Journal of Cardiovascular Disease Research

ISSN:0975 -3583,0976-2833 VOL14, ISSUE 06, 2023

Original research article

A comparative study of onset, duration and intubating conditions of cisatracurium and atracurium during general anesthesia

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Abstract

Aim: The aim of the study was to compare the effectiveness of atracurium 0.5 (2 ED95) mg/kg IV versus two different doses of cisatracurium, i.e., 0.1 (2 ED95) and 0.15 (3 ED95) mg/kg IV for intubation with regard to onset time for intubation, intubating conditions, duration of blockade, and hemodynamic parameters.

Material & methods: A Prospective, randomized, single blinded study was conducted in the Department of Anaesthesiology in Chengalpattu medical college and hospital on patients undergoing surgery under General anaesthesia in between the duration of JUNE 2018-MAY 2019. 60 patients of ASA PS I and II were taken for the study. Institutional ethical committee approval was obtained. Permission from collaborating department was also obtained. The procedure was explained to the patient in their own mother tongue and written informed consent obtained.

Results: There were more number of female patients in group 1 and 2 and more number of male patients in group 3. The age difference among the groups was not statistically significant ($p>0.05$). There was no significant difference between group 1 and 3($p>0.05$) in jaw relaxation, vocal cord position and response to intubation. Heart rate, SBP and DBP were gradually returned to baseline at 5 minutes and may be due to stress response and was not statistically significant.

Conclusion: Cisatracurium 0.15 mg/kg provides excellent intubating conditions with rapid onset of action, with longer duration of action and no significant hemodynamic changes when compared with cisatracurium 0.1 mg/kg and atracurium 0.5 mg/kg and hence cisatracurium 0.15 mg/kg can be used as an ideal non-depolarizing muscle relaxant for intubation.

Keywords: Atracurium, cisatracurium, general anesthesia, intubation

Introduction

Endotracheal intubation is an integral part of the administration of general anesthesia during the surgical procedure.[1] The neuromuscular blocking drugs have revolutionized the management of balanced General Anaesthesia. Since the introduction of d tubocurarine and succinylcholine, there has been significant advances in the field of neuromuscular blockade. Succinylcholine, introduced by Thesleff and associates in 1952, a depolarizing muscle relaxant with rapid onset of action and short duration is still the relaxant of choice to facilitate tracheal intubation. Succinylcholine has many side effects such as bradycardia, dysrhythmias, increased release of potassium, post-operative myalgia, increased intra ocular pressure, intracranial tension, intragastric pressure, prolonged recovery in patients with pseudocholinesterase deficiency, masseter spasm, and triggering malignant hyperthermia Since these side effects are due to the depolarizing mechanism of action of succinylcholine, search has been focused onto find an ideal non-depolarizing muscle relaxant (NDMR) with rapid onset time and offering excellent intubating conditions.[2,3] The ideal neuromuscular blocking agent for intubation should have a rapid onset, brief duration of action, free from hemodynamic changes, devoid of residual paralysis and provide excellent intubating conditions like fully relaxed jaw, widely open vocal cord and negligible response to intubation which reduces the time for intubation and thereby reduces the untoward hemodynamic stress response.

Atracurium and Cisatracurium are intermediate-acting nondepolarizing NMB. Cisatracurium is approximately four times as potent as atracurium. In contrast to atracurium, cisatracurium is devoid of chemically mediated histamine release. Routinely atracurium is used for the neuromuscular blockade in most pediatric surgeries. Cisatracurium is comparatively a newer drug with lesser histamine release. [4-6] Although Cisatracurium is more potent than the parent mixture (95% effective dose (ED95) 0.05 mg/kg vs. 0.2mg/kg), its pharmacodynamics profile is similar to that of Atracurium, except for a reportedly slower onset. Cisatracurium unlike Atracurium is devoid of histamine induced cardiovascular effects. On the other hand, 2 ED95 doses of Cisatracurium (0.1mg/kg) do not yield satisfactory intubating conditions

ISSN:0975 -3583,0976-2833 VOL14, ISSUE 06, 2023

such as those seen with equipotent doses of Atracurium. The recommended intubating dose of Cisatracurium is 3 ED 95(0.15 mg/kg).
Hence the aim of the study was designed to compare regarding onset time, Intubating conditions, Duration of action and Hemodynamic effects between Atracurium and 2 different doses of Cisatracurium.

Material & Methods
A Prospective, randomized, single blinded study was conducted in the Department of Anaesthesiology in Chengalpattu medical college and hospital on patients undergoing surgery under General anaesthesia in between the duration of JUNE 2018-MAY 2019. 60 patients of ASA PS I and II were taken for the study. Institutional ethical committee approval was obtained. Permission from collaborating department was also obtained. The procedure was explained to the patient in their own mother tongue and written informed consent obtained.

Inclusion criteria
- Age 18 to 50 years of both sexes.
- ASA PS I and II.
- MPC I and II.
- Elective surgeries.

Exclusion criteria
- Patients with neuromuscular disease.
- Known or anticipated difficult airway.
- Patient receiving drugs known to interact with neuromuscular blocking agents.
- Pregnant and lactating women.
- Patients with cardiovascular, hepatic and renal disorders.
- Family history of malignant hyperthermia.
- Patients with drug allergy.

Detailed history of the patients was collected and routine investigations like CBC, Blood glucose, Renal function tests, Liver function tests were done as per as institution protocol. Patients fulfilling the inclusion criteria were randomly allocated to one of the groups. Block randomization was used to select the patients.
Sample size is 60 and patients were randomly divided into 3 groups of 20 in each group.
Group 1: Atracurium 0.5 mg/kg.
Group 2: Cisatracurium 0.1 mg/kg.
Group 3: Cisatracurium 0.15 mg/kg.

In all patients, age, I.P number, surgery, baseline vital parameters were recorded. History regarding previous anaesthesia, surgery, any significant past medical illness, drug intake and allergy were recorded. General and systemic examination was done. Airway assessment was done, and investigations were recorded. After pre anaesthetic evaluation all patients were advised an overnight fasting of 8 hours.
On the day of surgery, patient was shifted to the theatre and connected to a multipara monitor displaying ECG, Pulse rate, oxygen saturation, Non-invasive blood pressure were recorded.
IV line was secured in a vein on the dorsum of the hand and IV fluids was started on maintenance. For stimulation of the ulnar nerve, the ECG electrodes are applied at the volar aspect of the wrist. The ulnar nerve motor point is located 1.5 to 2.5 cm proximal to the pisiform bone on the thumb side of flexor carpi ulnaris tendon. The distal electrode was placed about 1 cm proximal to proximal flexion crease of the wrist. The proximal electrode was placed 2 -5 cm proximal to the distal electrode. Electrical stimulation elicits thumb adduction. Placement of negative electrode distally elicits greatest neuromuscular response normally. Premedication was done. Preoxygenation with 100% oxygen for 3 minutes. Induction with inj Propofol 2 mg/kg given over 15 seconds. Following loss of consciousness, the ulnar nerve was stimulated using the neuromuscular monitor. The current strength was progressively increased, and single twitch noted. Current strength for maximal thumb adduction was noted and one and a half times the strength was used for train of four stimulation. Vital parameters recorded. A bolus of Inj Atracurium 0.5 mg/kg or Inj. Cisatracurium 0.1 mg/kg or Inj. Cisatracurium 0.15 mg/kg depending on the group was given over period of 5 to 10 seconds. Patient was ventilated with 66.6% Nitrous oxide and 33.3% oxygen, Train of four was elicited every 10 seconds and intubation attempted after disappearance of all 4 responses. Anaesthesia is maintained with 66.7% nitrous oxide and 33.3% oxygen and isoflurane 0.8 to 1% using closed circuit system with controlled ventilation. Blood pressure and pulse rate were noted at 1 minute, 3 minutes and 5 minutes after intubation. Neuromuscular function monitored using train of four stimuli every 5 minutes. The interval between injections of bolus dose to reappearance of 2 responses to train of four was taken as the duration of the action.

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Results

Table 1: Demographic data

	Group 1	Group 2	Group 3	P Value
Gender (M/F)	9/11	8/12	11/9	>0.05
Age (Years)	31.0±7.07	31.8±6.80	30.9±5.58	>0.05
Weight (KG)	58.45±6.58	59.65±6.41	54.75±5.53	>0.05

There were more number of female patients in group 1 and 2 and more number of male patients in group 3. The age difference among the groups was not statistically significant (p>0.05).

Table 2: Jaw relaxation, Vocal cord position and response to intubation

Jaw relaxation	Impossible to open	Open with difficulty	Moderate opening	Easy opening	Mean ± SD
Group 1	0	0	11	9	2.45±0.47
Group 2	0	2	13	5	2.15±0.5
Group 3	0	0	6	14	2.7±0.45
Vocal cord position	0-Closed	1-Closing	2-Moving	3-Open	Mean ± SD
Group 1	0	1	5	14	2.65±0.57
Group 2	1	3	4	12	2.35±0.90
Group 3	0	0	1	19	2.95±0.21
Response to intubation	Severe coughing	Mild coughing	Slight diaphragmatic movement	No movement	Mean ± SD
Group 1	0	1	7	12	2.55±0.58
Group 2	0	3	13	4	2.05±0.58
Group 3	0	0	4	16	2.8±0.4

There was statistical difference between group 2 and 3(p<0.05) on mean jaw relaxation, no statistical difference between group 1 and 3 (p>0.05). There was statistical difference among the three groups on mean vocal cord position (p<0.05), but there was no significant difference between group 1 and 3(p>0.05). There was significant difference among the three groups on mean response to intubation (p<0.05), but there was no significant difference between group 1 and 3(p>0.05).

Table 3: Heart rate

Time	Group 1	Group 2	Group 3	P Value
Baseline	82.55±8.75	80.5±8.68	85.15±8.15	>0.05
Induction	82.7±8.11	80.9±7.6	86.7±8.2	>0.05
Intubation	89.8±9.1	90.6±8.47	93.15±9	>0.05
1 Min	83.7±7.2	85.5±7.5	89.3±7.25	>0.05
3 Min	82.4±6.9	82.9±6.5	86.3±5.9	>0.05
5 Min	82.2±6.5	81±5.69	85.25±6.19	>0.05

Heart rates were noted down before induction, during induction, intubation, 1, 3, 5 minutes after intubation for patients belonging to all 3 groups. Mean and standard deviation were calculated for all the 3 groups and were tabulated. p values were calculated. The results obtained from the analysis showed that there was an increase in heart rate compared to baseline in all 3 groups at intubation and 1 min after intubation. It gradually returned to baseline at 5 minutes and may be due to stress response and was not statistically significant.

Table 4: Systolic and Diastolic blood pressure

Time (SBP)	Group 1	Group 2	Group 3	P Value
Baseline	118±5.8	118.1±8.8	121.5±7.2	>0.05
Induction	118.4±7	120.9±4.97	120.5±6.37	>0.05
Intubation	126.7±4.69	127.6±5.06	128.25±4.84	>0.05
1 Min	119.2±5.18	119.2±4,27	121.3±5.17	>0.05
3 Min	118.3±5.09	117.4±5.5	120.15±6.2	>0.05
5 Min	118.6±6.24	116.85±5.27	121.1±5.72	>0.05
Time (DBP)	**Group 1**	**Group 2**	**Group 3**	**P Value**
Baseline	75±3.87	76.15±6.9	77.5±7.91	>0.05
Induction	74.35±4.27	78.65±5.19	77.45±7.05	>0.05
Intubation	80.45±4.9	84.7±4.3	83.6±6.17	>0.05
1 Min	75.2±4.8	79.5±3.66	78.2±5.22	>0.05
3 Min	75.4±4.05	77.3±4.18	77.1±5.2	>0.05

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5 Min	74.1±4.5	77±3.9	77.6±4.8	>0.05

Systolic blood pressures and Diastolic blood pressures were noted down before induction, during induction, intubation, 1, 3, 5 minutes after intubation for patients belonging to all 3 groups. Mean and standard deviation were calculated for all the 3 groups and were tabulated. p values were calculated. The results obtained from the analysis showed that there was an increase in systolic and diastolic blood pressure compared to baseline in all 3 groups at intubation and 1 min after intubation. It gradually returned to baseline at 5 minutes and may be due to stress response and was not statistically significant.

Table 5: Mean arterial pressure

Time	Group 1	Group 2	Group 3	P Value
Baseline	89.2±4.16	89.8±7.33	91.8±7.27	>0.05
Induction	88.7±4.5	92.15±4.5	91.45±6.09	>0.05
Intubation	95.5±4.3	98.6±3.7	98.15±5.02	>0.05
1 Min	89.7±7.2	85.5±7.5	89.3±7.2	>0.05
3 Min	89.3±3.3	90.3±4.1	91.1±4.9	>0.05
5 Min	88.6±4.1	90±3.95	91.85±4.4	>0.05

Mean arterial pressures were noted down before induction, during induction, intubation, 1,3, 5 minutes after intubation for patients belonging to all 3 groups. Mean and standard deviation were calculated for all the 3 groups and were tabulated. P values were calculated. The results obtained from the analysis showed that there was an increase in mean arterial pressure compared to baseline in all 3 groups at intubation and 1 min after intubation. It gradually returned to baseline at 5 minutes and may be due to stress response and was not statistically significant.

Table 6: Onset time and duration of action

	Group 1	Group 2	Group 3
Onset (Min)	3.28±0.43	4.65±0.47	2.98±0.39
Duration (Min)	31±4.89	31.1±4.11	41±4.63

There was significant difference among the three groups on mean onset time (p<0.05), but there was no statistical difference between group 1 and 3 (p>0.05).

Discussion

Muscle relaxants have made anaesthesia much safer and provide good operating conditions. They are used for endotracheal intubation and for surgical relaxation. An ideal muscle relaxant minimizes the time for intubation and reduces the untoward haemodynamic stress response. Cisatracurium is one such drug which has the properties of an ideal muscle relaxant. It is similar in chemical structure to Atracurium but has an added advantage of rapid onset of action, no histamine release and less Laudanosine production.

In our study, the mean± SD time for onset of action for group 1 (Atracurium 0.5mg/kg) was 3.28±0.43 minutes, group 2(Cisatracurium0.1mg/kg) was 4.65±0.47 minutes and group 3 (Cisatracurium 0.15mg/kg) was 2.98±0.39 minutes. Onset of action in group 3 was rapid compared to other groups with statistical significance (p<0.05). This is in concurrence with findings of the studies of Mellinghoff *et al*. [7], Bluestein *et al*. [8] who had also reported the onset time similar to our study. Intubating conditions with Atracurium (Group 1) were excellent in 65% of the patients and good with 30% of the patients. With 2 ED 95of Cisatracurium (Group 2), intubating conditions were excellent in 30%, good in 50% and fair in 15% of the patients and with 3 ED 95 of Cisatracurium (Group 3) intubating conditions were excellent with 90% of the patients and good in 10% of the patients. Comparison between group 2 and 3 was statistically significant (p<0.05). These findings were in concurrence with El Kasaby *et al*. in which excellent intubating conditions of Cisatracurium was found in higher doses than at 2 ED 95. This study finding was also similar to the finding of Bluestein *et al*. in which he recommended intubating dose of Cisatracurium as 0.15 mg/kg. The mean and standard deviation of the duration of action of the intubating dose in Group 1 was 31±4.89 mins, group 2 was 31.1±4.11 mins and group 3 was 41±4.63 mins. The duration of action was found to be more prolonged in group 3 with a p value<0.05 which is statistically significant. Our study finding was in concurrence with study by Bluestein *et al*. [8] and El Kasaby *et al*. [9].

Infants are more sensitive to the effects of neuromuscular blockers than children. Taivanen T *et al*. studied safety and efficacy of 0.15mg/kg of Cisatracurium in children during nitrous oxide opioid anaesthesia and found that onset of action is more rapid in infants than children. Duration of action was also prolonged in infants than children. The changes in heart rate, mean arterial pressures at the different time intervals after intubation were also comparable in all the groups and had no statistical difference. This is in concurrence with the studies of Lien *et al*. [10] and Basta *et al*. [12] concluded that the mean heart rate and mean arterial pressure changes of patients receiving Cisatracurium were small and similar in

ISSN:0975 -3583,0976-2833 VOL14, ISSUE 06, 2023

patients receiving Atracurium. In their study, no patient developed decrease in blood pressure or increase in heart rate. No signs of histamine release like flushing at the site of injection, hypotension, tachycardia or erythema were noted in any of the three groups. According to Suresh S.N *et al*. [12], monitoring of neuromuscular activity of adductor pollicis using Train of four to determine the appropriate tracheal intubation time and duration is clinically more relevant than monitoring the Orbicularis oculi muscle. Patient's readiness for intubation cannot be judged by the loss of four responses of train of four stimuli monitored at adductor pollicis. This may be because of earlier blockade of laryngeal muscles than adductor pollicis. Adductor pollicis muscle is a good reflection of paralysis of upper airway muscles, especially when considering recovery.

Conclusion

Atracurium is a more effective neuromuscular blocking agent than cisatracurium at the same dose, while higher doses of cisatracurium provide efficient, more rapid onset, with longer duration of action, stable hemodynamic status with no signs of histamine release clinically. Recovery was normal in all the three groups.

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