Comparison of Two Muscle Relaxants for Tracheal Intubation in Patients Undergoing Surgery at Goa Medical College and Hospital

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ABSTRACT

BACKGROUND

Cisatracurium and atracurium are intermediate acting muscle relaxants which do not depend on renal or hepatic metabolism for elimination since they undergo Hofmann elimination. Despite the advantages of cisatracurium such as minimal effects on the cardiovascular system, no accumulative effects, no metabolite toxicity, and metabolic product has no neuromuscular blocking effects, due to slow onset and unsatisfactory intubating conditions, the use of cisatracurium is limited compared with those seen with equipotent doses of other neuromuscular blocking agents. This study was undertaken to find onset time and intubating conditions with 3 × ED_{95} doses of atracurium versus cisatracurium.

METHODS

ASA grade 1 or 2 patients, (N = 220) were randomly allocated into 2 groups to receive equipotent doses of either atracurium or cisatracurium. Intubating conditions were assessed using Cooper et al scale and neuromuscular monitoring done using TOF Watch SX. Haemodynamic responses and any adverse effects were noted.

RESULTS

The onset time was 167.36 ± 75.41 seconds (2.78 ± 1.25 minutes) in atracurium group whereas in cisatracurium group, onset time was 249.26 ± 75.90 seconds (4.15 ± 1.26) and the difference was statistically significant with p value of < 0.001. The difference in intubating conditions between the groups was statistically insignificant. However, atracurium produced a higher incidence of clinically acceptable conditions (excellent in 94.4 %) than cisatracurium (excellent in 87.3 %). The incidence of adverse effects such as erythema, flushing and bronchospasm was greater in Atracurium group though hypotension was observed in both groups.

CONCLUSIONS

Onset time and intubating conditions are significantly better with equipotent doses of atracurium compared to cisatracurium. But atracurium is associated with higher incidence of adverse effects such as erythema, flushing and bronchospasm, though the potential of cisatracurium to cause anaphylactoid reactions cannot be ignored.

KEYWORDS

Cisatracurium, Atracurium, Muscle Relaxants, Neuromuscular Blocking Agents, Erythema, Flushing, Bronchospasm, Hypotension, Anaphylactoid Reactions

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BACKGROUND

Endotracheal intubation requires relaxation of laryngeal musculature leading to total inactivity of vocal cords. Hence muscle relaxants have become an essential part of the anesthesiologist's armamentarium. Various muscle relaxants used for endotracheal intubation vary in their onset and duration, mechanism of action, pharmacokinetics and pharmacodynamics and side effects. Depending upon these differences, they are used in clinical practice.[1]

Cisatracurium besylate is a relatively new nondepolarizing neuromuscular blocking agent which is approximately three times as potent as atracurium with an ED_{95} of 0.05 mg / kg during balanced anaesthesia.[2,3,4] Similar to atracurium, cisatracurium is also an intermediate acting neuromuscular blocking agent that does not depend upon renal or liver function for elimination since it undergoes Hofmann elimination and ester hydrolysis. The main advantage of cisatracurium is that there has been no evidence of histamine release at doses up to eight times the ED_{95} whereas with atracurium, histamine release has been observed in humans at doses greater than 2.5 times ED_{95}.[5]

Compared to equipotent doses of atracurium, 2 × ED_{95} doses of cisatracurium (100 µg / kg) do not yield satisfactory intubating conditions. The recommended intubating dose of cisatracurium is 3 × ED_{95}.[6] Hence this study was conducted to compare the intubating conditions and time to onset of neuromuscular blocking action of equipotent doses (3 × ED_{95}) of cisatracurium versus atracurium.

Objectives

1. To compare the intubating conditions in terms of jaw relaxation, vocal cord paralysis and response to intubation.
2. To compare time taken for onset of action of muscle relaxant after administration of equipotent doses (3 × ED_{95}) of cisatracurium versus atracurium.

METHODS

The study was carried out as a prospective randomized double blind trial over a period of 1 year from November 2017 to October 2018 and included patients of both sexes who underwent surgery under general anaesthesia at our tertiary care hospital. Ethical Committee Clearance was obtained from the Institutional Ethical Committee bearing the reference number GMC / IEC / Appr - Nov 17 / 15.

Inclusion Criteria

- Patients aged between 18 to 60 years
- Classified by the American Society of Anaesthesiologists as ASA I or II
- Scheduled to undergo general anaesthesia with oral endotracheal intubation
- Consent to participate in study

Exclusion Criteria

- Any disorders of the cardiovascular, renal, hepatic or neuromuscular systems, ascertained either from medical history or clinical examination
- Patients with anticipated difficult airway
- Patients on medications which interact with neuromuscular blocking drugs ; e.g. antibiotics (aminoglycosides and tetracyclines), anticonvulsants, antiarrhythmics (calcium channel blockers and quinidine), antidepressants and magnesium sulphate
- Pregnant or breastfeeding females
- Patients with bronchial asthma
- Inadequately nil by mouth patients

Sample Size Calculation

Sample size of 220 patients was calculated by using an α error of 0.05, confidence interval of 95 % for an infinite population, calculated power of 80 %. Standard deviation was calculated using a previous similar study.[6]

The purpose of the study and study protocol was explained to the patient in a language the patient understood and a written informed consent was obtained. The patient's age, sex, ASA status, weight and type of surgery were recorded.

Patients were randomly divided into 2 groups using an online research randomizer (http : / / www. randomizer. Org /) by the principal investigator. Patients who would receive atracurium were allocated into group A (n = 110), and those to be given cisatracurium were allocated to group C (n = 110).

Monitoring included electrocardiogram, non - invasive blood pressure monitoring, pulse oximetry, capnography, temperature monitoring and neuromuscular monitoring. TOF - Watch SX was used to measure the onset of the neuromuscular block. To avoid hypothermia, the hand, wrist and half of the forearm were wrapped with crepe bandage.

Patients were preoxygenated with 100 % oxygen for 3 min and premedicated using intravenous 0.03 mg / kg midazolam. General anaesthesia was induced with fentanyl (2 µg / kg), propofol (2 mg / kg) intravenously followed by an infusion of propofol at the rate of 100 µg / kg / min.

Ventilation was ascertained and Train of Four (TOF) calibration done. Muscle function was monitored using a TOF - Watch SX monitor system. A sensor was attached to the palmar thumb to measure the contraction velocity of the thumb adductor. A stimulating electrode was placed on the wrist surface, where the ulnar nerve was stimulated. TOF stimulation at 2 Hz, with a 0.2 ms wave width, and a 15 - second interval, was used to stimulate the ulnar nerve on the forearm. TOF monitoring was done every 15 seconds. After a stable baseline period of at least 5 min, 3 × ED_{95} dose of cisatracurium (0.15 mg / kg) or atracurium (0.75 mg / kg) was administered over 5 - 10 seconds to patients in Group C and Group A respectively. Patients were ventilated with 100 % oxygen. The patient was intubated when TOF % was 0. Laryngoscopy and intubation was done by skilled anaesthesiologist who was blinded to the muscle relaxant administered. Male patients were intubated orally with 8mm internal diameter PVC tube and female patients were

intubated with 7mm internal diameter PVC tube. The anaesthesiologist noting the findings was also blinded.

Vital parameters Heart rate (HR), systolic blood pressure (SBP), diastolic blood pressure (DBP) and mean arterial pressure (MAP) and oxygen saturation (SpO_2) were noted. The above were recorded at induction of anaesthesia, before giving muscle relaxant, before intubation, immediately after intubation and at 3 and 5 minutes after intubation.

Intubating conditions were graded based on scoring scale devised by Cooper et al.[7,8] Conditions were classified as excellent (8 - 9), good (6 - 7), poor (3 - 5), or impossible (0 - 2).

	Score			
Criteria	**3**	**2**	**1**	**0**
Jaw relaxation	Complete	Moderate	Minimal	None
Vocal cord Status	Open	Slight Moving	Closing	Closed
Response to intubation	None	Slight Moving	Coughing	Bucking

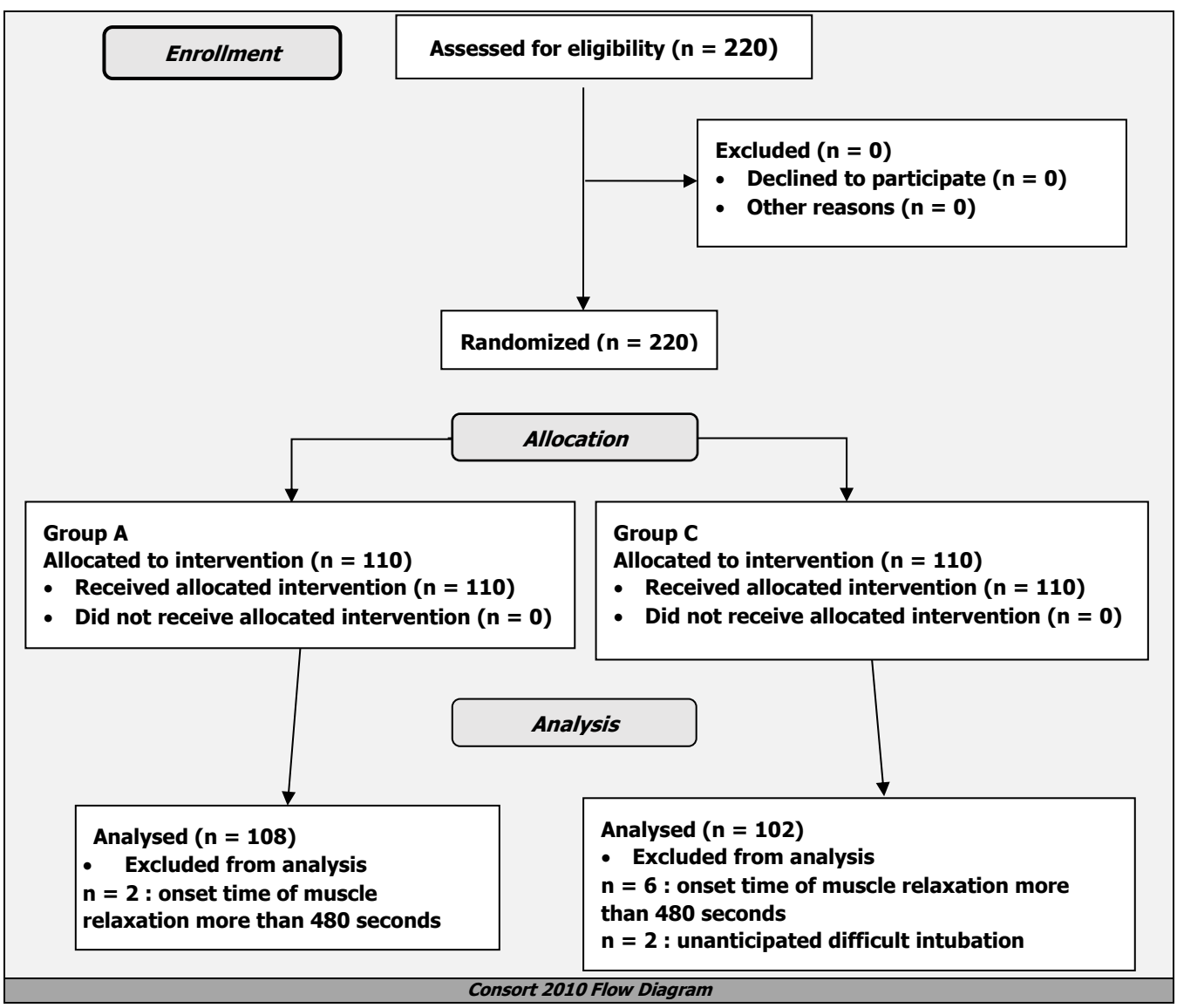
Table 1. Cooper et al Scale

The onset time was determined as the interval from the end of muscle relaxant injection until maximal suppression of T_1 %.

Patients were monitored for any signs of histamine release clinically through skin changes such as

- Flush (if redness lasted > 120 s)
- Erythema, or wheals
- Presence of any haemodynamic changes such as hypotension (defined as decrease in MAP less than 60 mm Hg).[9]
- Bronchospasm

Anaesthesia was maintained with a mixture of 50 % N_2O in O_2, propofol infusion, boluses of the muscle relaxant (10 % of the initial dose) and intravenous fentanyl. Ventilation was controlled by the Datex - Ohmeda™ ventilator with end tidal CO_2 maintained at 30 - 35 mmHg. Intra-operative haemodynamic changes were continuously displayed on the monitor including : heart rate (HR), mean arterial pressure (MAP) every 5 min, oxygen saturation (SO_2), and end tidal carbon dioxide (CO_2). At the end of operation, reversal was achieved by administration of neostigmine and glycopyrrolate and trachea was extubated when TOF - ratio was > 0.9.



Consort 2010 Flow Diagram

Statistical Analysis

The data was entered in Microsoft excel and analysed using SPSS. The outcome variables were expressed as percentage for categorical variable and as mean with standard deviation for numerical variable. The association between outcome variable and the intervention were measured by Student T test and Chi square test and statistical significance at 5 % level of significance. The demographic variables were compared using student t test and chi square test.

RESULTS

Both groups were comparable in terms of age, gender, ASA grading and weight.

Parameters	Group A (n = 108) Atracurium	Group C (n = 102) Cisatracurium	P Value
Age in years (mean ± SD)	41.47 ± 13.778	40.49 ± 13.818	0.607
Gender (male / female)	55 / 53	50 / 52	0.782
Weight in kgs (mean ± SD)	57.21 ± 10.208	57.25 ± 11.028	0.983
ASA grades (1 / 2)	81 / 27	79 / 23	0.677

Table 2. Comparison of Age, Gender, Weight and ASA Grades

Parameters		Group A (n = 108) Atracurium (Mean ± SD)	Group C (n = 102) Cisatracurium (Mean ± SD)	P Value
Baseline	Pulse rate	80.14 ± 13.514	80.57 ± 14.522	0.824
	Systolic blood pressure	130.52 ± 15.674	132.31 ± 17.115	0.428
	Diastolic blood pressure	80.06 ± 8.949	79.15 ± 9.121	0.467
	Mean arterial blood pressure	96.55 ± 10.405	97.24 ±11.262	0.645
After induction	Pulse rate	76.4 ± 14.645	76.76 ± 13.288	0.85
	Systolic blood pressure	104.78 ± 16.165	106.54 ± 16.929	0.441
	Diastolic blood pressure	65.26 ± 12.418	64.53 ± 11.295	0.657
	Mean arterial blood pressure	78.22 ±13.139	78.73 ± 13.258	0.783
Before intubation	Pulse rate	71.01 ± 14.897	73.02 ± 13.422	0.306
	Systolic blood pressure	88.82 ± 15.047	94.75 ± 14.038	0.004
	Diastolic blood pressure	53.95 ± 12.751	57.18 ± 9.934	0.043
	Mean arterial blood pressure	66.04 ± 12.112	69.64 ±10.797	0.024
After intubation	Pulse rate	87.99 ± 15.545	84.75 ± 17.585	0.159
	Systolic blood pressure	116.63 ± 21.356	122.14 ± 20.106	0.056
	Diastolic blood pressure	74.44 ± 16.72	78.11 ± 16.051	0.106
	Mean arterial blood pressure	88.4 ± 17.956	99.58 ± 69.698	0.109
At 3 min	Pulse rate	81.1 ± 14.232	81.17 ±15.937	0.975
	Systolic blood pressure	108.3 ± 17.12	113.58 ± 20.077	0.041
	Diastolic blood pressure	68.02 ± 14.247	71.01 ± 15.032	0.14
	Mean arterial blood pressure	80.98 ± 13.683	84.83 ± 15.938	0.061
At 5 min	Pulse rate	77.64 ± 14.605	76.85 ± 14.765	0.699
	Systolic blood pressure	104.89 ± 16.369	107.68 ± 17.949	0.241
	Diastolic blood pressure	65.69 ± 13.071	67.14 ± 13.374	0.43
	Mean arterial blood pressure	78.6 ± 13.252	80.63 ± 14.188	0.286

Table 3. Comparison of Pulse Rate, Systolic Blood Pressure, Diastolic Blood Pressure and Mean Arterial Blood Pressure

Parameters		Group A (n = 108) Atracurium	Group C (n = 102) Cisatracurium	P Value
Onset time in Seconds (mean ± SD)		167.36 ± 75.41	249.26 ± 75.902	< 0.001*
Intubating conditions (frequency and % within group)	excellent	102 (94.4 %)	89 (87.3 %)	0.156
	good	6 (5.6 %)	12 (11.8 %)	
	poor	0 (0.0 %)	1 (1.0 %)	

Table 4. Comparison of Onset Time and Intubating Conditions

*indicates significant statistical difference

Adverse Effects	Group A (n = 108) Atracurium (Frequency and % within group)	Group C (n = 102) Cisatracurium (Frequency and % within group)	P Value
Hypotension	24 (22.2 %)	20 (19.6 %)	0.642
Flushing	8 (7.4 %)	0 (0.0 %)	0.005
Erythema	3 (2.8 %)	1 (1.0 %)	0.341
Bronchospasm	13 (12.0 %)	0 (0.0 %)	< 0.001*

Table 5. Comparison of Adverse Effects between 2 Groups

*indicates significant statistical difference

DISCUSSION

Cisatracurium is a new intermediate acting benzylisoquinolinium neuromuscular blocking agent that is one of the ten stereoisomers contained in atracurium besylate.[10] It is approximately 3 times as potent as atracurium. Similar to atracurium, it undergoes Hofmann elimination and ester hydrolysis and, therefore, does not depend upon renal or liver function for elimination.[5]

Advantages of cisatracurium over other agents are it does not release histamine[11,12] at doses up to eight times the ED_{95} (whereas atracurium causes histamine release in humans at doses greater than 2.5 times ED_{95}),[5] has minimal effects on the cardiovascular system, has no accumulative effects, has no metabolite toxicity, and its metabolic product has no neuromuscular blocking effects.[11] 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.

Despite these advantages, due to slow onset and unsatisfactory intubating conditions, the use of cisatracurium is limited compared with those seen with equipotent doses of other neuromuscular blocking agents.[13,14,15] Hence we conducted this prospective randomized double blind study to compare the intubating conditions, onset time, haemodynamics and adverse effects of Cisatracurium versus Atracurium for endotracheal intubation.

Inhalational agents were not used for induction since they interfere with onset of action of muscle relaxants. It is seen that deep anaesthesia induced with potent volatile anaesthetics (in the absence of neuromuscular blockade) causes a slight reduction of neuromuscular transmission, as measured by depression of sensitive indicators of clinical neuromuscular function, such as TOF. Inhaled anaesthetics also enhance the neuromuscular blocking effects of nondepolarizing NMBDs. Hence propofol infusion at the rate of 100 µ / kg / min was used to maintain the depth of anaesthesia.[16]

Intubating conditions were assessed according to scale devised by Cooper at al.[8] Both groups were comparable in terms of age, gender, ASA grading and weight. The differences observed were statistically insignificant between the two groups. In our study the heart rates in both groups remained comparable throughout the monitoring period and the difference was not statistically significant. Tachycardia was not observed in any group.

Baseline SBP, DBP and MAP between the 2 groups were comparable and difference between them was statistically not significant. There was fall in blood pressure after

induction of anaesthesia. The fall in blood pressure compared to baseline values may be attributed to haemodynamic effect of propofol. Induction of anaesthesia with propofol causes a reduction in systemic arterial pressure, reportedly because of decrease in cardiac output, decrease in systemic vascular resistance, or both.[17] Just before intubation (after injection of muscle relaxant), comparison of mean systolic blood pressure, mean diastolic blood pressure and mean arterial blood pressure between two groups shows that the pressures are higher in group C compared to group A and the difference between the two groups was statistically significant. This may be attributed to histamine releasing property of atracurium which results in fall in blood pressure[18] along with the haemodynamic effects of propofol.

Our findings are consistent with those of R. P. F. SCOTT et al[18] who concluded that atracurium 0.8 mg / kg will produce a significantly more rapid onset of blockade than 0.5 mg / kg with a similar intubation score 1 min earlier which may be associated with a transient but significant decrease in mean arterial pressure.

Mean systolic blood pressure, mean diastolic blood pressure and mean arterial blood pressure after laryngoscopy and endotracheal intubation showed no statistical difference between the two groups but a rise in blood pressure is observed after laryngoscopy and endotracheal intubation which may be attributed to pressor response.[19]

At 3 min, the difference in mean systolic blood pressure between two groups was statistically significant. This may be attributed to histamine releasing effect of Atracurium which is transient lasting for 1 - 5 minutes. Comparison of the diastolic blood pressure and mean arterial blood pressure at 3 min between the two groups showed no statistical significance between two groups.

SBP, DBP and MAP between the 2 groups were comparable at 5 min after intubation and difference between them was statistically not significant. This showed that although there is a transient significant fall in blood pressure after Atracurium, the effect is short lasting. The effect of histamine release is usually of short duration (1 to 5 minutes), is dose related, and is clinically insignificant in healthy patients.[16]

The onset time was 167.36 ± 75.41 seconds (2.78 ± 1.25 minutes) in atracurium group whereas in cisatracurium group, onset time was 249.26 ± 75.90 seconds (4.15 ± 1.26) and the difference was statistically significant with p value of < 0.001. The slower onset of action of cisatracurium is probably due to its greater potency compared to atracurium, a mechanism that has been proposed for other relaxants.[20] There is an inverse relationship between onset and potency.[21]

This relationship can be explained on the basis of the density of receptors at the neuromuscular junction. Irrespective of their potency, Neuromuscular Blocking Drugs (NMBDs) must bind to a critical number of acetylcholine receptors for blockade to occur. These receptors are concentrated at the neuromuscular junction where access is limited. When a potent NMBD is administered, fewer molecules are administered than in the case of an equipotent dose of a less potent drug. Because of this lower concentration gradient, more time is required for enough molecules of a potent drug to be delivered to the neuromuscular junction. Thus, onset time is longer.[16]

This slower onset of action has been demonstrated in other studies too. Linda S. Bluestein et al[5] compared atracurium with 3 different doses of cisatracurium during N_20 / O_2 / Propofol / fentanyl anaesthesia and concluded that increasing the initial dose of cisatracurium (from 0.1 to 0.15 and 0.2 mg / kg) decreased mean time of onset (from 4.6 to 3.4 and 2.8 min, respectively).

Similarly AM El - Kasaby et al[6] compared atracurium (2 × ED_{95}) and different doses of cisatracurium (2 × ED_{95}, 4 × ED_{95}, 6 × ED_{95}) regarding onset time and found that onset time was 3.24 ± 0.55 min with atracurium whereas it was 4.37 ± 0.46, 2.9 ± 1.4 and 2 ± 1.2 min with 2 × ED_{95}, 4 × ED_{95} and 6 × ED_{95} doses of cisatracurium.

The difference in intubating conditions between the groups was statistically insignificant. However, atracurium produced a higher incidence of clinically acceptable conditions (excellent in 94.4 %) than cisatracurium (excellent in 87.3 %).

In a study conducted by El - Kasaby A M et al, with regards to the conditions of intubation, it was estimated that only 6 × ED_{95} dose of cisatracurium showed a statistically significant difference versus the atracurium dose with excellent conditions of intubation. 4 × ED_{95} and 6 × ED_{95} doses of cisatracurium were significantly better than 2 × ED_{95} dose of cisatracurium.[6]

Similarly, Linda S. Bluestein et al in their study found that there were no differences in intubation scores in patients treated with equipotent doses of cisatracurium or atracurium.[5]

Besides binding to the nicotinic receptors at the neuromuscular junction neuromuscular blocking drugs also interact with other acetylcholine receptors such as the nicotinic receptors in autonomic ganglia and the carotid body chemoreceptors, as well as the muscarinic receptors of the heart. Binding to these receptors results in adverse effects that vary with the potency and specificity for the cholinergic receptor in question.[22]

Initially the adverse effects of aminosteroidal compounds were vagolytic and the benzylisoquinolines often released histamine. However, newer NMBs do not necessarily display the same adverse effects despite structural similarities.

Cisatracurium does not cause any dose-dependent increase in plasma histamine level, and rapid intravenous administration does not cause cardiovascular changes,[22] whereas atracurium causes histamine release in humans at doses greater than 2.5 times ED_{95}.[5]

In our study in group A, 8 patients (7.4 %) developed flushing whereas none of patients in group C developed flushing. This difference was statistically significant with p value of 0.005. In 4 cases it was associated with hypotension, 1 case was associated with bronchospasm whereas 1 case was associated with both hypotension as well as bronchospasm. In all our cases flushing was short lived and subsided on its own without any intervention. Flushing in atracurium group may be attributed to histamine releasing property of atracurium.

3 patients (2.8 %) in group A and 1 patient (1 %) in group C developed erythema which was not statistically significant. In group A, in one case erythema was associated with bronchospasm whereas 2 cases were associated with hypotension. Although the presence of rash after atracurium administration has been taken as an indicator of significant cardiovascular changes, Alfred Doenicke et al in their experimental study found that this is not the case. Cutaneous manifestations of atracurium administration were independent of systemic levels of plasma histamine and cardiovascular effects in their study.[23]

Krombach J et al in their study concluded that, the anaphylactoid potential of cisatracurium may not be proportionally less although it is known to be a less potent histamine liberator than atracurium.[24] They observed anaphylactoid reactions in 6 patients manifesting as wheezing, arterial hypotension, urticaria and flush. Three patients developed wheezing with increased airway resistance that was associated with arterial hypoxemia in one patient. Arterial hypotension was seen in five patients, tachycardia in three, and bradycardia with ventricular conduction block in one. In one patient, urticaria and flush were the only anaphylactoid manifestations. All patients survived. They confirmed their findings by skin testing and found that all patients reacted to the Cisatracurium solutions 1 : 100 or 1 : 1000.

This may be contrary to findings of Bryson HM et al[25] which state that cisatracurium does not release histamine in doses up to 8 times ED_{95}. In our study, 24 patients (22.2 %) in group A had hypotension whereas 20 patients (19.6 %) in group C had hypotension, but the difference was statistically insignificant with p value of 0.642. In our study, in all the patients, hypotension was transient in both the groups and blood pressure (BP) improved after intubation and was thought to be due to BP lowering effect of inducing agents. The histamine release caused by atracurium or cisatracurium may be a contributing factor.

Signs of bronchospasm are high peak airway pressure, upsloping of the end - tidal carbon dioxide ($EtCO_2$) waveform, wheezing, and desaturation. During surgery, bronchospasm may be due to several causes such as light plane of anaesthesia, histamine release by drugs used, etc.[26] 13 patients (12 %) in group A and none of the patients in group C developed bronchospasm. The difference between the 2 groups was statistically significant with p value of < 0.001. Comparison of the airway pressure between the two groups immediately after intubation, at 3 minutes and 5 minutes after intubation showed that airway pressure in atracurium group was higher than in cisatracurium group and the differences were statistically significant. In all our cases bronchospasm subsided after deepening the plane of anaesthesia and administration of β2 - agonist via the ET tube except in one case where bronchospasm persisted despite all manoeuvres and resolved only after subcutaneous adrenaline was administered.

Miraj A et al[27] reported a life - threatening anaphylactic reaction in a 58 – year - old woman who was scheduled for subacromial decompression of right shoulder joint with 30 mg atracurium leading to cardiac arrest. Patient was revived after 1 min of CPCR. Raised serum tryptase levels and a positive intradermal reaction to atracurium confirmed atracurium anaphylaxis.

Similarly, Maitra S, et al[28] reported severe anaphylactic reaction after administration of atracurium 15 mg, patient developed, tachycardia, hypotension and severe bronchospasm which required management with 2 doses of intravenous adrenaline (1: 10000), steroid and chlorpheniramine.

CONCLUSIONS

Onset time and intubating conditions are significantly better with equipotent doses of atracurium compared to cisatracurium. But atracurium is associated with higher incidence of adverse effects such as erythema, flushing and bronchospasm, though the potential of cisatracurium to cause anaphylactoid reactions cannot be ignored.

Data sharing statement provided by the authors is available with the full text of this article at jebmh.com.
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