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

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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, benzylisoquinoline compounds.\(^{(4)}\) Cisatracurium is 1Rc1s-1’Rc1s 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\(_2\)O 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% N2O in O2, 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 (SpO2), and end tidal CO2. 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](image-url)
Mean duration of action (DOA) of 1\textsuperscript{ST} dose in Cisatracurium besylate group was 61.50 minutes which was significantly more as compared to 38.57 minutes in Atracurium besylate group. (Student t test, p value: 0.001) (figure 2)

![Figure 2](image1.png)

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](image2.png)

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)
DISCUSSION

Two non-depolarising muscle relaxants of intermediate duration of action, Atracurium and Cisatracurium 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×ED95 dose has a faster onset of action as compared to cisatracurium 4×ED95 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×ED95 dose) group was 3.75 minutes and atracurium (2×ED95 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×ED95, 4×ED95, 6×ED95 dose) with 1 group of atracurium (2×ED95 dose). They observed that with the higher doses of cisatracurium (4×ED95 and 6×ED95) 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 3 different doses of cisatracurium (2×ED95, 3×ED95, 4×ED95 dose) with 1 group of atracurium (2×ED95) 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.
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 74 minutes 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 40-50cmH\(_2\)O 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 concentration 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 ED95) 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

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