Original Research Article

Comparison of efficacy of atracurium versus cisatracurium on patients going for surgery under general anaesthesia

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Abstract

Background: Problem Statement: Compare the effectiveness of cisatracurium and atracurium in terms of intubation and hemodynamic effects in abdominal surgeries. **Methods:** Patients of ASA I and II class, undergoing procedure under general anaesthesia were included in the study during the period between January 2017 to December 2018 in Shri Guru Ram Rai Institute of Medical and Health Sciences, Dehradun. Total 100 patients were selected and thus divided randomly in two groups: Group A (who received Atracurium with initial dose of 0.5 mg/kg, maintenance dose of 0.1mg/kg)and Group B (who received Cisatracurium with initial dose of 0.15 mg/kg maintenance dose of 0.03mg/kg) consisting 50 patients in each group. **Results:** the ASA status among the study subjects according to their respective groups. In both groups majority of patients were of ASA type II i.e. 64% in atracurium and 68% in cis-atracurium group. ASA type I included 36% patients of atracurium group and 32% patients of cisatracuriumm group. Majority of patients (28%) of both groups had cholecystectomy. In atracurium group the next common type of surgery was inguinal hernia involving (26%) followed by appendectomy and caesarean section (20%) patients each. In cis-atracurium group after cholecystectomy the next common type of surgery was appendectomy and inguinal hernia consisting of (24%) patients each followed by caesarean section (16%) patients. The mean duration of recovery from reversal in cis-atracurium group was 2.18 ±0.82 minutes which was significantly more as compared to 1.8 ±0.75 minutes of atracurium group as the p value we found was 0.02. **Conclusion:** Cis-atracurium in a dose of 0.15mg/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 from reversal upto was faster with cis-atracurium group and statistically significant.
Key Word: cisatracurium.

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INTRODUCTION

The neuromuscular blocking drugs (NMBDs) have revolutionized management of balanced General Anaesthesia (GA). Since the introduction of d tubocurarine and succinyl choline, there have been significant advances in the field of neuromuscular blockade. The NMBDs offer many advantages during the conduct of General Anaesthesia viz; Long Surgeries can be performed without voluntary and reflex movements, They don't cross blood brain barrier, hence no increase of ICP (except succinyl choline). Reduction of intra operative awareness and recall, allows proper muscle relaxation for prolonged period of time, facilitates complete control of airways, breathing and circulation, maintenance of stable Haeamodynamics, lack cerebral side effects hence can be used in cerebral trauma cases also .These drugs have minimal side effects, rapid metabolism to inactive products, action confined to neuromuscular junctions only can be used in liver and renal diseases also, they don't cross placenta can be used in obstetrtic cases. They are not without dis advantages

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like cardiovascular effects by benzyl iso quonololinium agents other than doxa curium can cause histamine release, Miva curium cause maximum histamine release can result into broncho constriction, flushing . Pancronium and Gallamine can cause tachycardia, Tubo curarine causes vasodilation and hypotension .Now with the introduction of newer Benzyl isoquonolinium derivatives like Atracurium and Cis Atra curium duration of action is maximum as compared to Doxa curium and Miva curium more than 30 to 40 minutes, Their elimination is through ester hydrolysis and holfman elimination a process dependant on pH and temperature whereas steroid derivativtes like Pancuronium and Vecronium, Rocuronium, Piercoronium have elimination through renal or hepatic route. Cisatracurium is a new intermediate duration, non-depolarizing, benzylisoquinolinium neuromuscular blocking drug which is a stereoisomer of atracurium with a potency of approximately 3 to 4 times greater than that of atracurium[1,2]. Despite the higher potency, cisatracurium is associated with more stable hemodynamics than atracurium and does not cause histamine release even at doses of up to 0.4mg/kg ($8\times ED_{95}$).[3] The same dose ($2\times ED_{95}$) atracurium is more effective neuromuscular blocking agent than cisatracurium. However, higher doses of cisatracurium 0.2mg/kg ($4\times ED_{95}$) and 0.3mg/kg ($6\times ED_{95}$) provide more effective, more rapid neuromuscular blocking with longer duration of action, stable hemodynamic status and no signs of histamine release clinically during abdominal surgery.[4,5]

METHODS

Patients of ASA I and II class, undergoing procedure under general anaesthesia were included in the study during the period between January 2017 to December 2018 in Shri Guru Ram Rai Institute of Medical and Health Sciences, Dehradun. Total 100 patients were selected and thus divided randomly in two groups: Group A (who received Atracurium with initial dose of 0.5 mg/kg, maintenance dose of 0.1mg/kg)and Group B (who received Cisatracurium with initial dose of 0.15 mg/kg maintenance dose of 0.03mg/kg) consisting 50 patients in each group. After obtaining Institutional Ethical Committee approval and written informed consent from the patients, a prospective comparative randomized clinical study was conducted. A thorough preoperative evaluation through relevant history, general physical examination, systemic examination and airway assessment were obtained. Demographic data including age, sex, weight, height, ASA status and BMI were collected. Patients were randomly divided into two groups consisting of 50 each. Group A patients received Atracurium with initial dose of 0.5 mg/kg, maintenance dose of 0.1mg/kg and Group B patients received Cisatracurium with initial dose of 015 mg/kg maintenance dose of 0.03mg/kg. In the operating room all the multiparameter monitoring including Heart Rate (HR), Non-Invasive Blood Pressure (NIBP), Oxygen Saturation (SpO2), Capnography (EtCO2) and Temperature (T) probe were attached to the patient. A baseline HR, BP and oxygen saturation were recorded. Intravenous access (i/v) was established and fluids started. All the patients were premedicated with injection 0.03 mg/kg midazolam IV. After preoxygenation with 100% oxygen, general anaesthesia was induced with 2 mg/kg of fentanyl and 2 mg/kg of propofol. For neuromuscular blockade Group A patients received Atracurium with initial dose of 0.5 mg/kg, maintenance dose of 0.1mg/kg and Group B patients received Cisatracurium with initial dose of 0.15 mg/kg maintenance dose of 0.03 mg/kg. Neuromuscular blocker was given intravenously diluted in isotonic normal saline over 10 seconds followed by a fluid rush. Patients were intubated with an appropriate size polyvinyl chloride Endotracheal Tube (ETT). The ETT placement was confirmed using capnography. Anaesthesia was maintained with 50% N2O in O2 and isoflurane 0.6-1%. On completion of surgery, patient was reversed with injection neostigmine 0.05 mg/kg and 0.5 mg glycopyrrolate. 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 10µk/kg glycopyrrolate) through slow IV injection. Patient was then shifted to the recovery room for post - operative monitoring.

Statistical Analysis: Data were recorded in a Microsoft excel spread sheet and analysed using Statistical Package for the Social Sciences (SPSS version 19.0). Quantitative data were expressed as means±SD while qualitative data were expressed as numbers and percentages (%).Student 't' test was used to test significance of difference for quantitative variables (HR, BP) that follow normal distribution and chi square was used to test the significance of difference for qualitative variables. A probability value (p-value) <0.05 was considered statistically significant.

RESULTS

Table 1: Age Distribution

Age (years)	Atracurium (Group A)		Cis-Atrcurium (Group B)		P Value
	Frequency	Percentage (%)	Frequency	Percentage (%)	
18-30	12	24	8	16	0.503
31-40	23	46	26	52	
41-50	15	30	16	32	
Total	**50**	**100**	**50**	**100**	
	35.560 ± 8.246		**36.640 ± 8.052**		

The age distribution of the study subjects according to their respective group. From the above table it is evident that 31-40 years was the commonest age group in both groups involving 46% of atracurium group and 52% of cis-atracurium group followed by 41-50 years involving 30% of atracurium and 32% of cis-atracurium group. The least common age group was 18-30 years involving 24% of atracurium and 16% of cis-atracurium group with no statistical difference for age group between two groups, as the p value was 0.503.

Table 2: ASA Type

ASA Type	Atracurium (Group A)		Cis-Atracurium (Group B)	
	Frequency	Percentage (%)	Frequency	Percentage (%)
ASA I	18	36	16	32
ASA II	32	64	34	68
Total	**50**	**100**	**50**	**100**

The ASA status among the study subjects according to their respective groups. In both groups majority of patients were of ASA type II i.e. 64% in atracurium and 68% in cis-atracurium group. ASA type I included 36% patients of atracurium group and 32% patients of cis-atracuriumm group.

Table 3: Type of Surgery

Type of Surgery	Atracurium (Group A)		Cis-Atrcurium (Group B)	
	Frequency	Percentage (%)	Frequency	Percentage (%)
Appendectomy	10	20	12	24
Cholecystectomy	14	28	14	28
Inguinal Hernia	13	26	12	24
Caesarean Section	10	20	8	16
Others	3	6	4	8
Total	**50**	**100**	**50**	**100**

Distribution of study participants according to the type of surgery is mentioned. Majority of patients (28%) of both groups had cholecystectomy. In atracurium group the next common type of surgery was inguinal hernia involving (26%) followed by appendectomy and caesarean section (20%) patients each. In cis-atracurium group after cholecystectomy the next common type of surgery was appendectomy and inguinal hernia consisting of (24%) patients each followed by caesarean section (16%) patients.

Table 4: Comparison between Onset Time

Onset Time (Seconds)	Atracurium (Group A)		Cis-Atrcurium (Group B)		p value
	Frequency	Percentage (%)	Frequency	Percentage (%)	
160-180	10	20	14	28	0.075
181-200	29	58	30	60	
>200	11	22	6	12	
Total	**50**	**100**	**50**	**100**	
Mean ±SD	**188.30±11.59**		**183.20±18.00**		

The comparison of onset of action between two groups. It is evident from the above table that the mean onset of action in atracurium group was 188.30±11.59 seconds which was slower as compared to 183.20±18.00 minutes in Atracurium group but above analysis we found the difference was not statistically significant as the p value was 0.075.

Table 5: Comparison of Mean Heart rate

Heart rate	Atracurium (Group A)		Cis-Atrcurium (Group B)		p value
	Mean	±SD	Mean	±SD	
Baseline	77.50	±3.30	85.08	±4.37	<0.001
Prior Intubation	79.30	±3.01	82.12	±3.65	0.001
Post Intubation	85.70	±3.69	88.08	±3.12	<0.001
1 minute	94.88	±3.50	96.72	±3.14	0.003
5 minutes	87.36	±3.60	90.54	±2.94	<0.001
10 minutes	79.68	±3.66	86.66	±3.11	<0.001
15 minutes	80.24	±2.69	88.02	±3.38	<0.001
20 minutes	83.08	±3.60	89.30	±3.52	<0.001
25 minutes	87.14	±3.18	89.80	±2.04	<0.001
30 minutes	85.30	±3.25	91.70	±2.02	<0.001

The comparison of heart rate between two groups at different time intervals. There was a statistically significant increase in heart rate of post intubation when compared to baseline reading of atracurium group and cis-atracurium group.

Table 6: Intubating Condition according to Copenhagen consensus scoring system variables

Parameter	Patient's response		
Laryngoscopy	Easy	Fair	Impossible
	40	9	01
Vocal cords position and movement	Opened	Moving	Closed
	41	08	02
Cough	None	≤2	>2
	42	05	03
Jaw Relaxation	Relaxed	Increased Tone	Rigid
	38	10	02
Limb Movement	None	Slight	Severe
	37	08	05
CCS	Excellent	Good	Poor
	39	09	02

Table 7: Adverse reaction Profile (Histamine Release)

Adverse reaction	Atracurium (Group A)		Cis-Atrcurium (Group B)		p value
	Frequency	Percentage (%)	Frequency	Percentage (%)	
Flush	1	2	0	0	1.00
Erythema	1	2	0	0	
Wheals	0	0	0	0	

The comparison of adverse reaction profile or histamine release between two groups. No signs of histamine release were noted in cis-atracurium group. While in atracurium group it was noted with two cases, 1 case showed flush and the other one showed erythema.

DISCUSSION

Cisatracurium has many advantages, compared with other neuromuscular blocking agent. Cisatracurium is a nondepolarising neuromuscular blocking agent with an intermediate duration of action. It is the cis isomer of atracurium besilate, and is approximately 3 to 4-fold more potent than the mixture of isomers that constitute the parent drug. However, cisatracurium produces laudanosine about five times less than atracurium, and accumulation of this metabolite is not thought to be of any consequence in clinical practice. Relative to atracurium, cisatracurium has a lower propensity to cause histamine release, which is more potent but has a slightly longer onset time at equipotent doses In the present study we found that data was comparable between atracurium group and cis-atracurium group regarding age distribution, sex distribution, ASA type and type of surgery as above analysis we found the p value was >0.05 in these aspects. Similar findings were observed in the study conducted by El-Kasaby, *et al.*., Harpreet Kaur *et al.* and M.T. Carroll *et al.*[6-8]. The speed of onset is inversely proportional to the potency of non-depolarizing neuromuscular blocking agents[9]. It has been reported earlier that 2×ED95 dose of atracurium has a faster onset

of action as compared to 4×ED95 dose of cisatracurium. Presumably cisatracurium has greater potency than atracurium resulting in fewer molecules being administered even with the higher doses[9]. So cisatracurium with higher doses has faster onset of action as compared to atracurium. In our study in terms of onset of action between two groups we found that the mean onset of action in atracurium group was as compared to Atracurium group but with no statistically significant difference as the p value was 0.075. 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[6]. M.T. Carroll *et al.*, also had similar observations in their study[8]. Bluestein and colleagues also compared 3different 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[10]. 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. In our study mean duration of action of 1st dose in Cisatracurium group was 70.14 ±1.87 minutes which was more and statistically significant (p = 0.001) as compared to 44.9 ±2.45 minutes of atracurium group. Similar results were observed by El – kasaby *et al.*. where they found statistically significant difference in both the drugs[6]. 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)[10]. C.E. Smith, Also observed that duration of action of cisatracurium and atracurium were comparable but statistically not significant[11]. 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)[12]. In the present study the mean duration of 25% recovery from reversal in atracurium group was 32.4 ±1.90 minutes which was significantly less as compared to 49.46 ±1.86 minutes of cis-atracurium group as the p value we found was <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 statisticaly significant[8]. Shyamlal Thukral *et al.* also in their study found the mean 25% recovery in Atracurium group was 32.11±3.2. The mean 25% recovery in Cisatracurium besylate group was 51.61±2.5. This difference was statistically statistically significant. (p <0.05). 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[9]. 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[8]. 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. The mean duration of recovery from reversal in cis-atracurium group was 2.18 ±0.82 minutes which was significantly more as compared to 1.8 ±0.75 minutes of atracurium group as the p value we found was 0.02 in the present study. Shyamlal Thukral *et al.* also found the mean time of recovery from reversal in atracurium and cis atracurium was 2.1±0.3 and 2.5±0.2 respectively.this difference was statistically significant. (p<0.05)[13]. 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 statistically significantly different between the doses in adults, but recovery time increased, 23 and 24 minutes respectively[14]. On comparing the haemodynamic profile which included the HR and MAP, the results were found to be statistically significant (p value = < 0.05). In terms of mean heart rate between two groups we found that there was a statistically significant increase in heart rate of post intubation when compared to baseline reading of atracurium group and cis-atracurium group. The comparison of mean arterial blood pressure between two groups showed that there was a statistically significant increase in MABP of post intubation compared to baseline reading. 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. In their study they found that there was a statistically significant increase in HR and MABP post-intubation 120s post-injection of the muscle relaxant when compared to baseline and post-injection of 2×ED95 dose of atracurium in group 1 and the same dose of cis-atracurium in group 2 because of stress intubation and the patients were not fully relaxed. However, changes in HR and MABP 5-20 minutes later

were not statistically significant with administration of 4×ED95 and 6×ED95 doses of cisatracurium in groups 3 and 4, respectively[6].

Similar findings were observedby Taivainen T *et al.*, Shahram A *et al.*[15,16]. Lien *et al.* and Basta *et al.* concluded that the maximal MABP and HR changes of patients receiving cisatracurium were small and similar to those observed in patients receiving two times the ED95 of atracurium. In his study no patient developed a decrease in blood pressure >20% or an increase in heart rate >20% that was attributable to muscle relaxant administration[17,18]. Yazdanian F *et al.* had comparable hemodynamic effects in atracurium and cisatracurium patients but cost benefit was observed with atracurium[19]. 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.*[20]. On observing the signs of histamine release, we observed that two cases of histamine release were noted in atracurium group, one case showed flush and the other one showed erythema. No signs of histamine release were noted in cis-atracurium group. None of the patients in any group had episodes of hypotension, bronchospasm, tachycardia or urticaria. 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[6]. 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[18]. Shyamlal Thukral *et al.* also reported 2 cases of histamine relase in atracurium group where none were observed in cis-atracurium group[13]. Hosking MP *et al.*., have stated that by using H1 and H2 receptor blockers before administering large dose atracurium (six times ED95), the haemodynamic manifestations of histamine release can be effectively prevented. They used diphenhydramine 1 mg/kg and cimetidine 4 mg/kg 30 minutes before giving 1.5 mg/kg atracurium intravenously and found that atracurium induced reduction in MAP was decreased by 30 mmHg[21]. Hughes R and Chapple DJ that despite a 10-20 times increase in the plasma histamine levels atracurium is not vagolytic and does not block the innervation by autonomic ganglia[22]. In a study conducted by Kumar A *et al.*., the frequency of urticaria after administration of atracurium was assessed. They concluded that in conventional doses atracurium is not associated with formation of urticarias although significant changes in haemodynamics may occur[23]. Like previous several studies, our study also shows that cisatracurium has a faster onset, good intra-operative hemodynamic parameters and better recovery profile with no side effects.

CONCLUSION

While comparing in terms of mean heart rate between two groups we found that there was a statistically significant increase in heart rate of post intubation when compared to baseline reading of atracurium group and cis-atracurium group.

The comparison of mean arterial blood pressure between two groups showed that there was a statistically significant increase in MABP of post intubation compared to baseline reading.

- In the present study two cases of histamine release were noted in atracurium group, one case showed flush and the other one showed erythema. No signs of histamine release were noted in cis-atracurium group.
- Cis-atracurium in a dose of 0.15mg/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 from reversal upto was faster with cis-atracurium group and statistically significant.

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