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Original Research Article

A Study to Compare the Use of Atracurium in 2ED^{95} Dose with Cistracurium in Different Doses 2ED^{95}, 3ED^{95} and 4ED^{95} in Patients Undergoing Abdominal Surgery under General Anaesthesia in Indian Population

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Abstract:

Background: The time interval between suppression of the protective reflexes by induction of anaesthesia and the development of satisfactory intubating conditions is a critical period. Atracurium (2×ED^{95} dose) is more effective neuromuscular blocking agent than cisatracurium (2×ED^{95}) for favourable intubating condition.
Objective: To understand these differences, we compared potency and duration of action of atracurium and incremental doses of cisatracurium.
Materials and Methods: It was a prospective randomized controlled clinical trial in which 80 patients divided in four groups of 20 each undergoing abdominal surgery under general anaesthesia at our hospital. The Group-1 received 2×ED95 (0.5mg/kg) dose of atracurium, Group-2 received 2×ED95 (0.1mg/kg) dose of cisatracurium, Group-3 received 3×ED95 (0.15mg/kg) dose of cisatracurium, while Group-4 received 4×ED95 (0.2mg/kg) dose of cisatracurium. Relaxograph [NMT-MINDRA, CE0123, PN:115-018518-00, SN: CGB4C000574, Ver:1.0] was used for neuromuscular monitoring.
Results: HR, MABP was statistically significant increased post-intubation with administration of 2×ED95 dose of atracurium in Group-1 and the same dose of cisatracurium in Group-2 but 5-20 min later was not statistically significant with administration of 3×ED95 and 4×ED95 doses of cisatracurium in Groups-3 and 4, respectively. Onset time was found to be significantly lower with 2×ED95 dose of atracurium than with the same dose of cisatracurium. At the same time, higher doses of cisatracurium (3×ED95 and 4×ED95) showed onset time and longer duration of action that was significant with atracurium and with lower dose of cisatracurium (2×ED95). 4×ED95 & 3×ED95 dose of cisatracurium showed statistically significant difference versus the atracurium dose with higher percentages of patients with excellent condition of intubation 100% and 95% respectively.
Conclusion: The same dose (2×ED^{95} dose) atracurium is more effective neuromuscular blocking agent than (2×ED^{95}) cisatracurium, while higher doses of cisatracurium 3×ED$_{95}$ and 4×ED$_{95}$ provide more effective, more rapid neuromuscular blocking with longer duration of action, stable hemodynamic status, and no associated signs of histamine release clinically.

Keywords: Atracurium, Cisatracurium, ED95 Dose, Neuromuscular Monitoring.

Introduction

After the use of curare to help relax muscles in a healthy man having an appendectomy was first reported by Griffith and Johnson in Montreal in 1942, neuromuscular blocking drugs (NMBDs) have become a standard component of anaesthetic practise.

Atracurium is a nondepolarizing, intermediate-duration intravenous muscle relaxant. Ester hydrolysis and Hofmann elimination account for 90% of the drug's metabolism.[1] Hofmann elimination occurs at pH 7.4 and temperature 37.c; a drop in pH, and particularly a drop in temperature, slows this process down. ED-95 - 0.25 mg/kg [2]; 0.3-0.6 mg/kg (2×ED) for intubation; Duration: 20–40 minutes; Onset: 2-4 minutes.

The drug may cause histamine to be released. Clinical signs of the condition appear at 0.5 mg/kg (2×ED^{95}) or higher when injected quickly and large dosages administered quickly may cause bronchospasm. Laudanosine is a CNS-entering

tertiary amine that is a significant metabolite of Atracurium. Although no specific causes have been identified in humans, very large dosages of laudanosine (5–15 mg/kg) may excite the central nervous system in lab animals.

Cisatracurium is an intravenous skeletal muscle relaxant with an intermediate half-life that is nondepolarizing. Intubating dose: 0.10 mg/kg to 0.20 mg/kg (2×ED); Onset: 1.5-3 min (0.15-0.2 mg/kg in adult); Duration: 55-65 min; ED-95: 0.05 mg/kg.[3] Unlike atracurium, ciprofloxurium has no cardiovascular side effects caused by histamine.[4]

Materials and Methods

After obtaining institutional ethical committee approval and informed consent from participating patients, this study was conducted in 80 patients divided in 4 groups of 20 each undergoing abdominal surgery under general anaesthesia at hospitals attached to Govt. medical college, kota (Raj).

The study was a prospective randomized controlled clinical trial in ASA I & II patients aged between 20 & 65 years of either sex, posted for abdominal surgeries with anticipation of 1-2 hours. Patients who had any of the exclusion criteria (Patients with expected difficult intubation: pregnant or lactating women. Patients on medication known to interact with neuromuscular blocking drugs e.g. Antibiotics-aminoglycosides and tetracycline, antidepressants, anticonvulsants, antiarrhythmics - CCBs & quinidine, and $MgSO_4$) were excluded from the study.

All patients in the pre-operative area received IVs containing 40 mg of pantoprazole and 10 mg of metaclopramide one hour before to general anaesthesia. Using intravenous infusions of midazolam (2 mg) and glycopyrrolate (0.2 mg) 20 minutes beforehand, all patients underwent preoxygenation for three minutes. The patient is wearing monitoring equipment, such as a temperature probe, non-invasive blood pressure, pulse oximetry, capnography, and a three-lead ECG. For neuromuscular monitoring, use the Relaxograph [NMT-MINDRAY, CE0123, SN: CGB4C000574, Ver: 1.0]. To prevent hypothermia, the hand, wrist and partially of the forearm are covered with crepe bandages. The parameter that was employed for the pharmacodynamic measurements was the first response (T1) of the train of four (TOF) stimulation. Induced general anaesthesia using fentanyl (1–1.5 μg/kg) and a gradual intravenous injection of propofol (2 mg/kg).

With oxygen and assisted ventilation, isoflurane (1%–1.5%) was used to maintain anaesthesia. After determining the control values, neuromuscular monitoring was performed every 20 seconds to stimulate the ulnar nerve using surface electrodes at a supramaximal stimulation of 70 mA from a relaxograph (2 Hz/0.5 s; pulse width 0.2 ms). Patients received the muscle relaxant in accordance with their needs after stable baseline duration of at least five minutes. Group 1(n=20) Atr2×ED^{95} (0.5mg/kg); Group 2(n=20) Cisatr2×ED^{95} (0.1 mg/kg); Group 3 (n=20); Cisatr3×ED^{95} (0.15 mg/kg); Group 4 (n=20) Cisatr4×ED^{95} (0.2 mg/kg) IV within 5-10 s. After 2 min, intubation was attempted using proper size tube and the condition of intubation assessed and recorded according to the following [5]:

Excellent: Easy passage of the tube without coughing. Vocal cords relaxed & abducted.

Good: Passage of the tube with slight coughing and/or bucking. Vocal cords relaxed and abducted.

Poor: Passage of tubes with moderate coughing and/or bucking vocal cords moderately adducted.

Not possible: Vocal cords not relaxed, tightly adducted

The time gap between the end of the muscle relaxant injection and the maximum inhibition of T1% is known as the onset time. In order to achieve a 25% recovery of responsiveness to T1%, study medication increments were administered during maintenance. To prolong the surgery, an incremental dose of 25% of the initial dose was administered. The ventilator (CMV), which regulates end tidal CO2 at (30–35 mmHg), controls ventilation. Following induction, neuromuscular blockade was seen and recorded every five minutes as well as whenever a supramaximal train-of-four (TOF) stimulus was used to give a muscle relaxant dosage increment.

Duration of the muscle relaxant: Time from the end of injection of the drug until 25% recovery of T1% was recorded. The patient's skin was observed for any clinical indications of histamine release, such as flushing (if the redness persisted for more than 120 seconds), erythema, or wheals, as well as any hemodynamic abnormalities or bronchospasm. The monitor showed all intraoperative hemodynamic changes, such as heart rate (HR), mean arterial blood pressure (MABP), oxygen saturation (SO2), and end-tidal CO2, constantly.

Body temperature is kept between 35 to 37°C with the use of warming blankets and IV fluids. Every study-related parameter is recorded on a proforma. At the conclusion of skin closure, the inhalation agent was ceased.

Reversal of anesthesia: At the end of operation with 25% recovery of T1%, reversal (induced recovery) achieved by administration of 2.5 mg

neostigmine: 0.5mg Glycopyrrolate slow IV injection.

Recovery characteristics: Like Tongue protrusion, head lifting >5Seconds, orientation and, TOF >0.9 were sufficient for safe extubation.

Statistical Methods

Data were processed using SPSS version 15. Quantitative data were expressed as mean ± SD while qualitative data were expressed as numbers and percentages (%). Student t test and ANOVA test were 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

The studied patients were matched regarding age and sex with no statistically significant difference being recorded regarding age sex, weight and duration of surgery [Table 1].

There was a statistically significant increase in HR, MABP post intubation when compared to baseline and post injection of 2×ED95 dose of atracurium in group 1 and the same dose of cisatracurium in group 2. HR, MABP changes 5-20 minutes later were not statistically significant with administration of 3×ED95 and 4×ED95 doses of cisatracurium in groups 3 and 4, respectively [Tables 2 and 3].

Table 1: Demographic characteristics of the studied patients

		Atracurium group 2×ED95	Cisatracurium group 2×ED95	Cisatracurium group 3×ED95	Cisatracurium group 4×ED95	P value
Age (Mean± SD)		43.25±6.50	45.05±7.67	45.7±8.94	44.3±9.48	P>0.05 NS
Sex	Male	12	10	10	7	
	Female	8	10	10	13	

NS- No statistically significant difference

Table 2: Heart rate changes before & after administration of atra or cisatra

Heart rate/min Mean±SD	Group-1 Atracurium 2×ED95	Group-2 Cisatracurium 2×ED95	Group-3 Cisatracurium 3×ED95	Group-4 Cisatracurium 4×ED95
HR basal	74±3.24	76.2±4.38	75.65±4.34	78.7±3.83
HR after muscle relaxant	78.35±3.34	76.8±4.05	74.3±3.34	80.7±3.81
HR after intubation	88.4±5.37*	89.05±2.98*	82.95±3.72	81.75±3.58
HR at 5 min	83.8±4.45	84.2±2.8	76.05±3.22	78.05±3.94
HR at 10 min	76.75±3.54	78.25±4.26	74.3±3.58	77.65±3.91
HR at 15 min	74.1±3.37	75.85±4.43	75.5±3.5	77.4±3.72
HR at 20 min	73.65±3.44	76.15±3.82	75.15±3.13	76.4±3.95

*Statistically significant difference versus baseline reading (p-value < 0.05)

The study revealed that the time onset of atracurium at 2×ed95 was substantially less than that of cisatracurium at the same dose. Simultaneously, lower dosages of cisatracurium (2×ed95) and higher doses of cisatracurium (3×ed95 and 4×ed95) had a much shorter onset time than atracurium. In terms of duration of effect, greater doses of atracurium (2×ed95) and cisatracurium (3×ed95 and 4×ed95) demonstrated a statistically significant longer duration of action compared to lower doses of both. [table 4].

The only cisatracurium dose that was statistically significant was 4×ed95, as compared to an atracurium dose that had a higher percentage of patients with excellent intubation conditions. The cisatracurium dosages of 3×ed95 and 4×ed95 were shown to be significantly superior to the 2×ed95 dose. Only two patients (10%) in group 1 and three patients (15%) in group 2 had non-intubating circumstances. In terms of vocal cord assessment, 2×ed95 of atracurium was superior to 2×ed95 of cisatracurium; 3×ed95 and 4×ed95 of cisatracurium were comparable; however, 4×ed95 of cisatracurium was significantly superior to both 2×ed95 and atracurium [table 5]. While histamine release was observed with atracurium (one patient in group 1 had facial flushing and one patient had erythema), no symptoms of histamine release were observed with any dosage of cisatracurium. In terms of recuperation time, no statistically significant variation was seen.

Table 3: mean arterial blood pressure changes before & after administration of atra or cisatra

MAP (In mm of Hg) Mean ± SD	Group-1 Atracurium 2×ED95	Group-2 Cisatracurium 2×ED95	Group-3 Cisatracurium 3×ED95	Group-4 Cisatracurium 4×ED95
MAP basal	83.6±3.13	86.3±4.21	86.85±3.98	85.25±4.7
MAP after muscle relaxant	84.5±3.68	85.1±4.45	85.9±3.43	87.1±4.61
MAP after intubation	94.2±7.55*	97.3±3.92*	90.4±4.31	88.35±4.46
MAP at 5 min	91.95±4.97	93.75±4.41	87.4±3.99	86.2±4.42
MAP at 10 min	84.05±2.84	87.05±4.39	87.1±3.81	85.6±3.98
MAP at 15 min	83.1±2.79	85.45±3.98	85.75±3.52	84.9±3.57
MAP at 20 min	82.05±2.58	84.5±3.58	85.2±3.32	85.15±3.38

Statistically significant difference versus Baseline recordings ($p<0.05$)

Discussion

The hemodynamic status (heart rate, blood pressure), onset time, duration of effect, clinical symptoms of histamine release, state of intubations, and vocal cord assessment were evaluated for each patient. The age and sex of the patients in each of the four study groups was matched. Due to stress intubation and partially tense patients, there was a statistically significant increase in HR and MABP 120 s after the muscle relaxant injection compared to baseline and post injection of 2×ED95 dose of atracurium in group 1 and the same dose of cisatracurium in group 2. Nevertheless, after receiving 3×ED95 and 4×ED95 doses of cisatracurium in groups 3 and 4, respectively, increases in HR and MABP did not reach statistical significance 5–20 minutes later.

Table 4: Neuromuscular blockade after administration of atra & cisatra

	Onset time (Time to maximum suppression of T1%) (min)	Duration of action (25% recovery T1%) (min)
Group-1Atracurium 2×ED95	3.2±0.58	44.4±2.52
Group-2 Cisatracurium 2×ED95	4.65±0.59*	43.25±2.27
Group-3 Cisatracurium 3×ED95	2.85±0.49#	55.6±3.95*#
Group-4 Cisatracurium 4×ED95	2.15±0.37*#	65.45±6.62*#

* Statistically significant difference versus 2×ED95 dose of atracurium (P-value < 0.05); # statistically Significant difference versus 2×ED95 dose of cisatracurium (P-value < 0.05)

According to Lien et al[4] and Basta et al[2], patients receiving cisatracurium experienced little changes in their maximal MABP and HR, which were comparable to those seen in patients receiving twice the ED95 of atracurium.

No patient in his study experienced a heart rate spike or drop of more than 20% that could be linked to the use of muscle relaxants. Following the delivery of atracurium, two patients in this trial displayed signs of histamine release in the form of a brief facial flushing erythema; nevertheless, these patients did not exhibit hypotension or tachycardia.

The length of the muscle relaxant's activity was defined as the period from the disappearance of TOF stimulation to 25% recovery of T1, and the onset time was defined as the interval from the end of the muscle relaxant injection till the commencement of the peak suppression of T1.

Compared to the equivalent dose of cisatracurium (2×ED95), the atracurium dose (2×ED95) exhibited a statistically significant faster onset of action. However, it was discovered that cisatracurium at larger dosages (3×ED95 and 4×ED95) had a statistically significant longer duration of action and quicker start than the 2×ED95 dose of atracurium and cisatracurium. Mellinghoff H et al[6]. (1996) discovered that the onset times for cisatracurium (0.1 mg/kg) and atracurium (0.5 mg/kg) were 3.1±1.0 min and 2.3±1.1 min, respectively.

This was fairly close to the current outcome. According to Bluestein LS et al [7], the mean time of start fell from 4.6 to 3.4 and 2.8 minutes, respectively, with an increase in the dose of cistracurium from 0.1 to 0.15 and 0.2 mg/kg. This was pretty much the current outcome. In a 2010 study by M.EI-Kasaby et al [8], the study found that the same dose of cisatracurium (4.37±0.46 min) considerably increased Onset time, whereas the atracurium dose of 2×ED95 decreased it to 3.24±0.55 min.

In addition, the onset time and longer duration of action of larger doses of cisatracurium (4×ED95 and 6×ED95) (2.9±1.4 min and 2±1.2 min) were considerably lower than those of atracurium and lower doses of cisatracurium (2×ED95). This was pretty much the current outcome.

Table 5: Intubating Conditions Of Patients

		Group-1	Group-2	Group-3	Group-4
Intubating condition N%	Excellent	6(30)	1(5)	10(50) $	18(90)*$
	Good	10(50)	6(30)	9(45)	2(10)
	Poor	2(10)	10(50)	1(5)	0(0)
	Not possible	2(10)	3(15)	0(0)	0(0)
Vocal cord assessment	Open	5	1	9	16*$
	Abducted	11	6	10	4
	Adducted	4	13	1	0

*Statistically significant difference versus 2×ED95 dose of atracurium (P-value < 0.05); $ statistically significant difference versus 2×ED95 dose of cisatracurium (P-value < 0.05); Figures in parenthesis are in percentage.

The longest group 4 in our study had an action time of 65.45± 6.62 minutes, while group 1 had an action duration of 44.4±2.52 minutes, group 2 had an action duration of 43.25±2.27 minutes, and group 3 had an action duration of 55.6±3.95. For each of the four groups, there was a statistically significant difference.

According to a 2010 study by M.EI-Kasaby et al[8], the mean clinical duration of action was observed to be substantially less than that of atracurium and cisatracurium at a lower dose (2×ED95). The study findings indicate that the clinical durations were 44.4±4.13 min, 43.6±4.15 min, and 65.5±10.5 min for atracurium doses of 0.5 mg/kg, 0.1 mg/kg, and 0.2 mg/kg, respectively. This was pretty much the current outcome.

In Our Investigation, The Quality of Intubation Was Found to Be So Good That Only A 4×ed95 Dose Of Cisatracurium Exhibited A Statistically Significant Difference From The Atracurium Dose. The Cisatracurium Dosages Of 3×ed95 And 4×ed95 were Shown To Be Significantly Superior To The 2×ed95 Dose. Vocal Cord Evaluation, 2×ed95 Atracurium Dose, And 2×ed95 Cisatracurium Dose Were Comparable; However, 3×ed95 and 4×ed95 Cisatracurium Doses Were Considerably Superior To Both Atracurium And 2×ed95 Cisatracurium Dose. Among The Groups under Study, There Were Three Instances of Intubation Being Impossible with A 2×ed95 Dose of Cisatracurium and Two Cases with A 2×ed95 Dose Of Atracurium.

Compared to the same dose of atracurium (10%), there were 10 cases (50%) with poor intubating conditions involving a 2×ED95 dose of cisatracurium and 1 case (5%) with a 3×ED95 dose of cisatracurium. These findings are statistically significant (P-value <0.05). 80% of patients with a 2×ED95 dose of atracurium had good to excellent intubating conditions, compared to only 35% of cases with the same dose of cisatracurium. This indicates that the assessment of vocal cords with the 2×ED95 dose of cisatracurium and the 2×ED95 dose of atracurium differed. In contrast, atracurium and the 2×ED95 dose of cisatracurium performed considerably worse than the 3×ED95 (95% excellent to good intubating settings) and 4×ED95 (100% excellent to good intubating conditions) doses of cisatracurium.

Over 90% of patients in all treatment groups had satisfactory or outstanding intubation circumstances, according to Bluestein et al[7].'s 1996 report. (2 min after approximately 2×ED95 doses of cisatracurium or atracurium and 1.5 min after 3× and 4×ED95 doses of cisatracurium). This was pretty much the current outcome.

In order to determine the lowest dose of cisatracurium that may be administered under general anaesthesia and yet produce excellent to good intubating circumstances, Mandal9 studied 60 adult patients of both sexes who had physical statuses of ASA grade I or 11. Based on the patients' prescribed dosage, three groups of patients were formed. Group I (n = 20) received 0.15 mg/kg, Group II (n = 20) received 0.20 mg/kg, and Group III (n = 20) received 0.25 mg/kg of cisatracurium following the normal procedure for inducing anaesthesia.

Patients were then separated into six subgroups based on whether laryngoscopy and intubation were attempted at 75 or 90 seconds for each group. Subgroups "a" and "b" represent the 75- and 90-second procedures, respectively. The degree of coughing, the location or movement of the vocal cords, and the ease of laryngoscopy were assessed in order to grade the intubating conditions. Only patients in group IIb (0.20 mg/kg at 90 s) and both subgroups (0.25 mg/kg at 7 5 s and 90 s) of group III patients were able to get excellent to good intubating circumstances.

M.T. Carroll et al10] conducted research on intubation circumstances after cisatracurium (2, 3 or 4 times ED95) was administered. In their investigations, almost all patients achieved satisfactory to excellent intubation circumstances in less than two minutes with a dosage of cisatracurium 0.15 mg/kg. In around 50% of patients, a 0.1 mg/kg dose of cisatracurium resulted in adequate intubation circumstances in the same amount of time. Their results support previous research and demonstrate the improvement in

intubation conditions brought about by raising the cisatracurium dosage to 0.15 mg/kg. They recommended waiting little over two minutes to achieve uniformly satisfactory intubation circumstances. This was pretty much the current outcome. In the current investigation, two patients with a 2×ED95 dose of atracurium (one patient with erythema and one with transient facial flushing) exhibited cutaneous manifestation; however, no case with cisatracurium was reported. The hemodynamic parameters (MAP and HR) did not significantly change in this investigation following the administration of a muscle relaxant. Hughes R et al[1].'s 1981 study showed that circulatory depression and hypotension were likely caused by histamine release. Bradycardia and hypotension were also evident following supramaximal dosages of 4 mg/kg i.v. One subject in Lien CA et al[4].'s trial experienced brief face flushing following atracurium injection. 51W89 is a nondepolarizing muscle relaxant of the benzylisoquinolinium type that has no effect on plasma histamine level. In healthy individuals undergoing elective surgical procedures, rapid injection of dosages up to and including 8 times its ED95 (0.4 mg.kg-1) did not cause cutaneous flushing or clinically significant cardiovascular effects. This match is almost complete. Based on this study, we can say that atracurium at the same dose (2×ED95) is a more effective neuromuscular blocking agent than cisatracurium at the same dose (2×ED95). On the other hand, higher doses of cisatracurium (3×ED95 and 4×ED95) result in more rapid and effective neuromuscular blocking with a longer duration of action, stable hemodynamic status, and no clinically significant signs of histamine release.

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