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Original Article

Anaesthesia Section

Prospective Cohort Study Comparing Varying Doses of Cisatracurium and Atracurium on Intubating Conditions in Patients Undergoing Laparoscopic Cholecystectomy

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ABSTRACT

Introduction: Cisatracurium and atracurium are non-depolarising muscle relaxants belonging to benzylisoquinolinium group. Intubating dose of cisatracurium is found to be safer than atracurium owing to the histamine release and resultant respiratory and cardiac side-effects associated with the latter. However, intubating conditions of twice the ED_{95} dose ($2xED_{95}$) of cisatracurium are not as satisfactory as equipotent dose of atracurium because of its higher potency.

Aim: To compare the time of onset, intubating conditions and mean duration of action of three and four times ED_{95} doses (3 and $4xED_{95}$) of cisatracurium with $2xED_{95}$ dose of atracurium so as to find out an ideal intubating dose of cisatracurium that is comparable with $2xED_{95}$ of atracurium.

Materials and Methods: The present study was a prospective cohort study that included 102 patients who underwent elective laparoscopic cholecystectomy. They were divided into three groups of 34 each to receive atracurium 0.5 mg/kg (group A), cisatracurium 0.15 mg/kg (group B) or cisatracurium 0.2 mg/kg (group C) for intubation. Onset and duration of neuromuscular block were assessed using Train of Four (TOF) stimuli. Total time for intubation and mean intubation scores were also noted. Statistical analysis was done using Statistical Package for the Social Sciences (SPSS) software version 18.0. Qualitative data were compared using Chi-square test and quantitative data compared using Analysis of Variance (ANOVA).

Results: Onset of neuromuscular blockade in groups A, B and C were 292.06±61.486, 204.71±39.407 and 120.88±37.284 seconds (p-value <0.001), respectively. Mean intubation score was highest in group C along with least intubating time (p-value <0.001). The mean duration of action in groups A, B and C were 40.44±5.275, 48.24±5.888 and 63.38±7.659 minutes, respectively (p-value <0.001).

Conclusion: The 3 and $4xED_{95}$ doses of cisatracurium was found to be superior to $2xED_{95}$ dose of atracurium in providing faster onset of action, better intubating conditions, shorter intubation time and longer duration of action. The $4xED_{95}$ dose of cisatracurium may be considered for rapid intubation in two minutes.

Keywords: Benzylisoquinoline, Intubation, Intratracheal, Neuromuscular blockade

INTRODUCTION

Laparoscopic Cholecystectomy (LC) is a common elective procedure for treating gall bladder diseases and is usually done under general anaesthesia with controlled ventilation. Atracurium and cisatracurium are intermediate acting Neuromuscular Blocking Drugs (NMBDs) that are used for providing optimal intubating conditions. Cisatracurium is devoid of histamine induced cardiovascular and respiratory side-effects and therefore preferred over atracurium for intubation [1].

Rapid onset of neuromuscular blockade is essential for securing an airway promptly. The speed of onset is inversely proportional to the potency of NMBDs because of lower concentration gradient for the potent drug. The neuromuscular blocking potency of cisatracurium is approximately four fold of atracurium, but onset is two minutes longer and intubating conditions are not satisfactory as seen with equipotent $2xED_{95}$ dose of atracurium [1]. Increasing the dose of cisatracurium improves onset time and intubating conditions. Hence, it is required to know what dose of cisatracurium produces intubating conditions similar to $2xED_{95}$ dose of atracurium.

Several studies have compared different intubating doses of cisatracurium and majority conclude that $3xED_{95}$ and $4xED_{95}$ cisatracurium provides good to excellent intubating conditions in 1.5 to 2 minutes [2-4]. At the same time, study comparing atracurium with cisatracurium showed that only $6xED_{95}$ of cisatracurium was significant versus $2xED_{95}$ atracurium dose in terms of intubating conditions [5]. Therefore, it is necessary to find out what dose of cisatracurium provides intubating conditions similar to that of $2xED_{95}$ dose of atracurium.

This study aimed to compare the time of onset, intubating conditions, time taken for intubation and mean duration of action of $3xED_{95}$ and $4xED_{95}$ doses of cisatracurium with $2xED_{95}$ dose of atracurium.

MATERIALS AND METHODS

The prospective cohort study was conducted at Government Medical College, Kozhikode, Kerala, India after obtaining approval from the Institutional Ethics and Research Committee (GMCKKD/RP2017/IEC/265). The study period was from March 2018 to December 2019.

Inclusion criteria: One hundred and two patients scheduled for elective laparoscopic cholecystectomy belonging to American Society of Anaesthesiologists' (ASA) physical status I and II, age between 20-65 years and body weight of 40-70 kg were recruited for the study.

Exclusion criteria: Patients with anticipated difficult airway, history of drug allergy, bronchial asthma as well as pregnant and lactating women were excluded from the study.

Sample size calculation: Sample size calculation was done using the formula $n=(Z\alpha+Z\beta)^2\ SD^2\times2/d^2$ where $Z\alpha=1.96$, $Z\beta=0.84$, SD=standard deviation, d=effect size. The standard deviation in the time of onset was 0.84 according to the study by El Kasaby AM et al., [5]. To detect a significant difference of 0.6, the sample size calculated was 31 in each group. To account for a loss of 10% drop outs, a sample size of 34 in each group was taken.

After obtaining written informed consent, patients who met the inclusion criteria were divided into three groups- group A, group B

and group C. Group A received inj. atracurium 0.5 mg/kg ($2xED_{95}$), group B cisatracurium 0.15 mg/kg ($3xED_{95}$) and group C cisatracurium 0.2 mg/kg ($4xED_{95}$) intravenously for intubation.

All patients were assessed preoperatively through detailed history, physical examination and laboratory evaluation. On the day before surgery, procedure was explained to each patient. They were given tab. alprazolam 0.5 mg, night before surgery. An anaesthetist in the premedication room, who was not involved in the study allocated patients into one of the three groups using computer generated random number chart and set the drug for each patient. A chart of the drug and the patient was maintained, which the attending anaesthesiologist had no access. The aforesaid anaesthetist did not take part in intraoperative or postoperative monitoring or statistical analysis. The drug was labelled with patient's name only. Both the anaesthetist involved in the study and the patients were unaware of the allotted group and drug.

On arrival to the operation theatre, pre-induction monitors including electrocardiography, pulse oximeter and non-invasive blood pressure was attached. Peripheral nerve stimulator was used to assess the depth of neuromuscular blockade. Adductor pollicis muscle of the right hand was used for the same.

All patients were premedicated with inj. midazolam 0.02 mg/kg, inj. glycopyrrolate 0.004 mg/kg, inj. ondansetron 0.1 mg/kg and inj. fentanyl 2 µg/kg intravenously. After pre-oxygenation, general anaesthesia was induced with propofol 2 mg/kg. Once the response to verbal commands was lost, supramaximal stimulus was identified. Muscle relaxant was then administered slowly, intravenously over 5-10 seconds and the time of completion of administration noted. Neuromuscular blockade was monitored every 30 seconds by supramaximal TOF stimuli. After 2 minutes of relaxant administration, 1.5 mg/kg of preservative free lignocaine was given intravenously. Intubation was performed when TOF count was zero, using McIntosh blade and endotracheal tube of appropriate size by the consultant anesthesiologist. Anaesthesia was maintained with isoflurane 1% in Oxygen (O_2), Nitrogen Oxide (N_2O), mixture. Time of onset was taken from time of completion of relaxant administration to the disappearance of all four twitches. Duration of action was calculated from time of completion of relaxant administration to return of second tactile TOF response. Time taken for intubation was taken as time from zero TOF to completion of endotracheal intubation. Intubating conditions were evaluated based on the criteria enumerated in [Table/Fig-1] [6,7].

Criteria	Score 3	Score 2	Score 1
Laryngoscopy			
Jaw relaxation	Relaxed	Acceptable	Poor relaxation
Resistance to blade	None	Slight	Active resistance
Vocal cords			
Position	Abducted	Intermediate	Closed
Movement	None	Moving	Closing
Intubation response			
Limb movement	None	Slight	Vigorous
Coughing	None	Diaphragmatic	Severe bucking/coughing

[Table/Fig-1]: Intubation score [6,7].

STATISTICAL ANALYSIS

Analysis of the data was done using SPSS, version 18.0. Qualitative data like sex, ASA physical status were compared using Chi-square tests. Quantitative data like age, height, weight, time of onset, duration of action, time to intubation and intubation scores were compared using ANOVA (Analysis of Variance). A p-value <0.05 was taken as statistically significant.

RESULTS

A total of 102 patients, 34 in each group, scheduled for elective laparoscopic cholecystectomy belonging to ASA physical status I and II were included in the study. The groups were comparable with respect to age, sex, height, weight and ASA physical status [Table/Fig-2].

Variable	Group A	Group B	Group C	p-value (Chi-square)
Gender (male, female)*	20, 14	20, 14	20, 14	1
ASA (I, II)*	23, 11	21, 13	22, 12	0.879
Age (years)†	45.56±11.466	47.44±12.337	47.76±9.798	0.684
Weight (kg)†	60.91±7.333	58.41±9.106	56.38±9.770	0.110
Height (cm)†	162.24±8.374	160.38±7.101	157.03±11.248	0.061

[Table/Fig-2]: Demographic data.
*Data expressed in number; †Data are expressed in mean±Standard deviation (ANOVA)

There was significant difference in the onset of neuromuscular block among groups with a p-value of <0.001. Group C had the fastest onset in 120.88±37.284 seconds followed by Group B with 204.71±39.407 seconds. A 292.06±61.486 seconds were needed for the TOF responses to disappear in group A [Table/Fig-3].

Parameter	Group A	Group B	Group C	p-value
Onset of neuromuscular block (seconds)*	292.06±61.486	204.71±39.407	120.88±37.284	0.001
Intubation score*	15.24±1.458	16.06±1.127	17.91±0.288	0.001
Time to intubation (seconds)*	33.38±4.418	28.65±4.119	19.94±3.805	0.001
Duration of blockade (minutes)*	40.44±5.275	48.24±5.888	63.38±7.659	0.001

[Table/Fig-3]: Intubating conditions and block characteristics.
*Data are expressed in mean±Standard deviation (ANOVA)
p-value <0.05 considered significant

Intubating condition as judged by the mean intubation score was best in group C (17.91±0.288) along with least mean intubating time of 19.94±3.805 seconds. The differences in mean intubation scores and the time taken for intubation among the three groups were statistically significant with p-value <0.001 [Table/Fig-3].

Mean duration of action was also longer in group C (63.38±7.659 minutes) whereas in group A it was only 40.44±5.275 minutes [Table/Fig-3]. Intraoperative haemodynamics were stable in all three study groups, though it was not recorded.

DISCUSSION

Potent NMBDs have a slower onset of action than less potent agents. This is because a large proportion of receptors must be occupied before blockade can be observed. Blockade of these receptors would occur faster and drug onset would be more rapid, if more drug molecules were available. Cisatracurium is a potent drug. Hence, its onset time is longer than that of atracurium. The $2XED_{95}$ dose of cisatracurium does not yield satisfactory intubating conditions as those seen with equipotent doses of atracurium. Therefore, recommended dose of atracurium for intubation is 0.5 mg/kg ($2xED_{95}$) and that of cisatracurium is 0.15-0.2 mg/kg ($3xED_{95}$-$4xED_{95}$) [1,8,9]. Increasing the dose of cisatracurium can improve intubating conditions.

In this study, of the 102 subjects, 34 received 0.5 mg/kg atracurium (Group A), 34 received 0.15 mg/kg cisatracurium (Group B) and the remaining 34 received 0.2 mg/kg cisatracurium (Group C). The study groups were comparable with respect to sex, ASA physical status, age, height and weight. The statistical analysis of results showed that 3 and $4XED_{95}$ doses of cisatracurium are superior to $2xED_{95}$ dose of atracurium in providing faster onset and longer duration of action along with better intubating conditions.

A randomised controlled clinical trial by El-Kasaby AM et al., compared block characteristics of atracurium 0.5 mg/kg ($2XED_{95}$), cisatracurium 0.1 mg/kg ($2xED_{95}$), cisatracurium ($4xED_{95}$) 0.2 mg/kg and cisatracurium ($6xED_{95}$) 0.3 mg/kg [5]. They assessed onset time, condition of intubation and duration of action along with

haemodynamic effects and signs of histamine release clinically. Higher doses of cisatracurium $4XED_{95}$ and $6xED_{95}$ showed faster onset time and longer duration of action than with atracurium and with lower dose of cisatracuirum ($2xED_{95}$). Only $6xED_{95}$ dose of cisatracurium was statistically significant versus the atracurium dose in terms of condition of intubation. Contrary to the findings of the above study, intubating conditions were better than atracurium even with $3xED_{95}$ and $4xED_{95}$ of cisatracurium in the present study.

In another study, of 80 patients by Jammar P et al., $3xED_{95}$ dose of cisatracurium was administered to 40 patients (Group A) and $4xED_{95}$ dose to the remaining 40 patients (Group B) [2]. Group B showed longer duration of action than Group A. They concluded that tracheal intubation can be accomplished with good to excellent intubating conditions at two minutes following 0.15 mg/kg and 0.2 mg/kg cisatracurium. However, the present study result showed that satisfactory intubating conditions could be achieved at two minutes only with $4xED_{95}$ of cisatracurium and it took 3.3 minutes for $3xED_{95}$ of cisatracurium.

A total of 60 patients were divided into three groups in a study by Mandal P, each group received 0.15 mg/kg, 0.2 mg/kg and 0.25 mg/kg cisatracurium respectively [3]. It was concluded that the minimum dose required to achieve excellent to good intubating conditions with cisatracurium is 0.2 mg/kg at 90 seconds after its administration. Bluestein LS et al., in their study evaluated the effect of increasing the dose of cisatracurium on the mean time of onset and the clinically effective duration [4]. Good or excellent intubation conditions were produced in 89% of patients two minutes following an initial dose of 0.1 mg/kg cisatracurium and in 100% of patients 1.5 minutes following an initial dose of 0.15 or 0.2 mg/kg cisatracurium. Increasing the initial cisatracurium dose also increased the duration of neuromuscular blockade. The above two studies show that 0.2 mg/kg of cisatracurium provides satisfactory intubating conditions in 1.5 minutes' time. Thus, 0.2 mg/kg of cisatracurium would be useful for rapid intubations in emergency situations like rocuronium.

Mellinghoff H et al., assessed onset of block after injection of a bolus dose (0.1 mg/kg cisatracurium and 0.5 mg/kg atracurium) and recovery profile after subsequent infusion [10]. At the end of procedure, neuromuscular block was reversed with neostigmine 45 microg/kg and atropine 20 microg/kg in one half of patients. Onset time of equipotent dose of cisatracurium was longer with p-value=0.008. This study showed that on a molar basis, during infusion cisatracurium was 3.3 times more potent than atracurium and recovery characteristics of equipotent doses of both drugs were identical after 75-192 minutes of infusion for constant 95±4% block. The results of another randomised prospective cohort study were similar to the above study that showed atracurium having faster onset and at the same time comparable recovery profile [11].

Another interesting study done in ICU patients by Moore L et al., deserves special attention in the current COVID-19 scenario [12]. The study aimed to compare the outcomes in severe Acute Respiratory Distress Syndrome (ARDS) patients who were treated with atracurium or cisatracurium. Primary outcome was improvement in oxygenation and secondary outcomes were ventilator free days at one month, length of hospital stay and mortality. They demonstrated no significant difference in clinical outcomes.

There was a statistically significant increase in heart rate and mean blood pressure following intubation in the first two groups of El-Kasaby AM et al., [5]. There were no signs of histamine release in cisatracurium group, while flushing and erythema were noted in two patients in atracurium group.

Limitation(s)

Though haemodynamics were monitored and found to be stable, the present study failed to record and analyse it statistically. This was the major limitation of this study.

CONCLUSION(S)

The 3 and $4XED_{95}$ doses of cisatracurium was found to be superior to $2xED_{95}$ dose of atracurium in providing faster onset and longer duration of action along with better intubating conditions. Satisfactory intubating conditions were achieved at two minutes with $4xED_{95}$ dose of cisatracurium and therefore this dose may be considered for emergency intubations in two minutes.

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