COMPARISON OF EFFICACY OF ATRACURIUM VERSUS CISATRACURIUM IN PATIENTS UNDERGOING SURGERIES UNDER GENERAL ANAESTHESIA

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ABSTRACT

Introduction: Cisatracurium is one of the ten stereoisomers of Atracurium and is devoid of histamine induced cardiovascular effects. The neuromuscular blocking potency of Cisatracurium is approximately three fold that of Atracurium. Neuromuscular transmission was assessed by recording the muscle twitch response to train-of-four nerve stimulation. A total of 60 patients were randomized to receive either 2xED95 dose of Atracurium (n=30) 0.5mg/kg or 2xED95 dose of Cisatracurium (n=30) 0.1mg/kg. Study design: Prospective, Randomised, double blinded study. Patients & Methods: The study included 60 patients (30 patients in each group, assigned by computer generated randomization code). Results: 2 x ED 95 dose of Atracurium showed a better onset of action than 2 ED x95 dose of Cisatracurium which was clinically significant (p<0.001) with similar intermediate duration of action. There was no significant difference in condition on intubation and hameodynamic changes. No adverse effects were noted in both the groups. Conclusion: The 2 x ED 95 dose of Atracurium is more effective neuromuscular blocking agent than 2 x ED 95 dose of Cisatracurium providing rapid onset of action with similar duration of action, stable hemodynamic status and with no associated signs of histamine release.

Keywords: General Anaesthesia, Atracurium, Cisatracurium, Neuromuscular monitoring.

INTRODUCTION

Neuromuscular blockers (NMB) are very important adjuvant to general anaesthesia. They aid endotracheal intubation, mechanical ventilation and facilitate surgery. The ideal neuromuscular blocking agent needs to take shortest time in endotracheal intubation, the best intubating condition and have the shortest duration of muscle paralysis.\(^{(1)}\)

Atracurium is a benzyl-isoquinolinium diester, non-depolarizing neuromuscular blocking agent of intermediate duration of action. Its introduction in early 1980’s has revolutionized anaesthetic practice by providing muscle relaxation with faster onset, a more rapid measurable recovery. \(^{(2)}\)

It is composed by a mixture of ten optical and geometrical isomers. Elimination of Atracurium from the plasma occurs by a number of mechanisms including ester hydrolysis as well as Hoffman elimination and organ dependent elimination.\(^{(3,4)}\)

Cisatracurium is a recently introduced benzylisoquinolinium nondepolarising neuromuscular drug which is a stereoisomer of Atracurium and constitutes about 15% of the commercially produced Atracurium and with a potency of three to four times greater than that of Atracurium with an ED95 of 0.05mg/kg.\(^{(4)}\)

Cisatracurium besylate is the purified form of one of the ten stereo-isomers of atracurium. It is eliminated by Hoffman degradation; it has one metabolite Laudanosine which does not trigger histamine release. \(^{(5,6)}\)

In clinical practice, tactile evaluation of the adductor pollicis response to Train-of-four (TOF) is observed. Stimulation of the ulnar nerve is the most common method used to evaluate neuromuscular block. The TOF count is often used in the guidelines for neostigmine induced reversal of neuromuscular block. \(^{(7)}\)

In addition, although a TOF ratio of 0.7 is the accepted norm for adequacy of reversal of neuromuscular block\(^{(8)}\), there is an increasing evidence that significant residual effects such as visual disturbances, decreased grip strength and depressed swallowing reflexes persists until the TOF ratio has reached 0.9. \(^{(9)}\)

PHARMACODYNAMICS:

Metabolism is largely independent of liver function, and because the organ-independent Hoffman elimination is the predominant pathway for its elimination, cisatracurium is preferred for use. The rate limiting step in the degradation of Cisatracurium is Hoffmann degradation similar to Atracurium.\(^{(10)}\)
Because cisatracurium is administered five times lesser than atracurium at equipotent (ED95) doses, cisatracurium does not induce histamine release. For this reason, the plasma concentrations of the metabolite laudanosine are similarly lower when cisatracurium is used.\(^{(11)}\)

**DRUG INTERACTIONS:**

Inhalational anesthetic agents that potentiate neuromuscular block are arranged in the descending order: Desflurane > Sevoflurane > Isoflurane > Halothane > Nitrous oxide. Higher concentration (minimum alveolar concentration) and longer agent exposure will potentiate the neuromuscular block to a greater extent.\(^{(12)}\) Local anesthetics can potentiate the effects of both depolarizing and nondepolarizing NMBAs, but are insufficient to significantly shorten the onset time.\(^{(11)}\)

Patients with disorders of neuromuscular transmission, disorders of muscle and muscle membrane, disorders of the central nervous system with neuromuscular manifestations have increased sensitivity to non-depolarizing blocking agents and patients with disorders of lipid or glycogen storage, peripheral neuropathies have variable sensitivity to non-depolarizing NMBAs.\(^{(13)}\)

Monitoring of neuromuscular function after administration of a neuromuscular blocking drug serves at least two purposes in clinical settings. Firstly, it allows the anesthesiologist to administer these agents with appropriate dosing; Secondly, it ensures that the patient recovers adequately from residual effects of the neuromuscular blockade, thus guaranteeing patient safety. Neuromuscular monitoring involves the stimulation of a peripheral nerve and evaluation of the response (contraction or twitch) of the innervated muscle.\(^{(14,15)}\)

**MATERIALS AND METHODS**

**Study Site:** This study was conducted in the Department of Anaesthesiology, in Chettinad Hospital and Research Institute, Kelambakkam.

Study population: Patients scheduled for surgery under General anesthesia requiring intubation in the Department of & Critical Care, who met the inclusion criteria.

**Study design:** Prospective, randomised, double blinded study.

**Sample size:** Sample size was calculated assuming the mean onset time in Atracurium group as 3.24 minutes and in Cistracurium group as 4.37 minutes with standard deviation of 0.55 and 0.46 respectively as per study by El Kasaby A M et al. The other parameters considered for sample size calculation include, 80% power of study and 5% alpha error, the required sample size was 29 subjects in each of the study groups.
RANDOMIZATION AND BLINDING:
Selected 60 patients were randomly divided into two groups (30 patients in each group) using a computer generated randomization code. Blinding was achieved using a sealed envelope technique.

ETHICAL CONSIDERATIONS:
The Institutional Human Ethics Committee reviewed and approved the proposal entitled “Comparison of Atracurium versus Cisatracurium in patients undergoing surgeries under general anaesthesia: A Randomized Control Study” - IHEC No: 68/ IHEC/3-18, dated 13.04.2018. Informed written consent was obtained from all study participants. The risks and benefits involved in the study and voluntary nature of participation was explained to the participants before obtaining consent. Confidentiality of the study participants was maintained.

METHODOLOGY:
After obtaining approval from Institutional Human Ethics Committee and written informed consent, 60 patients undergoing surgeries under general anaesthesia in Chettinad Hospital and Research Institute, Kelambakkam, Chennai meeting the selection criteria were included in the study.

Group A - (n = 30) - Patients received Inj. Atracurium (2 x ED95) / 0.5mg/kg IV
Group B - (n = 30) - Patients received Inj. Cisatracurium (2 x ED95) / 0.1mg/kg IV

All Patients underwent a routine pre-anesthetic evaluation. Patients were premedicated with Tab. Alprazolam 0.25mg and Tab. Ranitidine 150mg the night before the day of surgery and on the morning of surgery. After arrival to the operating room, 18 gauge IV line was secured for administration of fluids and drugs. 20 gauge IV line was secured for administration of study drug (muscle relaxant).

Standard monitoring included noninvasive blood pressure (NIBP), Electroencephalogram (ECG), Oxygen saturation (SpO2) by pulse oximetry. Baseline parameters were noted and monitoring continued throughout the intraoperative period. The anesthesiologist performing intubation was blinded to the study drug. Before induction of anaesthesia, surface electrodes were placed over the ulnar nerve at wrist for neuromuscular monitoring (TOF WATCH SX). The distal electrode was placed at the level of the distal crease on the ulnar surface of the wrist as close to the nerve as possible. The second electrode was placed 2 cm proximal to the first, along the course of the nerve. The positive lead (red) was connected to the proximal electrode and the negative lead (black) was connected to the distal electrode.

After preoxygenation with 100% oxygen, Inj. glycopyrollate 0.2mg IV and Inj midazolam 1.0mg IV was given and anaesthesia was induced with Inj. Fentanyl 2mcg/kg iv followed by Inj. Propofol 2mg/kg iv. After loss of consciousness, the ulnar nerve was stimulated at the wrist with supramaximal stimulus with 50mA current. Supramaximal stimulus was obtained by adding 25% of the strength of current required for maximal stimulation.

The muscle relaxant was loaded by an Anaesthesiologist who did not take part in data collection. The amount of drug according to group allocation was loaded initially in a 5 ml syringe, and saline was loaded later to make the total volume to 5 ml, to facilitate blinding. The muscle relaxant was given intravenously and a stop watch activated and TOF monitoring was performed for every 30 seconds from the administration of muscle relaxant till TOF becomes 0. The onset time was determined as the interval from the end of muscle relaxant injection until the maximal suppression of T1 %. (TOF O). Endotracheal intubation was performed using appropriate size Macintosh Laryngoscope and trachea intubated using an appropriately sized endotracheal tube.

**STATISTICAL ANALYSIS**

IBM SPSS version 22 was used for statistical analysis. Sample size was calculated assuming the mean onset time in Atracurium group as 3.24 minutes and in Cistracurium group as 4.37 minutes with standard deviation of 0.55 and 0.46 respectively as per study by El-KasabyAMet al. The other parameters considered for sample size calculation include, 80% power of study and 5% alpha error, the required sample size was 30 subjects in each of the study groups. Descriptive analysis was carried out by mean, median and standard deviation for quantitative variables, frequency and proportion for categorical variables. Data was also represented using appropriate diagrams like bar diagram, pie diagram. All Quantitative variables were checked for normal distribution within each category of explanatory variable by using visual inspection of histograms and normality Q-Q plots.
TABLE 1: Comparison of signs of histamine release between the study groups (N=60)

<table>
<thead>
<tr>
<th>Signs of Histamine Release</th>
<th>Study Groups</th>
<th>Chisquare</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>GroupA (N=30)</td>
<td>GroupB (N=30)</td>
<td></td>
</tr>
<tr>
<td>Flush</td>
<td></td>
<td></td>
<td>0.000</td>
</tr>
<tr>
<td>No</td>
<td>30(50%)</td>
<td>30(50%)</td>
<td>1.000</td>
</tr>
<tr>
<td>Erythema</td>
<td></td>
<td></td>
<td>0.000</td>
</tr>
<tr>
<td>No</td>
<td>30(50%)</td>
<td>30(50%)</td>
<td>1.000</td>
</tr>
<tr>
<td>Wheals</td>
<td></td>
<td></td>
<td>0.000</td>
</tr>
<tr>
<td>No</td>
<td>30(50%)</td>
<td>30(50%)</td>
<td>1.000</td>
</tr>
<tr>
<td>Bronchospasm</td>
<td></td>
<td></td>
<td>0.000</td>
</tr>
<tr>
<td>No</td>
<td>30(50%)</td>
<td>30(50%)</td>
<td>1.000</td>
</tr>
</tbody>
</table>

Group A and Group B had no signs of flush, erythema, wheals and bronchospasm detected clinically. The difference in signs of histamine release between the study groups was statistically not significant (P-value of 1.000) as shown in the above table.

DISCUSSION

After obtaining approval from Institutional Human Ethics Committee and written informed consent from the participants, 60 patients scheduled for elective and emergency surgeries under general anaesthesia in the Department of Anaesthesiology, in Chettinad Hospital and Research Institute were included in the study. While selecting neuromuscular agent for tracheal intubation or skeletal muscle relaxation, main aim of an anaesthesiologist is to select an agent with rapid onset, longer duration of action, better haemodynamic stability, no signs of histamine release. Though Atracurium and Cisatracurium are nondepolarizing neuromuscular blocking agents of intermediate duration of action, Cisatracurium has its own advantages over Atracurium. In my present study, all patients were compared between 2xED95 dose of Atracurium and 2xED95 dose of Cisatracurium and were assessed for onset time, duration of action, haemodynamic changes, condition on intubation and signs of histamine release clinically.
We chose 2xED95 dose of the muscle relaxant because it is the standard intubating dose required for proper relaxation of the vocal cords to facilitate the ease of intubation.

Similar to the present study El Kasaby, et al in 2010,\(^\text{(16)}\) compared 2xED95 doses of Atracurium and Cisatracurium and found that the onset of action of Atracurium was significantly rapid (3.24 minutes) than Cisatracurium (4.3 minutes).

In 1996 Linda S. Bluestein MD, et al,\(^\text{(17)}\) studied 80 ASA physical status I or II of 18 – 70 years of age who underwent abdominal surgery. They were randomly allocated into four groups (A-D). Group A received cisatracurium 0.1 mg/kg (2×ED95), Group B received atracurium 0.5 mg/kg (2×ED95). Patients in group C and group D were treated with cisatracurium 0.2mg/kg (4×ED95) and 0.15 mg/kg (3×ED95), respectively. They found that same dose of atracurium had 3.2 minutes of onset time and cisatracurium had 4.6 minutes of onset time. They also found on further increasing the doses of Cisatracurium (0.15 and 0.2 mg/kg), the onset time increased to 3.4 and 2.8 min respectively. They also found there was a significant increase in the effective duration of action (45 to 55 and 61 minutes) on increasing the doses of Cisatracurium.

Study conducted by Lepage et al\(^\text{(18)}\) in 1996 assessed the pharmacodynamics, doserresponse relationship of cisatracurium in adult surgical patients during N2O-O2-opioid anesthesia and observed clinical duration of action of 0.1mg/kg (2xED95) cisatracurium to be about 9 minutes shorter than 0.5mg/kg (2xED95) of atracurium.

In all the above studies, the mean duration of action of Atracurium and Cisatracurium are approximately 43-45 minutes and 35-40 minutes respectively which is of longer duration compared to our current study. Usually, lean body weight is preferred during administration of the non-depolarising neuromuscular blocking agents. But in our current study, total body weight has been considered for administration of the muscle relaxants which can be explained for the duration of action of Atracurium and Cistracurium.

Mellinghoff et al,\(^\text{(11)}\) 1996 conducted a study of 80 patients who were randomized to two groups. Each group received either 2xED95 dose of Cisatracurium (n=40) or 2xED95 dose of Atracurium (n=20) after anaesthesia was induced with fentanyl, Midazolam and Thiopental. They found there was a statistically significant difference in onset of action of Atracurium group (2.35 ± 1.1minutes) and Cisatracurium group (3.1±1.0 minutes) (p< 0.008). He concluded that Cisatracurium was 3.3 times more potent than Atracurium.

Study conducted by M.T.Carroll et al\(^\text{(19)}\) in 1998 compared the neuromuscular blocking effects and train – of – four fade of Cisatracurium with Atracurium, and found that the onset time of Cisatracurium was slower with
approximately equipotent doses of the Atracurium with similar intermediate duration of action. They found that there was clinically significant difference in onset of action were 2.7, 2.2 and 1.5 min following Cisatracurium 0.1 and 0.15 mg/kg and Atracurium 0.5 mg/kg, respectively.

As regarding the onset of action and effective duration, our results were in concordance with the previous studies. Doenicke et al. (20) 1998 performed a double blinded clinical trial in 60 patients with cisatracurium or vecuronium to determine the onset time and histamine release after induction with sodium thiopental. He observed 2 out of 60 patients had cutaneous manifestation (flush) in Cisatracurium group. Skin manifestations also occur after thiopental administration.

Lorenz W et al (21) 1977 stated that systemic reactions at comparable histamine release concentrations vary from one person to another. In our current study, we had a separate intravenous cannula for the administration of the muscle relaxant and no signs of histamine release attributable to 2xED95 doses of cisatracurium and atracurium were observed in our study. On comparing all the variables, we conclude that at the same dose (2xED95 dose) Atracurium is more effective neuromuscular blocking agent than Cisatracurium, with more rapid onset of action, similar duration of action, stable hemodynamic status, and with no associated signs of histamine release clinically.

CONCLUSION

This clinical study entitled “COMPARISON OF EFFICACY OF ATRACURIUM VERSUS CISATRACURIUM IN PATIENTS UNDERGOING SURGERIES UNDER GENERAL ANAESTHESIA” was conducted to compare the onset time, duration of action, hemodynamic changes like heart rate, systolic blood pressure, diastolic blood pressure, condition on intubation and signs of histamine release. 60 patients assessed under ASA Grade I and II of both sex between 18-70 years of age, scheduled for both elective and emergency surgeries under general anesthesia of duration more than one hour were included in the study. Patients were divided into two groups of 30 each. Group A – 30 Patients received Inj. Atracurium (2xED95) / 0.5mg/kg IV and Group B - 30 Patients received Inj. Cisatracurium (2xED95) / 0.1mg kg iv after induction of the patient. Both the groups were comparable with respect to age, sex, weight, height and duration of surgery. 2 x ED95 dose of Atracurium had better onset of action compared to 2 x ED95 dose of Cisatracurium which was statistically significant. (P < 0.001) There was no statistically significant difference between the two groups regarding haemodynamic parameters (systolic blood pressure, diastolic blood pressure, mean arterial pressure and heart rate), duration of action and signs of histamine release clinically. The present study demonstrated that same dose of (2xED95) Atracurium has a better onset of
action than Cisatracurium with similar duration of action and without any other significant differences in the haemodynamic parameters and no signs of histamine release clinically.

REFERENCES


