Section: Anaesthesia

Original Research Article

A COMPARATIVE STUDY OF THE NEUROMUSCULAR BLOCKING EFFECT OF SINGLE BOLUS DOSE OF CIS-ATRACURIUM & ATRACURIUM UTILISING TRAIN OF FOUR MONITORING

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Received : 08/01/2023
Received in revised form : 05/02/2023
Accepted : 17/02/2023

Keywords:
Neuromuscular Blocking, Cis-atracurium & Atracurium.

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DOI: 10.47009/jamp.2023.5.3.98

Source of Support: Nil,
Conflict of Interest: None declared

Int J Acad Med Pharm
2023; 5 (3); 455-460

Abstract

Background: Objective of this study to determine the difference in Train of Four activity (onset and duration of action) between single bolus dose of Cis-atracurium (2 x ED95) and Atracurium (2 x ED95), and to determine the difference of intubating condition, hemodynamic effects and signs of histamine release between single bolus dose of Cis- atracurium (2 x ED95) and Atracurium (2 x ED95). **Materials and Methods:** A Randomised Controlled trial was performed in the department of anaesthesiology, Darbhanga Medical College and hospital, darbhanga, Bihar from March 2021 to December 2022 to detect the difference in TOF activity between Atracurium and Cis-atrcurium. Permission of the Hospital Ethical Committee was obtained before proceeding for the study. The patients are divided into 2 groups of 40 each. Group A will receive single dose of 0.5mg/kg of atracurium of while single dose of o.15mg/kg of cis-atracurium was given to group B. **Result:** We found that association of age in years vs. group was not statistically significant (p=0.5499). It was found that In group-A (A), 20(50.0%) patients had female and 20(50.0%) patients had male. In group-B (C), 17(42.5%) patients had female and 23(57.5%) patients had male. Association of sex vs. group was not statistically significant (p=0.5011). It was found that in group-A (A), 23(57.5%) patients had ASA 1 and 17(42.5%) patients had ASA II. In group-B (C), 17(35.0%) patients had ASA 1 and 26(65.0%) patients had ASA II. Association of ASA vs. group was statistically significant (p=0.0435). It was found that in association of Co morbidity vs. group was not statistically significant (p=0.1044). **Conclusion:** This study showed no significant difference between the onset of action of Cis atracurium and Atracurium at equipotent doses. However, duration of action of Cis-atracurium was significantly longer than equipotent doses of atracurium.

INTRODUCTION

Atracurium besylate and cis-atracurium are related nondepolarizing neuromuscular blocking agents used to provide skeletal muscle relaxation during surgery or mechanical ventilation.

Cis-atracurium is a bis benzyl tetrahydroisoquinoline that has effect as a neuromuscular-blocking drug or skeletal muscle relaxant in the category of non-depolarizing neuromuscular-blocking drugs, used adjunctively in anaesthesia to facilitate endotracheal intubation and to provide skeletal muscle relaxation during surgery or mechanical ventilation.[1] Cis-atracurium is one of the ten isomers of the parent molecule, atracurium.

Methods for estimating the degree of neuromuscular block include valuation of muscular response to stimuli from surface electrodes, such as in the train-of-four test, wherein four successive stimuli are delivered at 2 HZ. At this frequency, the immediately available store of acetylcholine is depleted and the amount released by the nerve decreases with each successive stimulus until the fifth or sixth when it levels off.[2] Even this lesser amount of neurotransmitter is enough to elicit contraction of normal muscle because of the wide

ISSN (O): 2687-5365; ISSN (P): 2753-6556

margin of safety of neuromuscular transmission. In the presence of non-depolarizing relaxants, the margin of safety is decreased such that some end plates fail to develop propagated action potentials.[3] With increasing degrees of block, the twitches in train of four progressively fade starting with the fourth and one by one eventually disappear. The ratio of the height of the fourth response to the first has been defined as the train of four ratios. In the absence of non-depolarizing block, the T4/T1 ratio is approximately one. There is a fair relationship between single twitch depression and train of four responses. During depolarizing neuromuscular.[4,5]
Blockade the train of four does not fade significantly. The height of all the four twitches decreases simultaneously.
Use of peripheral nerve stimulator to monitor effect of NMBA by train of four activity in operating room, is gaining popularity due to ease of use, better monitoring and reduction of NMBA doses during surgery.
Neuromuscular blocking agents (NMBAs) are often used in association with adequate analgesia and sedation for the following conditions: management and facilitation of mechanical ventilation (MV), management of elevated intracranial or intraabdominal pressure, treatment of muscle spasms, and reduction in oxygen consumption. Recently, NMBAs became common intravenous medications used within the intensive care unit (ICU) since one study. Enhanced the role of NMBAs when they found a beneficial effect of a neuromuscular blockade on the mortality in acute respiratory distress syndrome (ARDS). The previous recommendations of the American and French critical care societies for sustained neuromuscular blockade are of C grade for indications and of B grade for monitoring.[4] In the clinical practice guidelines for sustained neuromuscular blockade in the adult critically ill patient published in 2016, NMBAs are suggested in ARDS patients with a ratio PaO2/FiO2 less than 150 (weak recommendation) but no dosage is mentioned.[5] The most commonly used tool is the train of four (TOF), and previous recommendations suggest dosing titration of NMBAs to one or two visualized muscle twitches.[6] Of note, in the study of one study, PNS was not permitted and in the 2016 practice guidelines no TOF objective is recommended. North American surveys.[6]
In critically ill patients, the duration of neuromuscular blockade is longer, sepsis and/or shock is often present, and pharmacokinetic is difficult to predict. Lastly, agreement between subjective and objective means of assessing the degree of neuromuscular blockade has been little studied in ICU.[7-9]

Aims and Objectives

Primary Objective

- To determine the difference in Train of Four activity (onset and duration of action) between single bolus dose of Cis- atracurium (2 x ED95) and Atracurium (2 x ED95).

Secondary Objective

- To determine the difference of intubating condition, hemodynamic effects and signs of histamine release between single bolus dose of Cis- atracurium (2 x ED95) and Atracurium (2 x ED95).

MATERIALS AND METHODS

A Randomised Controlled trial was performed in the department of anaesthesiology, Darbhanga Medical College and hospital, darbhanga, Bihar from March 2021 to December 2022 to detect the difference in TOF activity between Atracurium and Cisatrcurium. Permission of the Hospital Ethical Committee was obtained before proceeding for the study. The patients are divided into 2 groups of 40 each. Group A will receive single dose of 0.5mg/kg of atracurium of while single dose of o.15mg/kg of cisatracurium was given to group B.

Inclusion Criteria

- Patients of either sex.
- ASA grade I and II.
- Age between 18 to 65 years.
- Body weight between 45 to 85 kgs.

Exclusion Criteria

- Patients who have not given consent.
- Patients other than ASA 1 & 2

Every patient will undergo pre-anaesthetic check-up where detailed history were taken, initial pre-operative counselling and reassurance was given to gain their confidence. The nature of procedure was explained. Patients were physically examined and relevant routine and special investigations carried out. All patients were given 2 mcg/kg of Inj Fentanyl in pre-medication and induced with 2 mg/kg of Inj. Propofol IV.
Ulnar nerve at wrist of non-dominant hand is stimulated. Arm is to be extended with palm facing up. The 2 electrodes are placed over the path of the ulnar nerve. The distal electrode is 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 should be placed 1-2 cm proximal to the first, parallel to the flexor carpi ulnaris tendon. The negative (black) lead wire is attached to the distal electrode and the positive (red) lead wire is attached to the proximal. The expected response is to see the thumb twitching. Four successive stimuli are delivered at 2 Hz (every 0.5 sec) frequency and30 mA current (supramaximal current strength). Twitching of adductor pollicis was clinically visible and the ratio of the fourth to first response were given automatically by the stimulator. Before giving neuromuscular blocking agent, a control response of the patient was obtained after induction of anesthesia on the non-dominant hand by single stimulation of the ulnar nerve by the peripheral

ISSN (O): 2687-5365; ISSN (P): 2753-6556

nerve stimulator by 30 mA current at 2 Hz frequency

Patients was monitored for any signs of histamine release clinically through skin changes graded as flush (if redness lasts> 120 s), erythema, or wheals and presence of any hemodynamic changes or bronchospasm.

Intra-operative hemodynamic changes was continuously displayed and recorded on the monitor including: heart rate (HR), mean arterial blood pressure (MABP) every 5 min, oxygen saturation (SO2), and end tidal CO2.

Statistical Analysis:

For statistical analysis data were entered into a Microsoft excel spreadsheet and then analyzed by SPSS (version 25.0; SPSS Inc., Chicago, IL, USA) and Graph Pad Prism version 5. Data had been summarized as mean and standard deviation for numerical variables and count and percentages for categorical variables. Two-sample t-tests for a difference in mean involved independent samples or unpaired samples. Paired t-tests were a

Form of blocking and had greater power than unpaired tests. One-way analysis of variance (one-way ANOVA) was a technique used to compare means of three or more samples for numerical data (using the F distribution). P-value $\leq$ 0.05 was considered for statistically significant.

RESULTS

Table 1: Distribution of mean Duration of surgery (min) vs Group

		Number	Mean	SD	Minimum	Maximum	Median	P-value
Duration of surgery (min)	Group-A (A)	40	99.8000	63.9716	25.0000	29.0000	80.0000	0.6238
	Group-B (C)	40	106.4000	55.6107	45.0000	280.0000	90.0000	

In group-A (A), the mean onset of neuromuscular blocking effect (mean± s.d.) of patients was 3.1075 ± .1803 min. In group-B (C), the mean onset of neuromuscular blocking effect (mean± s.d.) of patients was 3.1200 ± .1937 min. Distribution of mean onset of neuromuscular blocking effect vs. group was not statistically significant (p=0.7660).

Table 2: Distribution of mean Duration of neuromuscular blocking effect in Min vs Group

		Number	Mean	SD	Minimum	Maximum	Median	P-value
Onset of neuromuscular blocking effect in Min	Group-A (A)	40	3.1075	0.1803	2.8000	3.5000	3.0000	0.7660
	Group-B (C)	40	3.1200	0.1937	2.7000	3.5000	3.1000	

In group-A (A), the mean onset of neuromuscular blocking effect (mean± s.d.) of patients was 3.1075 ± .1803 min. In group-B (C), the mean onset of neuromuscular blocking effect (mean± s.d.) of patients was 3.1200 ± .1937 min. Distribution of mean onset of neuromuscular blocking effect vs. group was not statistically significant (p=0.7660).

Table 3: Distribution of mean Duration of neuromuscular blocking effect in Min vs Group.

		Number	Mean	SD	Minimum	Maximum	Median	p-value
Duration of neuromuscular blocking effect in Min	Group-A (A)	40	34.7000	3.5820	30.0000	50.0000	35.0000	<0.001
	Group-B (C)	40	58.3250	5.0403	45.0000	69.0000	60.0000	

In group-A (A), the mean duration of neuromuscular blocking effect (mean± s.d.) of patients was 34.7000 ± 3.5820 min. In group-B (C), the mean duration of neuromuscular blocking effect (mean± s.d.) of patients was 58.3250 ± 5.0403 min. Distribution of mean duration of neuromuscular blocking effect vs. group was statistically significant (p<0.001).

DISCUSSION

Kwon SY et al found that neuromuscular block was monitored by train-of-four (TOF) electromyography, and the times taken to reach TOF 0 and TOF ratio (TOFR) 25% were recorded. The times taken to reach TOF 0 and TOFR 25% were significantly higher in Groups R 0.5 and R 1.0 than in Group S.[10]

In a study by Carroll MT et al,[11] found that the onset and recovery of block were also measured. Train-of-four fade during onset of block was greater with the lower dose of cis-atracurium compared with the higher dose of cis-atracurium and all other relaxants. Train-of-four fade during recovery was similar. The median times (and ranges) for the onset of maximum block were 3.4 (2.1-5.6), 1.5 (1.2-2.3), 2.1 (1.2-2.6), 2.0 (1.5-2.7) and 1.0 (0.7-1.3) min for cis-atracurium 0.1 mg.kg-1 and atracurium, mivacurium, vecuronium and rocuronium, respectively. The median times (and ranges) for the recovery of T1 to 25% of control and to a train-of-four ratio of 0.8 were 41 (21-50) and 65 (40-78); 43 (37-54) and 69 (58-79); 15 (11-20) and 25 (19-30); 31 (23-46) and 60 (45-117); and 33 (18-57) and 50 (28- 76) min following cis-atracurium, 0.1 mg.kg-1, atracurium, mivacurium, vecuronium and rocuronium, respectively.

ISSN (O): 2687-5365; ISSN (P): 2753-6556

Voss J et al,[12] found that the onset time (T1 = 5%), duration of effect (T1 = 25%), recovery index (T1 = 25%-75%) and the recovery time at a train-of-four-ratio (T4/T1) of 0.7. These parameters did not show any significant differences between both groups: onset time: 3.1 +/- 1.5 min in atracurium versus 3.4 +/- 1.1 min in cis atracurium, duration of effect: 34.1 +/- 5.5 min in atracurium versus 34.1 +/- 6.5 min in cis atracurium, recovery index: 9.3 +/- 3.3 min in atracurium versus 9.6 +/- 2.5 min in cis atracurium, recovery time at a TOF-ratio of 0.7:49.3 +/- 8.4 min in atracurium versus 52.3 +/- 6.6 min in cis atracurium.

We found that association of age in years vs. group was not statistically significant (p=0.5499). It was found that in group-A (A), 20(50.0%) patients had female and 20(50.0%) patients had male. In group-B (C), 17(42.5%) patients had female and 23(57.5%) patients had male. Association of sex vs. group was not statistically significant (p=0.5011). It was found that in group-A (A), 23(57.5%) patients had ASA 1 and 17(42.5%) patients had ASA II. In group-B (C), 17(35.0%) patients had ASA 1 and 26(65.0%) patients had ASA II. Association of ASA vs. group was statistically significant (p=0.0435). It was found that in association of Co morbidity vs. group was not statistically significant (p=0.1044).

Association of intubating condition vs. group was not statistically significant (p=0.2926). Hemmerling TM et al 48 (2008) found that Nondepolarising neuromuscular blocking drugs for cardiac surgery should therefore be easy to titrate, of rapid onset and short duration of action with a pathway of elimination independent from hepatic or renal dysfunction, and should equally not affect haemodynamic stability.

Bellini L et al,[13] found that permissive hypercapnia increased the duration of the atracurium effect and caused an increase in the intensity of the neuromuscular block in few swine.

Moore L et al,[14] found that Eighteen subjects (24%) were treated with atracurium, whereas 58 (76%) were treated with cis-atracurium. Equivalent dosages of sedation and analgesia as well as use of brain function monitoring technology were similar between both 93 groups. There were no differences in clinical outcomes. Specifically, improvement of PaO2/FIO2 was a median in the atracurium group and 66 in the cis-atracurium group (P = .65). Ventilator-free days at day 28 were 13 d in the atracurium and cis-atracurium groups, respectively (P = .72). ICU length or stay was 18 d (IQR 8–34 d) in the atracurium group and 15 d (IQR 9–22 d) in the cis-atracurium group (P = .34). In-hospital mortality was 50% for the atracurium population and 62% for the cis-atracurium group (P = .42).

El-Kasaby AM et al,[15] found that cis-atracurium in clinical practice is devoid of histamine-induced cardiovascular effects. On the other hand, 2 ED95 doses of cis-atracurium (100 µ g/kg) do not create satisfactory intubating conditions such as those seen with equipotent doses of atracurium. The recommended intubating dose of cis-atracurium is 3 ED95. HR, MABP was statistically significant increased post-intubation with administration of 2×ED95 dose of atracurium in group 1 and the same dose of cis-atracurium in group 2 but 5-20 min later was not statistically significant with administration of 4×ED95 and 6×ED95 doses of cis-atracurium 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. Higher doses of cis-atracurium (4×ED95 and 6×ED95) showed onset time and longer duration of action that was significantly lower than with atracurium and with lower dose of cis-atracurium (2×ED95). Only 6×ED95 dose of cis-atracurium showed statistically significant difference versus the atracurium dose with higher percentages of patients with excellent condition of intubation. 4×ED95 and 6×ED95 doses of cis-atracurium were significantly better than 2×ED95 dose of cis-atracurium. 2×ED95 dose of atracurium and 2×ED95 dose of cisatracurium were similar, while 4×ED95and 6×ED95 doses of cisatracurium were significantly better than atracurium and 2×ED95 dose of cisatracurium. The same dose (2×ED95 dose) atracurium is more effective neuromuscular blocking agent than cisatracurium, while higher doses of cisatracurium 4×ED95 and 6×ED95 provide more 94 effective, more rapid neuromuscular blocking with longer duration of action, stable hemodynamic status, and no associated signs of histamine release clinically.

We found that distribution of mean age vs. group was not statistically significant (p=0.8865). Distribution of mean weight vs. group was not statistically significant (p=0.7190). Distribution of mean duration of surgery vs. group was not statistically significant (p=0.6238). Distribution of mean onset of neuromuscular blocking effect vs. group was not statistically significant (p=0.7660).

In group-A (A), the mean duration of neuromuscular blocking effect (mean± s.d.) of patients was 34.7000 ± 3.5820 min. In group-B (C), the mean duration of neuromuscular blocking effect (mean± s.d.) of patients was 58.3250 ± 5.0403 min. Distribution of mean duration of neuromuscular blocking effect vs. group was statistically significant (p<0.001).

Lee LA et al,[16] found that pharmacokinetics and pharmacodynamics of neuromuscular blockade that may be altered in the elderly. Compartment distribution, metabolism, and excretion of drugs may vary due to age-related changes in physiology, altering the duration of action with a need for reduced dosage (eg, aminosteroids). Other drugs (atracurium, cisatracurium) have more reliable duration of action and should perhaps be considered for use in the elderly. The range of interpatient variability that neuromuscular blocking drugs may exhibit is then considered and drugs with a narrower range, such as cisatracurium, may produce more predictable, and inherently safer, outcomes. Ultimately, appropriate neuromuscular monitoring

ISSN (O): 2687-5365; ISSN (P): 2753-6556

should be used to guide the administration of muscle relaxants so that the risk of residual neuromuscular blockade postoperatively can be minimized. The reliability of various monitoring is considered.

Murphy GS et al,[17] found that the adductor pollicis is more sensitive to the effects of neuromuscular blocking agents (compared to the muscles surrounding the eye), and monitoring at this site may more accurately reflect recovery of pharyngeal muscles (the last muscles to recover from the effects of neuromuscular blocking agents, in which dysfunction may persist even at a TOF ratio of 1.0). Quantitative monitors are devices that measure and quantify the degree of muscle weakness and display the results numerically. Several different technologies have been developed, including mechanomyography, electromyography, acceleromyography, kineograph, and phonomyography. Lower doses of anticholinesterases may be used to effectively reverse neuromuscular blockade at TOF ratios of 0.4-0.6; quantitative monitoring is required to determine that this level of neuromuscular recovery has occurred. As clinical tests of muscle strength, peripheral nerve stimulators are unable to determine whether full recovery of neuromuscular function is present at the end of the surgical procedure.

Park WY et al,[18] found that there were no significant demographic differences between groups. Group L had a longer duration to onset (mean±standard deviation, 399.3±147.8 seconds) and shorter duration 25% (39.4±6.8 minutes) compared to Group I (212.8±56.0 s and 51.3±8.47 minutes, respectively) and Group S (230.7±60.6 s and 47.9±10.7 minutes, respectively). There were no other significant differences between groups. Our findings contribute to determining clinically effective combinations of rocuronium and cisatracurium, as well as to predicting the pharmacokinetic characteristics of the synergistic effects. They suggest that reducing doses of both drugs by approximately 10% of their respective ED95 values is sufficient to maintain neuromuscular relaxation during minor surgery.

Correa CM et al,[19] found that since atracurium can cause hypotension in humans, the hemodynamic effects of atracurium and cisatracurium as well as the hemodynamic protection. Doses of 4 mg.kg-1 of atracurium and cisatracurium decreased MAP to 62.8 ± 97 4.5% and 82.5 ± 2.3% respectively when compared to control levels. The effects on systolic and diastolic blood pressure were reflected in the levels of MAP. The isolated administration of diphenhydramine and cimetidine did not prevent the reduction in mean arterial pressure induced by atracurium. However, the association of both drugs was able to prevent the hemodynamic effects of atracurium. The doses of cisatracurium used in this study did not cause a reduction in blood pressure significant enough to justify the use of the preventive measures used in the atracurium groups.

Jellish WS et al,[20] found that Clinical duration was shorter for rocuronium compared with cisatracurium using either anesthetic. Cisatracurium T 1 75% recovery after the infusion was shorter with propofol compared with isoflurane. Cisatracurium TOF 75% recovery was similar after either bolus or infusion, but rocuronium TOF 75% recovery after the infusion was delayed. Infusion rates decreased for cisatracurium but remained relatively constant for rocuronium regardless of the anesthetic used. Isoflurane enhances the effect of both muscle relaxants but prolonged cisatracurium recovery more than rocuronium.

In a study by Mellinghoff H et al,[21,22] found that neuromuscular transmission was assessed by recording the mechanical twitch response to train-of-four nerve stimulation. Onset times were 3.1 +/- 1.0 min with cisatracurium and 2.3 +/- 1.1 min with atracurium which was statistically significant. The infusion rates for a 95% +/- 4% neuromuscular block was 1.5 +/- 0.4 micrograms.kg-1.min-1 for cisatracurium and 6.6 +/- 1.7 micrograms.kg1.min-1 for atracurium, 3.3 times those of cisatracurium when referenced to the active cations. After the infusion, the spontaneous recovery intervals 25%-75% of 18 +/- 11 min and 18 +/- 8 min for cisatracurium and atracurium (P = 0.896) were shortened to 5 +/- 2 min and 4 +/- 3 min (P = 0.921) after neostigmine.

In a RCT, Carroll MT,[23,24] compared that After cisatracurium 0.1 mg.kg-1 had been given, the median time to recovery of the train-of-four ratio to 0.8 (adequate recovery) was 74 min during spontaneous recovery, 48 min after reversal with neostigmine when the first twitch of the train-of-four had returned to 10% of control and 50 min after reversal when the first twitch of the train-of-four had returned to 25% of control. These times for cisatracurium 0.15 mg.kg-1 and atracurium 0.5 mg.kg-1 were 90, 66 and 57 min and 75, 56 and 54 min, respectively.

CONCLUSION

This study showed no significant difference between the onset of action of Cis atracurium and Atracurium at equipotent doses. However, duration of action of Cis atracurium was significantly longer than equipotent doses of atracurium. Mean heart rate of patients at baseline and at pre-determined intervals (5min, 10 min, 15 min, 20 min, 25 min, 30 min) receiving Cis atracurium was significantly less than the mean heart rate of patients receiving atracurium at equipotent doses. However, mean arterial pressure of both the groups were similar at the baseline and at every 5 min interval till 30 min, after giving muscle relaxants. There was no significant difference in intubating condition between Cisatracurium and atracurium at equipotent doses.

ISSN (O): 2687-5365; ISSN (P): 2753-6556

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ISSN (O): 2687-5365; ISSN (P): 2753-6556