lesser side effects. [4]

It was observed that even with the higher doses of cisatracurium (8 × ED95) bolus there was no sign of histamine release because of its stereospecific property and so no significant hemodynamic changes occur as described in the study done by Shang guan et al.[19]

In our study with the dose of cisatracurium (0.2mg/kg; 4× ED95) there was no signs of histamine release while skin rashes were noted in 2 patients who received atracurium (0.5mg/kg: 2× ED95)

Similarly A. M. El-Kasaby, in his study while comparing atracurium with different doses of cisatracurium observed similar results where 2 case who received atracurium had signs of histamine release. [10].

Also Basta SJ et al reported that atracurium releases histamine when doses of 0.5 mg/kg (two times ED_{95}) or more are injected rapidly. When plasma histamine levels increase to over 1000 pg/ml, a transient decrease in blood pressure, together with facial erythema, may be noted. The phenomenon of histamine release can be decreased by slower injection from 30 to 60 seconds. [22]

Our study concluded that cisatracurium has a faster onset, good intraoperative hemodynamic parameters and better recovery profile with no side effects.

CONCLUSION

Cisatracurium in a dose of 0.2mg/kg had a faster onset and duration of action as compared to atracurium(0.5mg/kg). TOF ratio 25% recovery from the last supplemental dose was prolonged with the cisatracurium group as compared to the atracurium group. Recovery after neostigmine reversal upto TOF 80% was faster with cisatracurium group and statistically significant. This concluded that even with the higher dose of cisatracurium(4 × ED95) recovery was faster and without any residual muscle paralysis.

There was no statistically significant hemodynamic variability noted in both the groups. There were no adverse drug reactions observed in cisatracurium group.

Like previous several studies, our study shows that cisatracurium even with the higher dose is safe and more efficacious as compared to atracurium.

Conflict of interest – None
Financial Support- None

REFERENCES

1. Movafeghetal, "Cost analysis and safety comparison of Cisatracurium and Atracurium in patientsundergoing general anesthesia" (European Review for Medical and Pharmacological Sciences; 2013; 17: 447-50)
2. Moore EW, Hunter JM. The new neuromuscular blocking agents: do they offer any advantagesBr.Janaesth 2001; 87: 912-25.
3. Mertes PM, Laxenaire MC. Adverse reactions to neuromuscular blocking agents. Curr Allergy Asthma Rep 2004; 4: 7-16
4. Mohamed Naguib & Cynthia A Lien:pharmacology of muscle relaxants and their antagonists chapter 29, Ronald D. Miller's Anaesthesia 7th ed.Millers Anaesthesia 7thed Churchill Livingston 2010 Pg.868,869, page876, table 29-6, page 872, table 29-4, 29-7, page 874, page 881 table 29-4, 890
5. T. Taivainen, G. H. Meakin, O. A. Meretoja, K. Wirtavuori, R. J. Perkins,A. K. Murphyetal, The safety and efficacy of cisatracurium 0.15 mg/kg during nitrous oxide±opioid anaesthesia in infants and children, Anaesthesia, 2000, 55, pages 1047-51
6. Lien CA, Belmont MR, Abalos A, et al. The cardiovascular effects and histamine-releasing properties of 51W89 in patients receiving nitrous oxide/opioid/barbiturate anesthesia. Anesthesiology 1995; 82: 1131-8.
7. Lepage J-Y, Malinovski J-M, Malinge M, et al. Pharmacodynamicdose±response and safety study of cisatracurium (51W89) in adult surgical patients during N2O-O2-opioid anesthesia. Anesthesia and Analgesia 1996; 83: 823-9.
8. Belmont MR, Lien CA, Quessy S, et al. The clinical neuromuscular pharmacology of 51W89 in patients receiving nitrous oxide/opioid/barbiturate anesthesia. Anesthesiology 1995; 82: 1139-45
9. .Saghaei M. Random allocation software for parallel group randomized trials. BMC Med Res Methodol.2004;4:26.
10. M. El-Kasaby, H. M. Atef, A. M. Helmy, and M. Abo El-Nas, Cisatracurium in different doses versus atracurium during general anesthesia for abdominal surgerySaudi J Anaesth. 2010 Sep-Dec; 4(3): 152–157. doi: 10.4103/1658-354X.71571)
11. .M. T. Carroll,1 R. K. Mirakhur,1 D. W. Lowry,1 K. C. McCourt1 and C. Kerr2, A comparision of the neuromuscular blocking effects and reversibility 0f cisatracurium and atracurium, Anesthesia 1998,53,page 744
12. .Bluestein LS, Stinson LW, Lennon RL, Wilson RM. Evaluation of cisatracurium, anew neuromuscular blocking agent for

tracheal intubation. CAN J ANAESTH. 1996;43:925–31.

13. Smith CE, van Miert MM, Parker CJ, Hunter JMA 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.)
14. Wright PM, Hart P, Lau M et al, cumulative characteristic of atracurium and vecuronium. A simultaneous clinical and pharmacokinetic study. Anaesthesi-ology 81:59-68,1994
15. Train Of Four Monitoring,Critical Care Program HRSRH Developed October, 2006 pg1-13
16. Jorgen Viby Mogensen, Ronald D Miller, Millers Anaesthesia 7th ed Churchill Livingston 2010 Neuromuscular Monitoring chapter 47. page1516-29
17. . Mellinghoff, Hermann MD; Radbruch, Lukas MD; Diefenbach, Christoph MD; Buzello, Walter MD , A Comparison of Cisatracurium and Atracurium: Onset of Neuromuscular Block After Bolus Injection and Recovery After Subsequent Infusion, Anesthesia & Analgesia: November 1996 - Volume 83 - Issue 5 – pg 1072-75
18. Bergeron L, Bevan DR, Berrill A, Kahwaji R, Varin F: Concentration-effect relationship of cisatracurium at three different dose levels in the anesthetized patient . Anesthesiology 95 314-23, 2001.
19. Shang Guan, WangNing; Lian, Qing Quan; Li, Jun; Gao, Fang Clinical pharmacology of cisatracurium during nitrous oxide-propofol anesthesia in children. Journal of Clinical Anesthesia 20.6 (2008): 411-4.
20. 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 anaesthesiology and intensive care 2008 , Volume 30 , Number 61; Page(s) 56- 66.
21. Robert K. Stoelting, Simon C.Hiller, Pharmacology & Physiology in Anaesthetic practice 4th edition chapter 8, Philadelphia, (USA): Lippincott Williams and Wilkins; 2006 Neuromuscular blocking drugs pg 210 table 8-2,pg 222-42
22. Basta SJ, Ali HH, Savarese JJ. Clinical pharmacology of atracurium besylate: a new nondepolarizing muscle relaxant. Anesth Analg. 1992;61:723–29.