Original Research Article

Comparative evaluation of hemodynamic changes after different doses of cisatracurium and atracurium

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Abstract

Background and aims: Neuromuscular blockers have become essential part of anaesthesiologist armamentarium. They aid endotracheal intubation, mechanical ventilation, reduce anaesthetic requirement, prevent patient movement and facilitate surgery. The ideal neuromuscular relaxant is an agent which has a quick onset time and short duration of action. We compare the efficacy of Atracurium besylate and different doses of Cisatracurium besylate for hemodynamic response during intubation and histamine response. **Material and methods:** Randomized trial was conducted in ninety patients of ASA grade I and II ,posted for elective abdominal surgeries were randomly allocated into three groups, of 30 patients each, depending on muscle relaxant and its doses used for intubation . **Results**: In our study, we found that cisatracurium with the dose of 0.2 mg/kg B.W. is better hemodynamic stable agent and lesser histamine response than cisatracurium 0.1mg/kg B.W. and atracurium 0.5 mg/kg B.W. **Conclusion**: Cisatracurium is lack of histamine release even at larger doses, which provides better hemodynamic stability in comparison to atracurium and other histamine releasing neuromuscular blocking agents.

Keywords: Atracurium besylate , Cisatracurium besylate, Hemodynamic stability, Histamine.

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Introduction

Neuromuscular blockers have become essential part of anaesthesiologist armamentarium. They aid endotracheal intubation, mechanical ventilation, reduce anaesthetic requirement, prevent patient movement and facilitate surgery. The ideal neuromuscular relaxant is an agent which has a quick onset time and short duration of action. The ideal drug should not accumulate when given during a continuous infusion, has no active metabolites with neuromuscular blocking properties, and is free of toxic adverse effectsp[1].

Curare was first introduced in clinical anaesthesia by **Griffith Jhonson et al[2].** (1942), it changed the pattern of anaesthetic practice. Succinylcholine was used to facilitate endotracheal intubation due to early onset and short duration of action, but its use is either hazardous or contraindicated in some conditions like burns, hyperkalemia, severe muscle trauma and myopathies.

Atracurium, an intermediate acting nondepolarizing neuromuscular blocking agent, is primarily metabolized by ester hydrolysis and has extra safe guard of metabolism by non-enzymatic Hoffmann degradation[3], so can be safely used in patients with hepatic and renal diseases, but histamine release in higher doses limit its use in the patients of asthma. Atracurium has also been associated with a decrease in mean arterial pressure (MAP) of up to 30 mmHg within 2 min of initiation, which could result in hypotension and may be associated with histamine release[4].

Cisatracurium is a newer nondepolarizing neuromuscular blocking agent with intermediate action. It is the isomer of atracurium, and has the neuromuscular blocking potency approximately three fold that of atracurium.

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Cisatracurium, unlike atracurium, is devoid of histamine induced cardiovascular effects in the range of clinical doses. Also, cisatracurium is metabolized by Hoffmann elimination to laudanosine and a monoquaternary acrylate such as atracurium[5]. Laudanosine is dependent on the liver and kidney for its elimination and its concentration is elevated in patients with hepatic or renal disease[6]. A cisatracurium dose provides superior hemodynamic stability with only minor release of histamine, and its metabolism via Hoffman elimination is independent of organ function. This made cisatracurium an appealing alternate to older agents for muscle relaxation. It does not trigger histamine release even in doses upto $6\times ED_{95}$ .Various studies has been done to evaluate and compare efficacy, potency and safety of cisatracurium in doses range of $2 \times ED_{95}$ to $8 \times ED_{95}$ with various observation and conclusions.

Magdy omera et al[7]. (2005) compared rocuronium with cisatracurium and they found that rocuronium has rapid onset and both are potent and safe without apparent histamine release.

These above studies inspired us to conduct a study to compare the efficacy and safety of cisatracurium in doses of 0.1mg/kg B.W and 0.2mg/kg B.W. and to compare with standard dose of atracurium 0.5 mg/kg B.W in patients undergoing elective abdominal surgeries under general anaesthesia.

Material and methods

The present study was carried out in the "Department of Anaesthesiology", Shyam Shah Medical College & associated Sanjay Gandhi and Gandhi Memorial Hospitals, Rewa (M.P.) from July 2018 to June 2019.After getting clearance from Institutional Ethics Committee (IEC), 90 patients of 18-60 years of age of either sex, ASA grade I-II and mallampatti grade I-II, posted for elective abdominal surgeries under general anaesthesia, were selected for the study. Patients who refused to give consent for the study, with psychological disorders, with neuromuscular, cardiovascular, renal and hepatic disease, on medication known to interact with neuromuscular blocking drugs e.g. antibiotics (aminoglycosides and tetracycline), antidepressants, anticonvulsants, antiarrhythmics

(calcium channel blockers and quinidine) and magnesium sulphate, history of COPD, asthma and allergy were excluded from the study.

A detailed history of all selected patients were taken. A thorough pre-anaesthetic evaluation including the airway assessment was performed. The patients were explained about the entire procedure and informed consent was taken, in a language of their understanding.

The patients were randomised using a computer based randomisation software, "Random Allocation Software 1.0" in 3 groups of 30 patients each, depending on muscle relaxant and its doses used for intubation as under:

Group A: Patients received atracurium with initial dose of 0.5 mg/kg.

Group B: Patients received cisatracurium with initial dose of 0.1 mg/kg.

Group C: Patients received cisatracurium with initial dose of 0.2 mg/kg.

All patients were kept nil by mouth for atleast 6 hours prior to surgery. The patients were shifted to the operation theatre. Monitor was attached and preoperative baseline parameters like heart rate, systolic blood pressure (SBP), diastolic blood pressure (DBP), mean arterial pressure (MAP), oxygen saturation (SPO_2), end tidal CO2 ($EtCO_2$) and electrocardiographic (ECG) tracings were observed and carefully recorded. Intravenous line was secured.

All the patients were pre-medicated with Inj. Midazolam 0.05mg/kg B.W. and Inj. Fentanyl 2mcg/kg B.W. given intravenously. Preoxygenation was done with 100% oxygen for 3 min. Anaesthesia was induced with Inj. Propofol 2.5mg/kg B.W. intravenously. Neuromuscular blockade was measured by twitch height in response to ulnar nerve stimulation. For monitoring of neuromuscular transmission, two surface electrodes of peripheral nerve stimulator were fixed over the path of ulnar nerve. The distal electrode was placed at the level of the wrist on the ulnar surface at the flexor crease, as close to the nerve as possible. The second electrode was placed 1-2cm proximal to the first, parallel to the flexor carpi ulnaris tendon. The negative (black) lead wire was attached to the distal electrode and the positive (red) lead wire was attached to the proximal. The transducer fixed on corresponding thumb and response was to see the thumb twitching.After a stable base line period of at least 5 min, calculated dose of neuromuscular blocking agent in coded syringes (drug prepared and coded by fellow resident) was injected intravenously. After 2 min, endotracheal intubation was attempted using proper size tube. Time from injection of muscle relaxant to > 90 % suppression of single twitch height was noted and considered as onset time. If intubation unsuccessful, it was reattempted after 30 seconds, but for all practical purposes the intubating conditions at first attempt were taken in to consideration .Correct placement of endotracheal tube was confirmed by auscultation and end tidal carbon dioxide ($EtCO_2$) values. After confirmation and fixation of endotracheal tube all patients were maintained on 70% N2O+ 30%O2 and Isoflurane. Time from injection to reappearance > 25% of twitch height or any respiratory movement in breathing bag and notch in capnography whichever is earlier was noted and considered as duration of action. Further dose of neuromuscular blocking agent was given if needed.

Patients were monitored for any signs of histamine release clinically through skin changes graded as flush (if redness lasted> 120 sec), erythema, or wheals and presence of any hemodynamic changes or bronchospasm.Intraoperative hemodynamic changes were continuously monitored and recorded including heart rate (HR), systolic blood pressure(SBP), diastolic blood pressure(DBP), mean arterial blood pressure (MABP), oxygen saturation (SPO_2), and end tidal CO2 ($EtCO_2$) baseline, after injecting muscle relaxant, after intubation and every 5 min upto 20 min. Body temperature was maintained between 35 and 37ºC by means of warmed IV fluids and warming blankets (skin temperature probe)At the end of surgical procedure, the reversal of residual neuromuscular block was done by administration of neostigmine 0.05mg/kg B.W. and glycopyrrolate 0.01mg/kg B.W. mixture through slow IV injection. Patient were extubated after orotracheal suction and then oxygenated for 5 min and shifted to post anaesthesia care unit (PACU) for observation.

Statistical analysis

Statistical analysis was performed by using SPSS version 20. Quantitative data were expressed as the means ± SD, while qualitative data were expressed as numbers and percentages (%). ANOVA 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(sex). A probability value (*P*-value)<0.05 was considered statistically significant.

Results

Table 1: Comparative evaluation of heart rate between groups.

Heart rate (in bpm) (Mean ±SD)	Group A	Group B	Group C	P value	Group A vs GroupB (P value)	Group A vs GroupC (P value)	Group B vs Group C (P value)
Baseline	76.27 ± 5.889	79.07 ± 6.220	76.43 ± 7.238	0.177	0.293	1.000	0.357
After intubation	88.97± 7.677	88.27± 8.578	80.93± 8.004	<0.001	1.000	0.001	0.002
After injecting muscle relaxant	80.93± 6.828	80.53± 8.233	77.80± 7.336	0.217	1.000	0.326	0.483
After 5 min intubation	86.13± 9.783	86.07± 7.755	78.97± 7.504	0.001	1.000	0.004	0.005
After 10 min intubation	83.67 ± 11.158	84.03± 8.873	77.63± 6.744	0.012	1.000	0.036	0.023
After 15 min intubation	80.77± 9.096	82.10± 9.430	77.20± 7.513	0.085	1.000	0.350	0.097
After 20 min intubation	77.83± 6.058	79.63± 5.353	76.33± 7.004	0.123	0.786	1.000	0.124

Table 1 shows the comparison of the heart rate at different time intervals. The difference in the heart rate base line, after injecting muscle relaxant and after 15 min intubation was statistically insignificant but after intubation upto 10 min the difference was found to be statistically significant. The difference in heart rate in patient belonging to group C was statistically significant after intubation upto 10 min, when compared to group A and group B. But when group A was compared group B, P value was nonsignificant at all point of comparison.

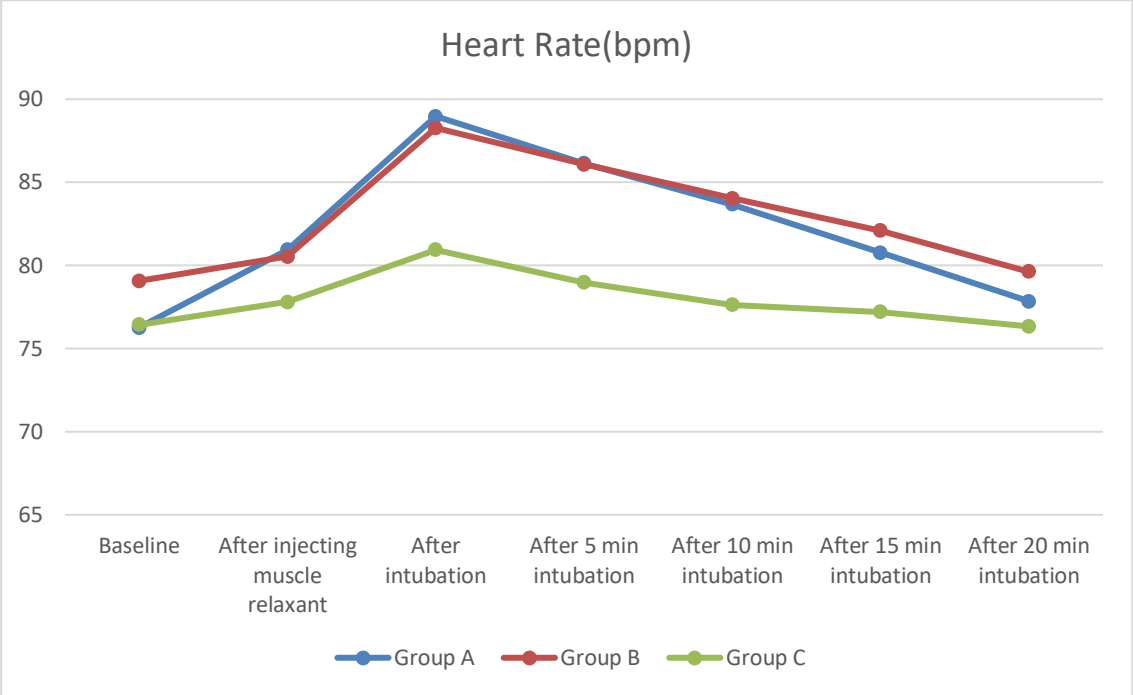

Fig 1: Comparison of Heart rate between groups

Table 2: Comparative evaluation of systolic blood pressure between groups

SystolicBlood Pressure(in mm Hg) (Mean ± SD)	Group A	Group B	Group C	P value	Group A vsGroupB (Pvalue)	Group A vsGroupC (Pvalue)	GroupBvs GroupC (Pvalue)
Baseline	125.83± 8.205	128.03± 6.552	127.37± 7.730	0.512	0.782	1.000	1.000
After injecting muscle relaxant	16.40 ± 7.713	118.33± 4.816	121.77± 6.966	0.008	0.782	0.007	0.142
After intubation	135.30± 8.384	137.33± 5.689	129.40± 8.422	<0.001	0.910	0.010	<0.001
After 5 min intubation	131.00± 6.700	133.77± 6.067	126.17± 6.526	<0.001	0.299	0.014	<0.001
After 10 min intubation	128.43± 5.987	130.77± 6.683	123.83± 6.281	<0.001	0.470	0.018	<0.001
After 15 min intubation	126.80± 6.294	128.53± 6.559	122.93± 5.225	0.002	0.812	0.046	0.002
After 20 min intubation	125.10± 6.900	127.77± 5.952	123.30± 6.753	0.033	0.355	0.870	0.029

Table 2 shows the comparison of the systolic blood pressure at different time intervals. The difference in the systolic blood pressure base line and after injecting muscle relaxant was statistically insignificant but after intubation upto 10 min the difference was found to be statistically significant.

The difference in the systolic blood pressure in patient belonging to group C was statistically significant after intubation upto 15 min, when compared to group A and group B. But when group A was compared group B, P value was nonsignificant at all point of comparison.So patient belonging to group C had more stable the systolic blood pressure, when compared to group A and group B.

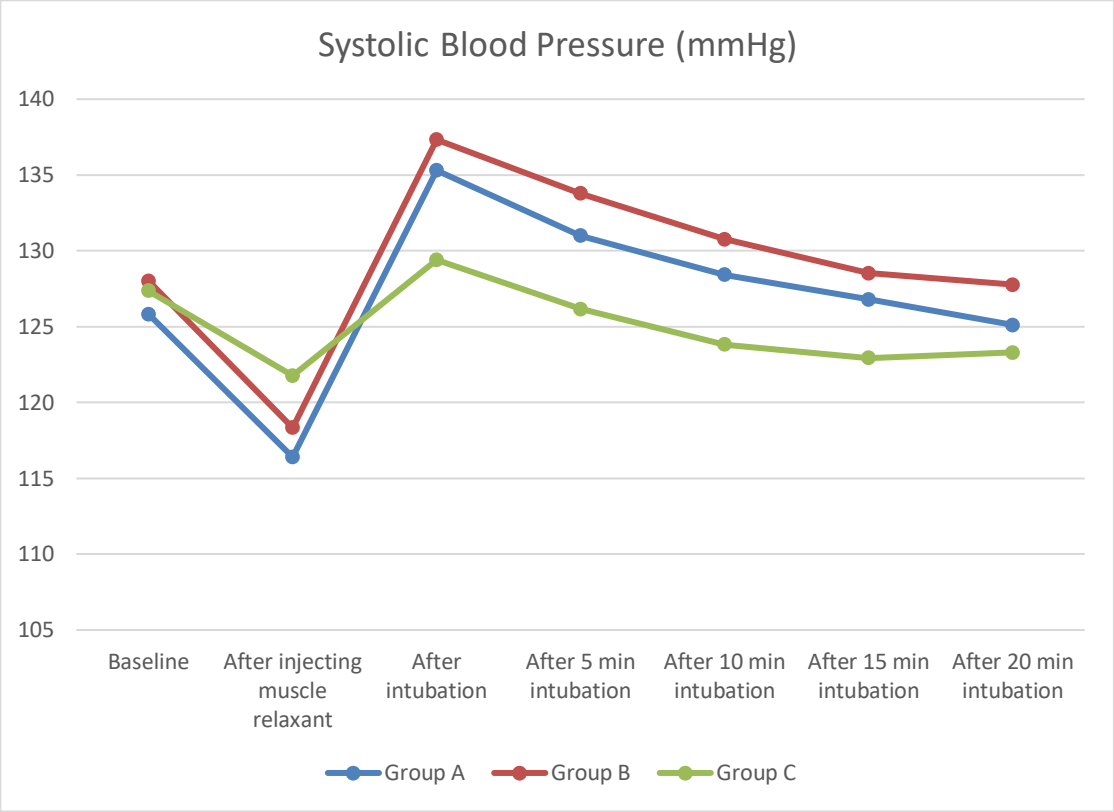

Fig 2: Comparison of Systolic blood pressure between groups

Table 3: Comparative evaluation of diastolic blood pressure between groups

DiastolicBlood Pressure (in mm Hg) (Mean ± SD)	Group A	GroupB	Group C	P value	Group A vsGroupB (Pvalue)	GroupAvs GroupC (Pvalue)	GroupBvs GroupC (Pvalue)
Baseline	80.37± 4.173	82.50± 8.270	79.73± 5.675	0.204	0.568	1.000	0.269
After injecting muscle relaxant	72.80± 7.172	74.80± 4.475	74.30± 5.466	0.278	0.387	0.701	1.000
After intubation	87.87±5.008	85.80± 3.167	82.43± 6.683	<0.001	0.373	<0.001	0.040
After 5 min intubation	83.93± 4.963	83.27± 2.651	79.10± 5.635	<0.001	1.000	<0.001	0.002
After 10 min intubation	81.27± 5.369	81.47± 2.460	78.03± 4.716	0.004	1.000	0.015	0.009
After 15 min intubation	80.10± 4.915	80.00± 3.107	77.80± 5.229	0.089	1.000	0.155	0.187
After 20 min intubation	80.03± 5.021	80.77± 2.897	77.70± 4.340	0.015	1.000	0.100	0.017

Table 3 shows the comparison of the diastolic blood pressure at different time intervals. The difference in the diastolic blood pressure base line and after injecting muscle relaxant was statistically insignificant but after intubation upto 10 min the difference was found to be statistically significant.

The difference in the diastolic blood pressure in patient belonging to group C was statistically significant after intubation upto 10 min, when compared to group A and group B. But when group A was compared group B, P value was nonsignificant at all point of comparison.

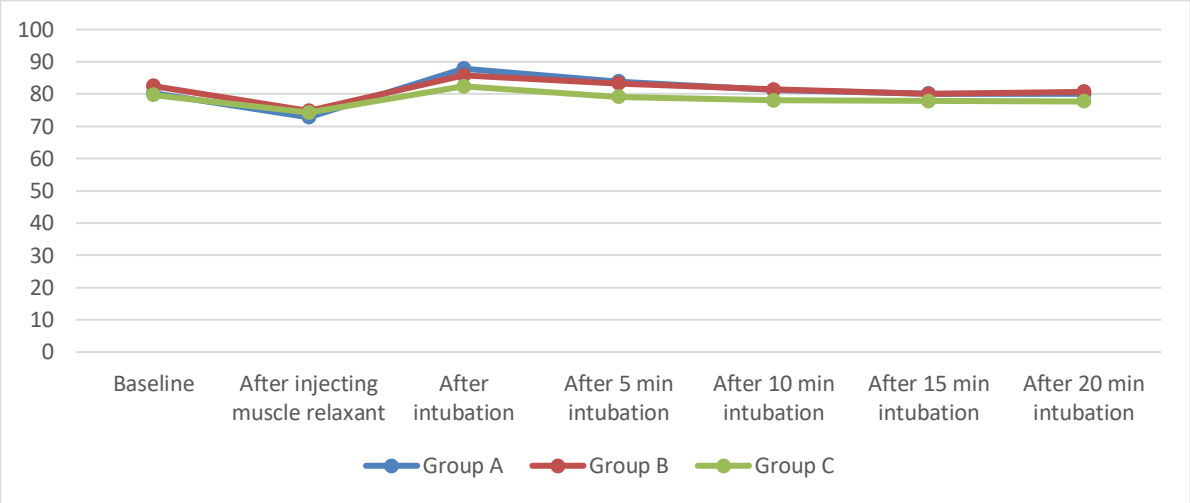

Fig 3: Comparison of diastolic blood pressure between groups

Table 4: Comparative evaluation of mean arterial pressure between groups

MeanArterial Pressure (in mmHg) (Mean ± SD)	Group A	Group B	Group C	P value	Group A vs Group B (Pvalue)	GroupAvs GroupC(P value)	GroupBvs GroupC(P value)
Baseline	95.52± 4.850	97.68± 6.035	95.61± 5.867	0.248	0.421	1.000	0.471
After injecting muscle relaxant	87.13± 6.472	89.31±4. 063	90.12± 5.474	0.094	0.371	0.107	1.000
After intubation	103.68 ± 4.314	102.98± 3.07	98.09± 6.687	<0.001	1.000	<0.001	0.001
After 5 min intubation	99.62± 3.834	100.10± 3.321	94.79± 5.592	<0.001	1.000	<0.001	<0.001
After 10 min intubation	96.66± 4.273	97.90± 3.321	93.30± 4.898	<0.001	1.000	0.003	<0.001
After 15 min intubation	95.67± 4.390	96.18± 3.738	92.84± 4.702	0.007	1.000	0.038	0.010
After 20 min intubation	95.06± 4.916	96.43± 2.778	92.90± 4.783	0.007	0.645	0.162	0.006

Table 4 shows the comparison of the mean arterial pressure at different time intervals. The difference in the mean arterial pressure base line and after injecting muscle relaxant was statistically insignificant but after intubation upto 20 min the difference was found to be statistically significant.The difference in the mean arterial pressure in patient belonging to group C was statistically significant after intubation upto 15 min, when compared to group A and group B. But when group A was compared group B, P value was nonsignificant at all point of comparison.

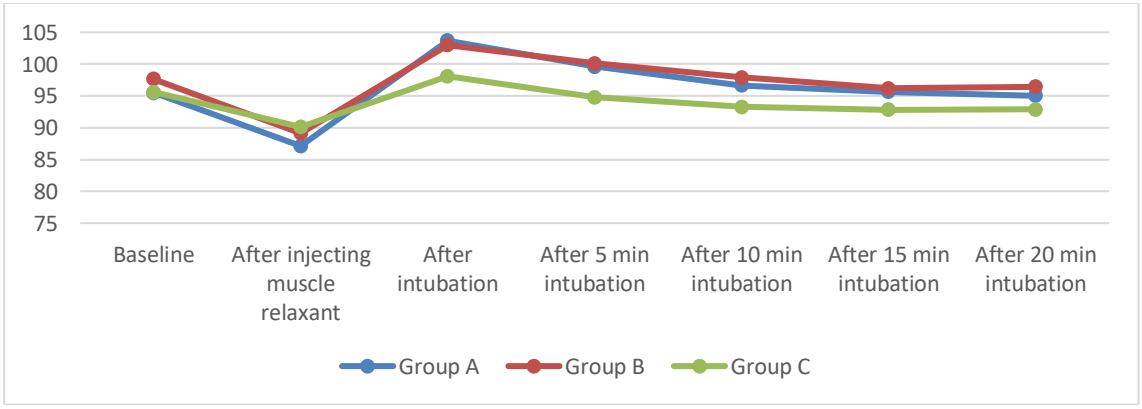

Fig 4 : Comparison of mean arterial pressure between groups

Table 5: Histamine release among the studied patients

Parameter	Group			Total
	A	B	C	
Flush	-	-	-	-
Erythema	01	-	-	01

Wheals	-	-	-	-
Hypotension	-	-	-	-
Bronchospasm	-	-	-	-
Others	-	-	-	-
Total	01	-	-	01

Table 5 shows that there is no signs of histamine release were noted with group B and group C with anyone of the two doses of cisatracurium, while 1 case showed erythema with atracurium in group A

Discussion

Cisatracurium has many advantages, compared with other neuromuscular blocking agents. 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.The present study was conducted in order to compare the hemodynamic parameters (i.e. heart rate, blood pressure) and signs of histamine release clinically.

In our study the difference in the heart rate base line, after injecting muscle relaxant and after 15 min of intubation was statistically insignificant but after intubation upto 10 min the difference was found to be statistically significant.

The difference in heart rate in patient belonging to group C was statistically significant after intubation upto 10 min, when compared to group A and group B. But when group A was compared group B, P value was not significant at all point of comparison. So patient belonging to group C had more stable heart rate, when compared to group A and group B.

The difference in the systolic blood pressure base line and after injecting muscle relaxant was statistically insignificant but after intubation upto 10 min the difference was found to be statistically significant. The difference in the systolic blood pressure in patient belonging to group C was statistically significant after intubation upto 15 min, when compared to group A and group B. But when group A was compared group B, P value was nonsignificant at all point of comparison. So patient belonging to group C had more stable the systolic blood pressure, when compared to group A and group B.

The difference in the diastolic blood pressure base line and after injecting muscle relaxant was statistically insignificant but after intubation upto 10 min the difference was found to be statistically significant. The difference in the diastolic blood pressure in patient belonging to group C was statistically significant after intubation upto 10min, when compared to group A and group B. But when group A was compared group B, P value was nonsignificant at all point of comparison.

The difference in the mean arterial pressure base line and after injecting muscle relaxant was statistically insignificant but after intubation upto 20 min the difference was found to be statistically significant. The difference in the mean arterial pressure in patient belonging to group C was statistically significant after intubation upto 15 min, when compared to group A and group B. But when group A was compared group B, P value was nonsignificant at all point of comparison.So we found that hemodynamic stability for heart rate, systolic blood pressure, diastolic blood pressure and mean arterial blood pressure were more evident in higher doses of cisatracurium 4×ED95 (group C) than lower dose cisatracurium 2×ED95 (group B) and standard dose of atracurium 2×ED95 (group A).

There was a statistically significant increase in heart rate, mean arterial pressure post intubation 120 sec post-injection of the muscle relaxant when compared to baseline and post-injection of 2×ED95 dose of atracurium in group A and the same dose of cisatracurium in group B. It is because of stress of intubation and the patients were not fully relaxed.

Lien et al[8]. (1995) 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. Signs of histamine release were shown in one patient in this study in the form of transient facial flushing after the administration of atracurium;

Konstadt S N et al[9]. (1995) studied cardiovascular effects of cisatracurium and vecuronium in patients with coronary artery disease. They concluded that there were no episodes of cutaneous flushing. There were no episodes of hypotension requiring therapy in any patient after cisatracurium. Results obtained by Konstadt et al were similar to our results.

Kumar A et al[10]. (2016) studied frequency of occurrence of urticaria and haemodynamic changes after the administration of atracurium in the conventional dose schedule. They concluded that atracurium in conventional dosage is not associated with urticaria. Haemodynamic changes after the administration of atracurium was found to be significant.

Clinical signs of Histamine release and other adverse effects

Histamine release is a major drawback with bis-benzylisoquinolinium muscle relaxants. The peak increase in plasma histamine concentration is observed at 1 min and returns to control value within 5 min of the administration of atracurium[51].

When a patient is given a histamine releaser drug, the clinical signs of elevated histamine concentration such as hypotension, tachycardia, head and face erythema seen once the plasma concentration is increased by 2-3 times its initial level, and the severity of these clinical signs depends on the dose and speed of administration[52]. It seems that cisatracurium compared to atracurium is an advantageous muscle relaxant for patients under coronary graft surgery as it causes less effect on hemodynamic indexes.

In our study no signs of histamine release were noted in any doses of cisatracurium, but signs of histamine release were shown in one patients with administration of 2×ED95 dose of atracurium in group A, one patient in the form of erythema at the site of injection in the ventral aspect of the forearm but the patient did not experience hypotension or tachycardia.

Salvatore J. Basta et al[11]. (1982) concluded that as a bis-benzylisoquinoline, atracurium has the potential for release of histamine. The syndrome becomes clinically evident when doses of 0.5 mg/kg 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.

Hosking et al[12]. (1988), 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 diphenylhydramine 1 mg/kg and cimetidine 4 mg/kg intravenously 30 min before giving a very large dose of atracurium.

Hughes et al[13]. (1981) concluded that despite 10-20 times increase in the plasma histamine levels, atracurium is not vagolytic and does not block the innervation by autonomic ganglia.

Limitation

In our study, we were unable to measure the plasma histamine levels due to non-availability of this facility in our institution.

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