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Research Article

CLINICAL EVALUATION OF ATRACURIUM AND ITS CIS ISOMER FOR PRODUCTION OF MUSCLE RELAXATION

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ABSTRACT

Background: Application of knowledge of isomerism is currently becoming popular to obtain drugs with better pharmacodynamic profile and without major side effects. We aimed in our study to compare the effects of the cis-isomer of Atracurium with its parent molecule Atracurium for producing muscle relaxation. **Methods**: We enrolled 60 adult patients of ASA status I and II who needed skeletal muscle relaxation under general anaesthesia in a comparative double blind randomised study. Patients were randomly placed in group A and group B to receive either Atracurium(0.5 mg/kg) or Cisatracurium(0.2 mg/kg) respectively to provide neuromuscular blockade during a Propofol/N_2O/O_2/Isoflurane anaesthesia. Each patient was studied for onset and duration of action of the drug, laryngoscopic and intubating conditions, haemodynamic profile, reversibility and side effects. **Results**: Both the drugs produced jaw relaxation within three(3) minutes of administration and had intermediate duration of action. Intubating conditions were excellent in both the groups in majority of patients. Patients who received Cisatracurium maintained better haemodynamic profile though this difference was statistically insignificant. Effects of both the drugs were easily reversible by Neostigmine and none of the patients showed signs of Histamine release. **Conclusion**: Neuromuscular blocking effects of Cisatracurium are similar to Atracurium with less haemodynamic changes.

INTRODUCTION

Isomers of drugs provide more therapeutic benefits with less adverse effects. Cisatracurium, a 'cis-isomer' of Atracurium is one such drug.

In balanced general anaesthesia, neuromuscular blocking drugs (NMBDs) provide skeletal muscle relaxation for intubation of trachea, controlled ventilation and optimal surgical field. They either depolarise the Nicotinic Acetylcholine receptors (Succinylcholine), or prevent depolarisation by Acetylcholine (Vecuronium, Atracurium, Rocuronium, etc).

Atracurium and Cisatracurium are benzylisoquinolinium group of synthetic non-depolarising NMBDs. Introduced into clinical practice in the 1980s, Atracurium has a slow onset and intermediate duration of activity.[1] It undergoes spontaneous degradation by Hofmann elimination, yielding Laudanosine and Monoquaternary acrylate as metabolites.[2,3,4] High concentration of Laudanosine stimulates the CNS causing convulsions. Atracurium has four stereocenters and thus 16 possible stereoisomers of three geometric isomer groups designated '*cis-cis'*, '*cis-trans'* and '*trans-trans'* according to their configuration about the tetrahydroisoquinoline ring system.[3] Primary clinical disadvantage of Atracurium being its propensity to release histamine, these isomers of Atracurium were investigated to isolate the ones that might possibly retain the desirable properties without histamine release. In 1989, D.A. Hill and G.L. Turner synthesised Cisatracurium, one of the three *cis-cis* isomers of Atracurium as an individual isomer molecule.[3] Cisatracurium is also metabolised by Hofmann elimination. Though approximately four to five times as potent as Atracurium, but it does not release histamine, thus indicating that histamine release may be stereospecific.[5,6,7] Cisatracurium has an intermediate onset and duration of action. The production of Laudanosine is five times less when compared to Atracurium.[2]

Atracurium 0.5mg/kg ($2xED_{95}$) is used as intravenous bolus dose to facilitate endotracheal intubation. But, $2xED_{95}$ dose of Cisatracurium (0.1mg/kg) – the dose equipotent to Atracurium, has been observed to produce unsatisfactory intubating conditions. Doses of 0.15mg/kg ($3xED_{95}$) or, 0.20mg/kg ($4xED_{95}$) have been advocated instead. But varying results have been reported.[8,9] Hence the present study was conducted with the aim to observe

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and compare the neuromuscular blocking effects of Cisatracurium and Atracurium.

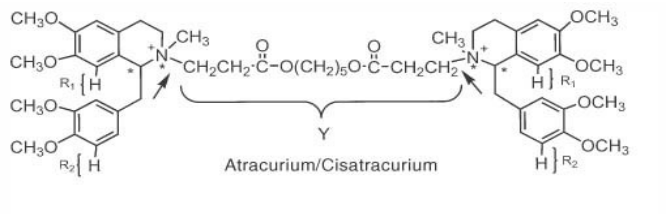

Figure 1 Molecular structure of Atracurium and Cisatracurium

Source: Internet

MATERIALS AND METHODS

It was a comparative, double blind, randomised study. Clearance was obtained from the Ethical Committee of our institution. The study was conducted in the Department of Anaesthesiology. Informed written consent was sought from the participants. Subjects were enrolled only if they accepted.

We studied on 60 patients of either sex, between ages 18-60yrs, of ASA Grades I and II,[2] having Mallampati grades I and II,[2] who required endotracheal intubation for elective surgical procedures. Patients with history of hypersensitivity, malignant hyperthermia, neuromuscular disorders, pregnancy, lactation, and those assessed to pose difficulty in intubation were excluded.

Patients were prescribed Tab. Ranitidine Hydrochloride (150mg) and Tab. Alprazolam (0.5mg) on the night before surgery and kept on overnight fasting. They were randomly allocated to one of the two study groups by draw of cards on morning of surgery.

Group A: Atracurium was used for muscle relaxation.
Group B: Cisatracurium was used for muscle relaxation.

Baseline heart rate (HR), blood pressures, oxygen saturation (SpO_2), five lead ECG, surface temperature and capnogram were recorded. All patients were intravenously premedicated with Inj.Glycopyrrolate (10µg/kg), Inj.Midazolam (0.05mg/kg) and Inj.Fentanyl (1µg/kg), preoxygenated with 10 liters/min of 100% Oxygen for three minutes. Intravenous Inj.Propofol (2mg/kg) was used to induce anaesthesia. Tracheal intubation was facilitated with Inj. Atracurium (0.5mg/kg) in Group A patients and with Inj. Cisatracurium (0.2 mg/kg) in Group B patients. Effects of the studied drugs were analysed based on clinical criteria.

After onset of apnoea (decrease in amplitude of reservoir bag excursion), patients were manually ventilated for three minutes and if jaw relaxation was found to be inadequate, then for another one minute. Time of adequate jaw relaxation was defined as 'the time from completion of injection of muscle relaxant to the time of complete jaw relaxation.' Laryngoscopy was performed with appropriate size Macintosh blade. The quality of laryngoscopic conditions were assessed as per following grading described by Schwarz et al(1985).[10]

Excellent (Grade III)

Jaw relaxed
Vocal cords apart
Vocal cords immobile
No diaphragmatic movement

Good (Grade II)

Jaw relaxed
Vocal cords apart
Vocal cords immobile
Some diaphragmatic movement

Poor (Grade I)

Jaw relaxed
Vocal cords moving
Coughing

Inadequate (Grade 0)

Jaw poorly relaxed
Vocal cords adducted
Coughing

Trachea was intubated with appropriate size cuffed oral endotracheal tube. Ease of intubation was assessed as follows according to grading described by Mehta et al(1985).[11]

Excellent (Grade I)

Easy passage of tube without bucking

Good (Grade II)

Passage of tube with slight bucking

Fair (Grade III)

Passage of tube with moderate bucking

Impossible (Grade IV)

Intubation could not be performed with three attempts.

Additionally, Copenhagen Consensus Conference (CCC) Score (1995) was also applied on all patients.[12]

Laryngoscopy	Easy	Fair	Difficult
Vocal Cords			
Position	Abducted	Intermediate	Closed
Movement	None	Moving	Closing
Reaction to Intubation			
Limbs	None	Slight	Vigorous
Coughing	None	Diaphragm	>10 sec
Scores	Excellent	Good	Poor

Excellent: All scores excellent -- clinically acceptable
Good: All scores excellent or good--- Clinically Acceptable
Poor: Any score poor--- Clinically Unacceptable

After confirmation of successful endotracheal intubation, anaesthesia was maintained with Isoflurane and a mixture of Nitrous oxide and Oxygen in 3:2 ratio. Ventilation was controlled. Further incremental doses of Inj.Atracurium (0.1mg/kg) or Inj.Cisatracurium (0.03mg/kg) were given when following features of insufficient muscle relaxation were noted:

1. Flickering respiratory movements
2. Tightness of Rebreathing bag
3. Limb movement
4. Inadequate surgical relaxation.

The duration of action (DOA) of muscle relaxant was calculated from 'the time of administration of the loading dose to the first incremental dose.' Monitoring of HR, Systolic blood pressure (SBP), Diastolic blood pressure (DBP), ECG, SpO_2., $ETCO_2$ and temperature was done throughout the intraoperative period. Observations were recorded one minute after administering loading dose of muscle relaxant and at five minutes intervals thereafter. On conclusion of surgery, all anaesthetic agents were withdrawn. Inj.Neostigmine (50 µg/kg), maximum upto 2.5mg with Inj.Glycopyrrolate (10 µg/kg) were given intravenously to reverse the action of muscle relaxant. After obtaining signs of adequate reversal, endotracheal tube was removed. Pharmacological quality of reversal was assessed based on the following criteria propounded by Nunn(1989):[13]

1. Sticking out of tongue
2. Wide opening of eyes
3. Sustained head lift for five seconds
4. Ability to take deep breaths
5. Obeying verbal commands
6. Moving and raising the legs.

After five minutes, if reversal was judged to be inadequate, repeated titrated doses of Inj. Neostigmine were given. Total amount of Neostigmine administered to reverse the block was taken as the measure of pharmacological quality of reversal. Adequacy of reversal was judged by the 3 point rating scale described below:- Good-Patient fully reversed with initial dose of Neostigmine

Fair-More than initial dose of Neostigmine was required Poor-Patient did not breathe even after additional doses of Neostigmine,

Any perioperative side effects including signs of histamine release like redness, erythema, wheal accompanied by haemodynamic changes or bronchospasm were noted and treated accordingly.

Statistical Analysis

The data observed were tabulated. Values were expressed as Mean± Standard Deviation, ratios and percentages. Statistical analysis was done using SPSS version 16.0. Student's t test and Chi square test were applied as indicated for analysis. The 'p' value<0.05 was noted as significant statistically.

RESULTS

Demographic and clinical characteristics of the two study groups were comparable (p value >0.05) [Table 1]

Table 1 Comparison of demographic and clinical characteristics

Study parameters	Group A	Group B	p value	Significance
Age (yrs)	31.9±14.11	36.4±12.4	0.489	Not significant
Sex (M:F)	18:12	13:17	0.196	Not significant
Weight (Kg)	54.4±9.6	58.5±10.3	0.925	Not significant
ASA (I/II)	27:3	24:6	0.278	Not significant

Values expressed in Mean±Standard Deviation and Ratios.
Age and Weight: Student's t test. Sex and ASA grade: Chi Square test. p value<0.05 was considered statistically significant.

Out of 60 patients, 23 were posted for general surgery in which 8 belonged to Group A and 15 to Group B. Of the remaining, 7 were gynaecological procedures, 17 underwent Ear, Nose and Throat surgeries and 13 had orthopaedic surgeries.[Figure 2]

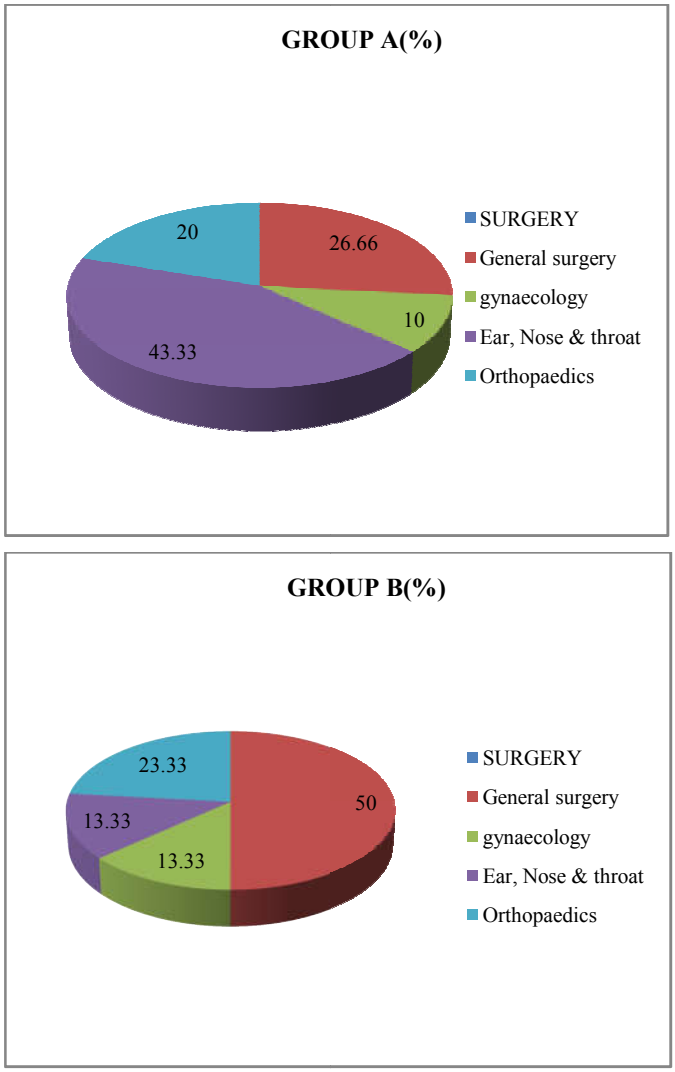

Figure 2 Distribution of cases according to surgical speciality

Jaw was relaxed within three minutes in 90% patients in Group A and 96.66% in Group B. Two patients(6.66%) of Group A and one(3.33%) of Group B required one extra minute to achieve adequate jaw relaxation. A single patient in Group A needed to be ventilated for five minutes for good jaw relaxation. But this difference was statistically insignificant on application of Chi Square test(p value-0.495).[Figure 3]

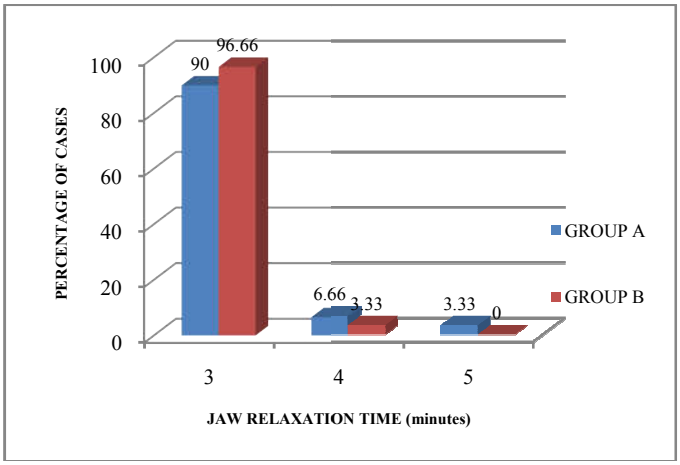

Figure 3 Jaw relaxation time

We obtained excellent direct laryngoscopic view in 70% , good in 10% and poor view in 20% patients in Group A. While in Group B, laryngoscopic view was excellent in 83.33%, good in 10% and poor in 20% cases. No significant statistical difference observed between the two groups (p value-0.309).[Figure 4]

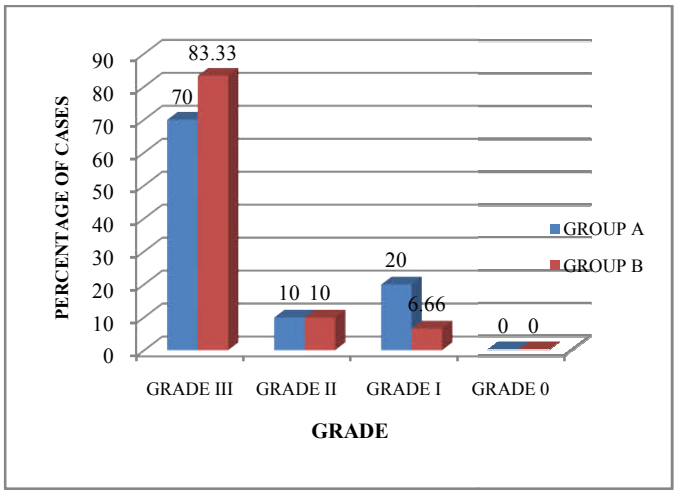

Figure 4 Laryngoscopy grading (Schwarz *et al*)

In 76.66% Group A and 83.33% Group B cases, endotracheal tube passed easily without bucking. In both groups, 16.66% patients showed slight bucking while moderate bucking was observed in 6.66% patients in Group A only. Intubation was possible in all our cases. Overall, no significant statistical difference in intubating conditions was obtained in both the groups (p value-0.353).[Figure 5]

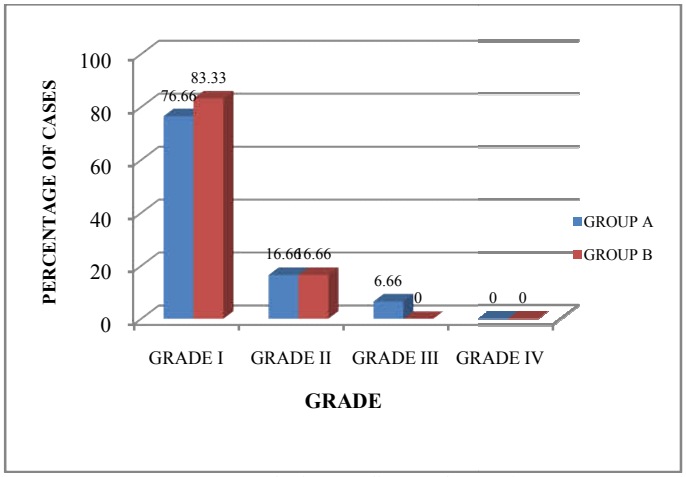

Figure 5 Intubation grading (Mehta *et al*)

We noted excellent CCC score in 70% Group A and 83.33% Group B patients. Score was good in 13.33% of Group A and 16.66% of Group B patients. None of the patients in Group B had poor score, while 16.66% patients in Group A had poor CCC score. Overall no statistically significant differences were observed between the two groups (p value-0.114).[Figure 6]

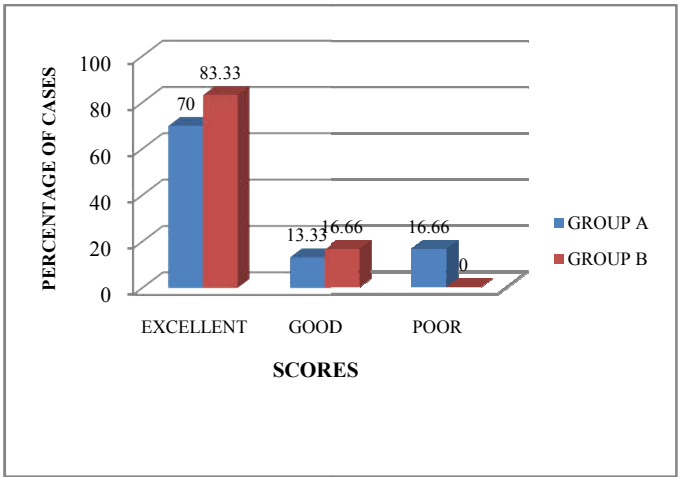

Figure 6 Copenhagen Consensus Conference score(CCC)

Though mean duration of action of Cisatracurium (41.06±12.05 minutes) was more than Atracurium (28.16±9.41 minutes), the difference was statistically insignificant. [Table 2]

Table 2 Duration of Action (DOA) [Mean ±SD]

Parameter	Group A (n=30)	Group B (n=30)	p value	Significance
Duration Of Action (min)	28.16±9.41	41.06±12.05	0.297	Not significant

Student's t test was applied; p value<0.05 was considered statistically significant.

One min after administration of muscle relaxant, in Group A patients the HR increased by 7.38% from baseline while it decreased by 0.41% in Group B, and was found to be statistically significant on application of Student's t test(p value-0.03). Five minutes later, HR increased by 20.59% and 14.38% from baseline in Group A and Group B respectively. This was statistically insignificant (p value-0.205). Intraoperative mean HR of 98.46±18.56bpm in Group A and 91.1±11.99bpm in Group B was statistically significant according to Student's t test(p value-0.012).[Figure 7]

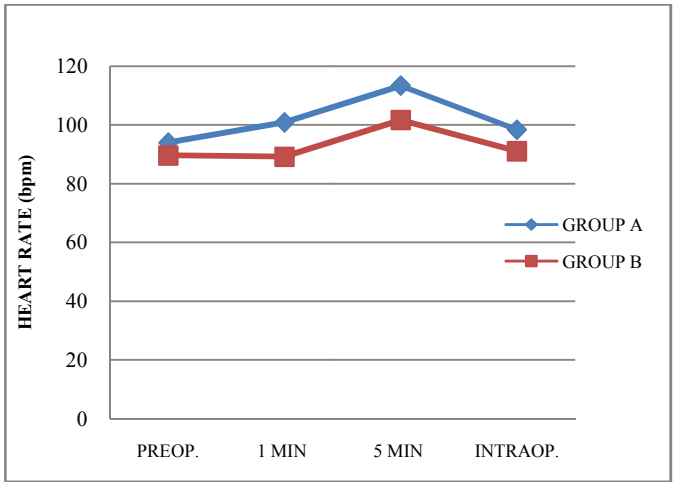

Figure 7 Mean Heart Rate

The preoperative mean SBP was 91.1±11.99mmHg and 127.03±13.93mmHg in Group A and B respectively. After one minute, the SBP increased by 18.11% in Group A, but decreased by 13.1% in Group B (p value-0.253). In both the groups, at five minutes, SBP increased above the preoperative value; but with a greater magnitude of 50.66% in Group A and only by 6% in Group B (p value-0.074).Mean SBP was 120.5±10.03mmHg in Group A and

125.06±9.25mmHg in Group B patients in the intraoperative period (p value-0.188).[Figure 8]

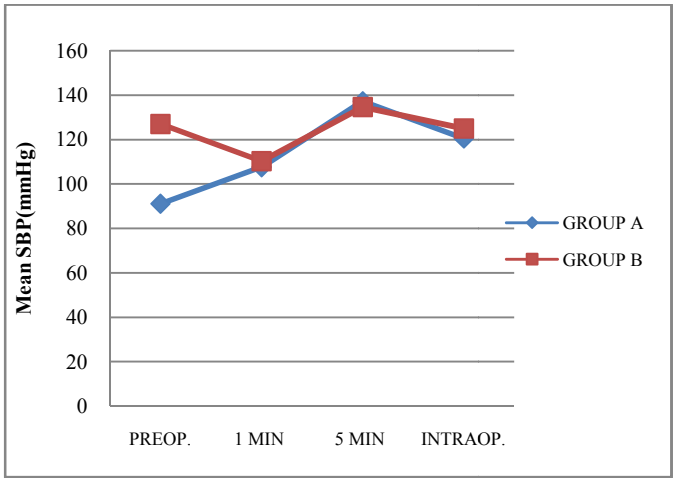

Figure 8 Mean Systolic Blood Pressure

The preoperative DBP values in both the groups were comparable (p value-0.08). After one minute of administration of muscle relaxant, DBP decreased by 17.13% in Group A and 15.06% in Group B from the preoperative values (p value-0.845). The DBP increased by 15.09% and 15.61% respectively in Group A and B after five minutes (p value-0.170). The mean intraoperative DBP in Group A and B was 80.56±8.07mmHg and 83.33±9.0mmHg respectively and the difference statistically insignificant (p value-0.594).[Figure 9]

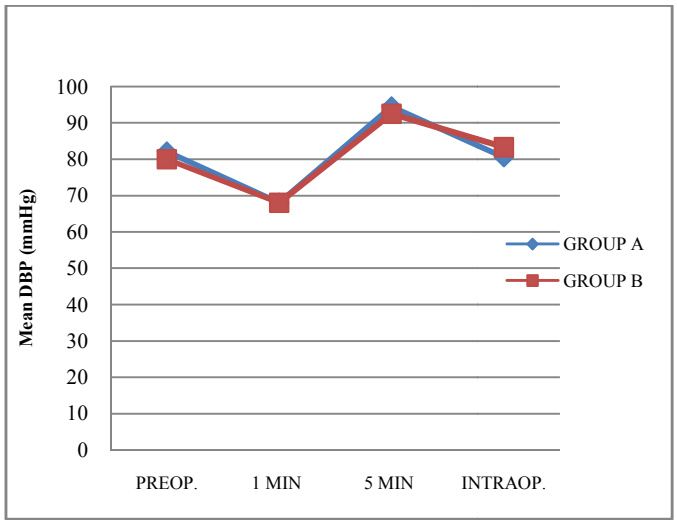

Figure 9 Mean Diastolic Blood Pressure

Adequacy of reversal judged by 3 point rating scale showed that 46.66% Group A patients and 30% of Group B patients didn't require extra Neostigmine (i.e., a GOOD rating). Extra dose was needed in 53.33% and 70% patients in Group A and B respectively. No case of failure of reversal occured. No statistically significant difference was observed (p value-0.184).[Figure 10]

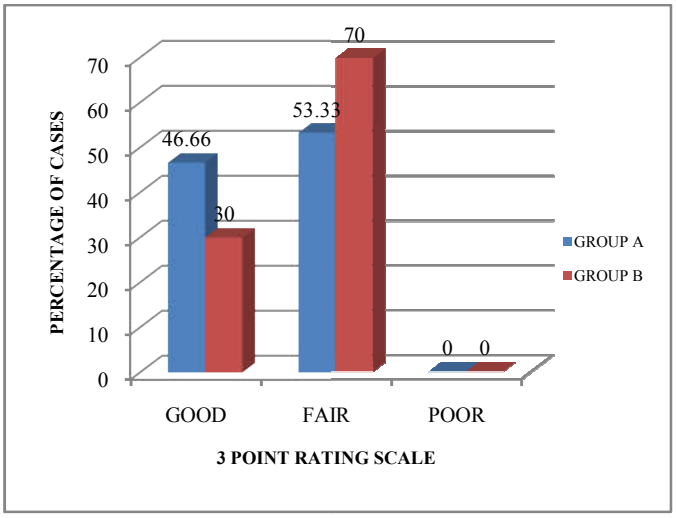

Figure 10 Adequacy of Reversal

Figure 11 shows that single patient in Group A had postoperative drowsiness and one in Group B had an incidence of laryngospasm just after reversal(p value-0.368).

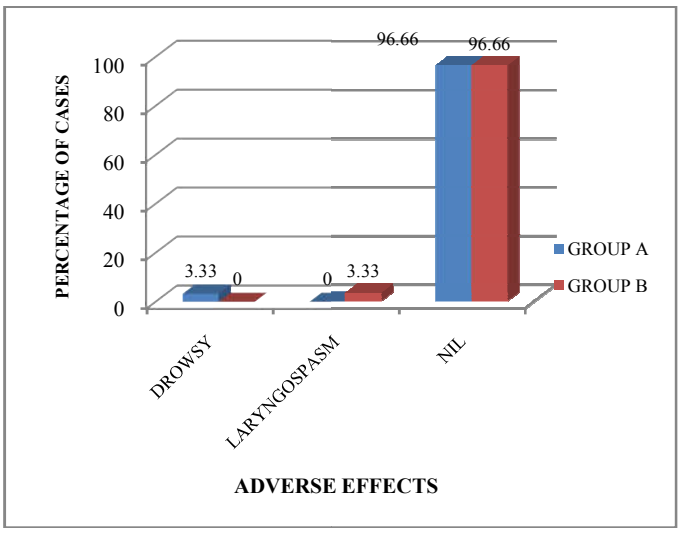

Figure 11 Perioperative adverse effects

DISCUSSION

Atracurium is a bis-benzyltetrahydroisoquinolinium compound with isoquinolinium nitrogens connected by a diester containing hydrocarbon chain.[3] It exhibits stereoisomerism and is a mixture of three geometric isomer groups: *cis-cis*, *cis-trans*, and *trans-trans* in the ratio of approximately 10:6:1, corresponding to 50%-55% *cis-cis*, 35%-38% *cis-trans*, and 6%-7% *trans-trans* isomers.[3] Cisatracurium is 1R *cis*–1′R *cis* Isomer of Atracurium. 'R' designates the absolute stereochemistry of the benzyltetrahydroisoquinoline rings, and '*cis*' represents the relative geometry of the bulky dimethoxy and 2-alkyester groups at C(1) and N(1) respectively.[5] Owing to this structure Cisatracurium is claimed as a 'cleaner' molecule, more potent than Atracurium, does not release histamine and produces clinically insignificant amount of Laudanosine.

Cisatracurium has been recently introduced in India for clinical use. We studied the effectiveness of this newly available isomer of Atracurium for clinical neuromuscular blockade in demographically comparable surgical

population (Table 1). As it involved action of two muscle relaxants in terms of effect on the airway, DOA, haemodynamic parameters and reversibility of muscle paralysis, we did not want our results to be influenced by difficult airways or systemic illnesses. Hence we only studied on patients with Mallampati class I and II airways belonging to ASA grades I and II.

We found that both Atracurium and Cisatracurium have similar time of onset. Majority of patients had adequate jaw relaxation in three minutes(Figure 3). Laryngoscopic view was excellent in 21/30 patients administered Atracurium, but in 25/30 patients given Cisatracurium (Figure 4). Although this difference was not significant statistically. In 23 patients of Atracurium group and 25 of Cisatracurium group, intubation was easy. Five patients in each group showed slight bucking during intubation(Figure 5). Overall ease of intubation was similar with both drugs. The mean DOA of Cisatracurium was found to be longer than Atracurium though not statistically significant.

Alteration in haemodynamic parameters occurs during the course of anaesthesia due to multitude of reasons and may aggravate in already susceptible individuals. Hence a drug with better haemodynamic profile is sought. We observed that, one minute after giving muscle relaxant, HR rose by 7.38% in Atracurium group but fell by 0.41% in Cisatracurium group (Figure 7). Similar fall in HR was reported by Jammer P *et al*. The magnitude of difference observed by us was statistically significant.[14] The mean SBP increased by 18.11% with Atracurium. The SBP in Cisatracurium group and DBP in both groups showed ≤20% fall one minute following muscle relaxant administration with no significant intergroup variability(Figures 8,9). This fall in blood pressure may be attributed to induction with Propofol.

The HR, SBP and DBP rose after five minutes in both the groups. But it was not statistically significant (Figure 7,8,9). This time interval corresponds with the post-intubation period and hence could be due to the stress response of laryngoscopy and intubation. Intraoperative minor increase in mean HR and the changes in SBP and DBP observed in both the groups were statistically insignificant. Both Atracurium and Cisatracurium demonstrated similar pharmacological qualities of reversibility (Figure 10).

Upon analysis of perioperative adverse effects, we noted drowsiness in one patient in our Atracurium group in the postoperative period though was maintaining spontaneous respiration (Figure 11); may be due to residual effects of Isoflurane. One patient in Cisatracurium group had an episode of laryngospasm just after extubation which was relieved with standard prescribed airway management procedures. The cause for laryngospasm was judged to be inadequate postoperative pain relief. No clinical signs of histamine release were noted in any patient. The intergroup variability in relation to perioperative adverse effects was not found to be statistically significant.

Lien ***et al*** studied cardiovascular effects and histamine-releasing properties of 51W89 (Cisatracurium) and Atracurium and reported that maximal blood pressure and HR changes in patients receiving 51W89 were small and statistically similar to patients receiving Atracurium, which was also our findings.[6] They observed no dose-related change in plasma histamine concentration with 51W89 administration; while one patient had transient facial flushing following Atracurium.[6] Neither group in our study showed any clinical signs of histamine release. But we did not measure the plasma histamine concentration.

Upon comparing equipotent doses of Atracurium and Cisatracurium, Bluestein *et al* obtained good or excellent intubating conditions in over 90% of their patients with both the drugs.[15] We obtained excellent to good intubating conditions in 99.99% patients given Cisatracurium but in 83.33% administered Atracurium. However this was found to be statistically insignificant.

Lepage *et al* did pharmacodynamic dose-response and safety study of Cisatracurium and concluded that it is a potent neuromuscular blocking agent with intermediate DOA, excellent cardiovascular stability and no apparent histamine release.[16] We too obtained excellent to good intubating conditions in 99.99% of our subjects; the effects lasted for 41.06±12.05minutes on an average pointing towards intermediate DOA. The changes in cardiovascular parameters remained ≤20% throughout the surgery and no clinical signs of histamine release were observed.

Mellinghoff *et al* in comparing the time-course of neuromuscular blockade after initial equipotent bolus doses of Cisatracurium and Atracurium concluded that the time of onset of both drugs was not different.[17] This was similar to our study although we used higher dose of Cisatracurium.

Carroll and Mirakhur *et al* compared the neuromuscular blocking properties and reversibility of Cisatracurium and Atracurium.[18] They observed significantly slower onset of action with Cisatracurium compared to Atracurium, which does not match with our observations. They obtained statistically significant higher incidence of clinically acceptable intubating conditions with Atracurium(100%) in comparison to Cisatracurium (73-87%). Whereas we obtained higher incidences of clinically acceptable intubating conditions with Cisatracurium (100%) in comparison to Atracurium (83.3%), though this was statistically insignificant. Which may probably be because we administered higher dose of Cisatracurium. In their study the median duration of clinical muscle relaxation with Cisatracurium (0.15 mg/kg) was longer(51–59 minutes) compared with both Cisatracurium (0.1 mg/kg) which was 45-48minutes and Atracurium (47–48 minutes), but the differences were not statistically significant. In our observations too the mean DOA with Cisatracurium (0.2mg/kg) was longer- 41.06±12.05minutes than Atracurium (28.16±9.41minutes) and also was statistically insignificant. As per Carroll and Mirakhur, the neuromuscular blocking effects of both Cisatracurium and Atracurium were similarly and easily reversible.[18] This was our observation too.

In 2007, Prakash Jammar *et al*, upon comparing two intubating doses of Cisatracurium (0.15 mg/kg and 0.2 mg/kg) noted decreased MAP and HR in both groups after induction.[14] This was also our findings. They noted better haemodynamic stability and longer DOA with Cisatracurium(0.2mg/kg) compared to Cisatracurium(0.15

mg/kg) with no adverse effects in both dosages.[14] We too obtained similar results with Cisatracurium(0.2mg/kg).

El-Kasaby *et al* in 2010 compared Atracurium ($2\times ED_{95}$) with different doses of Cisatracurium ($2\times ED_{95}$, $4\times ED_{95}$, $6\times ED_{95}$).[19] They concluded that $4\times ED_{95}$ dose of Cisatracurium had statistically significant shorter onset and longer DOA than $2\times ED_{95}$ dose of Atracurium. We had a different result. We obtained no statistically significant difference in onset and duration time of both drugs, probably because we did clinical assessment but they used neuromuscular monitoring which is more accurate. Their assessment of vocal cords and intubating conditions were statistically similar with both Atracurium ($2xED_{95}$) and Cisatracurium ($4\times ED_{95}$), which was also our observation. They noted better haemodynamic stability with Cisatracurium ($4\times ED_{95}$) in comparison to Atracurium ($2xED_{95}$). But we did not note any statistically significant difference. They reported two cases administered Atracurium showing clinical features of histamine release in terms of flushing and erythema.[19] But none of our patients in either group showed any signs.

Limitations

1.Small sample size.
2.First jaw relaxation assessment done at 3 minutes.
3.Clinical assessment of histamine release instead of the more accurate chemical analysis.

CONCLUSION

Thus we conclude that the neuromuscular blocking effects of Cisatracurium are similar to Atracurium.

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