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ORIGINAL RESEARCH ANESTHESIOLOGY

Comparative study to evaluate equipotent doses of cisatracurium and atracurium in patients undergoing abdominal laparoscopic surgery

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Abstract

Background & objectives: Muscle relaxant make an important part of the balanced anesthesia, especially for abdominal surgery. Over a period of time, newer relaxants have been developed with lower side effects and better recovery profile. This study compared two relaxants – cisatracurium and atracurium, as a part of general anesthesia for the laparoscopic medical procedures.

Methodology: A total of 120 patients, 18-60 y of age, scheduled for the laparoscopic cholecystectomy were selected. Patients were randomly divided into two groups; Group C received cisatracurium 0.1 mg/kg as muscle relaxant and Group A received atracurium 0.3 mg/kg IV. The mean onset time and duration of action for the two groups was done by Stockholm rules of the pharmacodynamic investigations of muscle relaxants activity. Intubating conditions, hemodynamic changes, and safety profile were noted.

Results: The mean onset time was 4.04 ± 0.28 min vs. 5.12 ± 0.42 min for cisatracurium and atracurium respectively. The mean duration of action was 42.21 ± 1.71 min vs. 51.23 ± 6.1 min for cisatracurium and atracurium respectively ($p < 0.001$). Intubating conditions, hemodynamic changes, recovery time and safety profile were comparable between the groups. Recovery time following administration of cholinesterase inhibitors were 4.27 ± 0.23 vs. 3.24 ± 0.36 min ($p < 0.001$)in the cisatracurium and atracurium group respectively.

Conclusion: Cisatracurium has a quicker onset time and provides better conditions for tracheal intubation, compared to atracurium. Cisatracurium was demonstrated to have a better safety profile than atracurium.

Abbreviations: BMI – Body mass index; MAC – Minimum alveolar concentration; NMBD – Neuromuscular blocking drug; NMJ – Neuromuscular junction

Key words: Cisatracurium, atracurium, neuromuscular blockade, neuromuscular monitoring.

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1. Introduction

The concept of balanced endotracheal anesthesia, with induced muscle paralysis with relaxant drugs is one of the foundations of the current anesthetic practice. Muscle relaxation not only provides a comfortable environment for the surgeons, but also allows for effective and safe management of gas exchange, circulation and metabolism of the patient. The use of muscle relaxants has not only revolutionized anesthesiology, but also marked the beginning of the modern era in surgery.[1]

Cisatracurium is comparatively a newer agent and there is still a limited experience in its use in various fields of surgery, including laparoscopic abdominal interventions in which short-term blockade of neuromuscular conduction is usually required.[1] It is the R-cis isomer of atracurium carrying 3-4 times more potency.[2] Unlike atracurium, it has significantly less histamine releasing effect and creates better hemodynamic stability. These distinctive qualities are the most significant, and according to many publications, these two muscle relaxants practically are not distinguishable from each other. In separate studies, it has been shown that the pharmacodynamic characteristics of cisatracurium and atracurium at equipotent doses are also very close to each other.[3] However, despite the fact that cisatracurium is a more potent muscle relaxant, its ED_{95} is 0.05 mg/kg compared to 0.2 mg/kg that of atracurium, otherwise the pharmacodynamics in many ways are similar. Some studies have shown a slower onset of neuromuscular block (NMB) with cisatracurium compared to atracurium.[4]

Few comparative assessments of the action of both muscle relaxants have been presented under the same conditions.[5, 6, 7] We conducted this study to have a comparative assessment of cisatracurium and atracurium for endotracheal anesthesia for abdominal laparoscopic surgery.

2. Methodology

This prospective, randomized study included 120 patients, aged from 18 to 60 y, ASA I-III class, who underwent laparoscopic abdominal surgery. The expected duration of surgery was 25-35 min. Written and informed consent was obtained from each of the patients.

Patients on medications, which could significantly affect neuromuscular conduction (e.g., carbamazepine, aminoglycosides, lincosamides and diuretics), patients with pathology of the nervous system, kidney or liver disease, were excluded from the study. Patients for whom additional doses of muscle relaxants were required, or an unstable control of neuromuscular transmission was observed, were also excluded from the study.

Patients were randomly divided into 2 groups using a computer generated program, each group consisting of 70 patients. Patients in Group C received cisatracurium in a loading dose of 0.1 mg/kg, and Group A received atracurium 0.3 mg/kg. Eight patients required additional doses of muscle relaxants due to prolonged operating time, and 2 patients had unstable control of neuromuscular transmission, so were excluded from the study. As a result, 60 patients completed the study in each group.

During anesthesia and surgery, standard monitoring was used, and non-invasive blood pressure, heart rate, pulse oximetry, capnography and ECG were recorded at the following stages: 1st; before the start of anesthesia (patient on the operating table), 2nd; –5 min after surgery started, 3rd;10 min after the surgery started, 4th; 20-30 min after surgery started; (the main stage operations), 5th; at the suturing the skin; and 6th–5 min after extubation.

Premedication and induction of anesthesia was performed similarly in all patients. All patients received inj. glycopyrrolate 0.2 mg IV and inj. diphenhydramine 10 mg IV, 30 min before the onset of anesthesia. Induction consisted of sequential administration of fentanyl 0.1 mg, propofol 1.5-2.0 mg/kg. Muscle relaxation either with cisatracurium or atracurium was done as per the study protocol.

The start time of intubation was determined by clinical signs and significance of TOF (Train-of-four). The conditions for intubation were assessed by an experienced anesthesiologist; the criteria included ease of laryngoscopy, location and/or movement of vocal cords, and the patient's response to intubation. Maintenance of anesthesia was carried out with sevoflurane (0.8-1.0 MAC in oxygen-air mixture (50:50) and an additional bolus of fentanyl. Mechanical ventilation during anesthesia was carried out by the Workstation. Inhalational agent was discontinued before the end of anesthesia. The suitability of extubation was determined by monitoring neuromuscular conduction and clinical signs of recovery: e.g., eye opening, the ability to raise and hold the head above the operating table for 5 sec, and the strength of the handshake. Anaesthesia was reversed using inj. neostigmine 0.05mg/kg IV and inj. glycopyrrolate 0.01 mg/kg IV.

All data obtained were noted in a performa with an interval of 5 min. The data was tabulated on Microsoft Excel Sheet. Student T Test was applied on all parametric data and Chi-Square test was applied on Non-Parametric data. A $p < 0.05$ was considered as statistically significant.

3. Results

Demographic data (e.g., age, gender, weight, stature, and BMI) were comparable between the groups. The majority of the patients underwent laparoscopic cholecystectomy. Type of surgery, mean duration of anesthesia, and mean duration of surgery were comparable. The volume of intravenous fluid administered was comparable between the two groups. Intraoperative core temperature was comparable in both the groups (Table1). The preoperative vitals i.e. pulse

Table 1: Demographic, surgical and anesthesia data

Variable		Group C	Group A	p-value
Age (y)		41.83 ± 12.79	41.97 ± 11.57	0.428
sex (m: f)		26:34	26:34	
BMI (kg/m 2)		28.41 ± 1.98	29.53 ± 2.58	0.063
Type of surgery	Cholecystectomy	43	41	
	Inguinal hernia repair	12	13	
	Ventral hernia repair	5	6	
Duration of surgery		66.41 ± 5.96	69.84 ± 10.98	0.234
Duration of anesthesia		72.12 ± 6.98	75.14 ± 11.87	0.243
Intraoperative fluid used		781 ± 6.97	813 ± 115.1	0.214
Temperature		37.01 ± 0.03	38.12 ± 0.02	0.536

Data presented as Mean SD or n (%)

Table 2: Neuromuscular blocking properties of cisatracurium and atracurium

Parameter	Group C (Mean ± SD)	Group A (Mean ± SD)	p-value
Onset of full relaxation	4.04 ± 0.28	5.12 ± 0.42	< 0.001
Duration	42.21 ± 1.71	51.23 ± 6.1	< 0.001
Recovery Time	4.27 ± 0.23	3.24 ± 0.36	< 0.001
No. of patients receiving top-up doses	8	8	

rate, BP (systolic, diastolic, and mean), SpO_2, were also comparable among the two groups.

The onset time in the Group C was significantly short in comparison to Group A (4.04 ± 0.28 vs. 5.12 ± 0.42 min,$p < 0.001$). Also, the duration of action in the Group C was significantly short compared to Group A (42.21 ± 1.71 vs. 51.23 ± 6.1 min, $p < 0.001$) (Table 2). The recovery times were between the two groups (4.27 ± 0.23 min in Group C vs. 3.24 ± 0.36 min in Group A ($p < 0.001$), and the difference was significant. Grading of intubating conditions accomplished by the senior anesthesiologist (blinded to the learning), showed excellent intubating conditions in all the patients in both groups.

There was a reduction in mean heart rate and mean blood pressure after administration of the muscle relaxants in comparison to the baseline values in both the groups (Table 3). All these hemodynamic parameters increased following intubation. There was neither any apparent signs of histamine release nor any episode of bradycardia or hypotension or hypertension in any patient.

4. Discussion

Traditionally, $2xED_{95}$ dose is considered to be the ideal intubating dose for most non-depolarizing muscle relaxants.[8] However, cisatracurium, at $2xED_{95}$, fails to provide satisfactory intubating conditions.[9] Various

Table 3: Mean hemodynamic parameters following injection in both groups

Time	Mean pulse rate (beats/min)		Mean MAP (mmHg)	
	Group C	Group A	Group C	Group A
Preoperative	70	72	93	93
1 Min	68	67	85	87
2 Min	65	68	88	85
6 Min	73	75	90	95
10 Min	75	76	95	95
After Intubation	90	92	110	112

researchers[10] have recommended $3xED_{95}$ dose of cisatracurium for intubation. A dose-response study was carried out by Mandal P[12] to discover the ideal intubating dose of cisatracurium by comparing $3xED_{95}$ (0.15 mg/kg), $4xED_{95}$ (0.20 mg/kg) and $5xED_{95}$ (0.25 mg/kg) and the author concluded that $4xED_{95}$ of cisatracurium provided very good to outstanding intubating situations in 90 sec in all the patients in comparison to $3xED_{95}$ dose of cisatracurium. However, $5xED_{95}$ of cisatracurium given very good to excellent intubating situations after 75 to 90 sec. But, in that study, the author had assessed the intubating condition clinically without any neuromuscular monitoring. Recently, Kaur et al.,[11] compared $2xED_{95}$ of atracurium and cisatracurium and observed prolonged onset time following administration of both the drugs by using neuromuscular monitoring.

The literature search did not reveal any studies comparing $3xED_{95}$ of both the drugs. In this clinical trial, we compared the equivalent intubating dose ($3xED_{95}$) of atracurium and cisatracurium for the first time in India.

Our study demonstrated that cisatracurium had a significantly slower onset time in comparison to atracurium at equipotent doses ($3xED_{95}$) ($p < 0.0011$). Our observations correlate very well with the results of other studies. It has been reported that the onset time of cisatracurium is also prolonged following $2xED_{95}$ in contrast to atracurium by El-Kasaby AM, et al. and Kaur H, et al. [13] This was attributed to the actuality that there is an opposite connection among the onset time and potency of NMBs by Maheshwari M, et al.[14] and cisatracurium is thrice more effective than atracurium.[15] Both the drugs provided excellent intubating conditions which may be due to the higher dose used ($3x\ ED_{95}$) and several studies have found comparable intubating conditions (very good to excellent) between the two. The period of action was prolonged with cisatracurium in contrast to atracurium. Our observations are in line with the findings of other researchers.[14-16]

Pulse rate and mean blood pressure throughout the surgery remained comparable in both groups. We did not observe any erythema, flushing, urticaria, sudden changes in hemodynamics and bronchospasm following administration of any of the NMBDs and during maintenance of anesthesia. Hemodynamics and safety profile of both the drugs were comparable. Movafegh and colleagues studied 100 patients for cost analysis and safety comparing equipotent doses ($3xED_{95}$) of cisatracurium and atracurium in patients undergoing general anesthesia and concluded that atracurium and cisatracurium had similar safety profile and both the drugs can be used safely during anesthesia.[17]

The recovery time after administration of cholinesterase inhibitors was faster in the cisatracurium group, ensuring recovery after the surgery. This observation is in sharp contrast to an earlier study.[18]

In our study, the mean time of operation was around 70 min. Only six patients in the cisatracurium group and eight patients in the atracurium group needed a single top-up dose. We could not analyze the time period of action of top-up dose as the surgery got over.

To summarize, the equipotent dose of cisatracurium had shorter start time, and duration of activity was remarkably prolonged compared to atracurium. Both the drugs are safe as regards to cardiovascular parameters and there were no indications of histamine release in any patient of both groups. Interestingly, the recovery profile of cisatracurium was significantly better than the atracurium group. The drug is especially suitable to be used as a single bolus for surgeries lasting around an hour.

5. Conclusion

We conclude that cisatracurium produces a more rapid onset and longer duration of neuromuscular block; and it offers better conditions for tracheal intubation compared to equipotent doses of atracurium.

6. Conflict of interest

None declared by the authors.

7. Authors' contribution

DN: Conceived and designed the analysis, data collection

AC: Data collection, contributed data or analysis tools

GK: Statistical analysis; manuscript writing

MKU: Data analysis, literature search, reference search, manuscript editing

8. References

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