

Research Article

Comparative Evaluation of Equipotent Dose of Cisatracurium and Atracurium in Patients Undergoing Abdominal Laparoscopic Surgeries.

¹Dr. Shaikh Fahd and ²Dr. Juwairiah Shaikh

¹Assistant Professor, Department of Anesthesia, Ayaan Institute of Medical Sciences Teaching Hospital & Research Center, India

²Assistant Professor, Department of Anesthesia, Ayaan Institute of Medical Sciences Teaching Hospital & Research Center, India

*Corresponding Author

Dr. Juwairiah Shaikh

Article History

Received: 03.08.2023

Revision: 09.08.2023

Accepted: 28.08.2023

Published: 06.09.2023

Citations:

Fahd S, et. al Comparative Evaluation of Equipotent Dose of Cisatracurium and Atracurium in Patients Undergoing Abdominal Laparoscopic Surgeries. *J Surg Radiol*, 02(03); 2023; 8-13.

Abstract: *Background & Objectives:* Literature on the comparative evaluation of the intubating dose of cisatracurium and atracurium is sparse in India. We evaluated neuromuscular blockade, recovery characteristics, and safety profile between the two non-depolarizing neuromuscular blocking drugs; cisatracurium besylate and atracurium besylate at equipotent doses (3xED95) in adult patients undergoing abdominal laparoscopic surgical procedures. *Methods:* Fifty surgical patients under general anaesthesia were randomised into two groups. Anaesthesia was induced with 2 mg/kg propofol and 2 µg/kg fentanyl in all the patients. Neuromuscular blockade was achieved using an equipotent dose of either cisatracurium 0.15 mg/kg (Group A) or atracurium 0.6 mg/kg (Group B). Onset time, duration of action, and recovery profile after administration of cholinesterase inhibitor were noted using neuromuscular monitoring using Train Of Four (TOF). Intubating conditions, haemodynamic changes, and safety characteristics were also evaluated. *Results:* The mean onset time and duration of action for cisatracurium were 4.44 ±0.45 minutes, 50.09 ±5.3 minutes while, for atracurium, the values were 3.14 ±0.23 minutes, 41.03 ±1.69 minutes respectively (p <0.001). Intubating conditions, haemodynamic changes, and safety profile were comparable between the groups. Recovery time following administration of cholinesterase inhibitors in the cisatracurium and atracurium group were 2.84 ±0.23 and 3.68 ±0.21 minutes respectively (p <0.001). *Conclusion:* Equipotent dose of atracurium had faster onset than cisatracurium. But, the duration of action was longer in cisatracurium as compared to atracurium. The recovery profile of cisatracurium was faster and better than atracurium. Both the drugs have comparable haemodynamic parameters, intubating conditions, and safety profile.

Keywords: Cisatracurium, atracurium, neuromuscular blockade, neuromuscular monitoring .

INTRODUCTION

Neuromuscular blocking drugs (NMBDs) interrupt transmission of nerve impulses at the neuromuscular junction (NMJ) that provides excellent intubating conditions and prevent patient movement to facilitate surgery. A plethora of NMBDs has been introduced into the anaesthetist's armamentarium. However, atracurium, because of its organ independent elimination and satisfactory neuromuscular blocking properties has stood the test of time (Khan, Z. H. et al., 2018). Its popularity amongst anaesthetists bears no bounds. But, histamine release following administration of atracurium is a major concern (Dewachter, P., & Mouton-Faivre, C. 2015).

Cisatracurium, a stereoisomer of atracurium, has a better metabolic and recovery profile. And above all, it has the least histamine-releasing property (Szakmany, T., & Woodhouse, T. 2015). Recently, cisatracurium has been approved for clinical use in India by the Drug Controller of India. Several studies have been published comparing intubating dose (2xED95) of atracurium with that of cisatracurium. But, the intubating dose of cisatracurium is more than 2xED95 dose (Dieye, E. et al., 2014), which may be 3 or 4xED95 dose. Not enough studies have been published comparing a 3xED95 dose of atracurium vis-à-vis cisatracurium.

Our hypothesis is 3xED95 dose of cisatracurium would provide faster and excellent intubating conditions in comparison to the same dose of atracurium. A randomized, prospective single-blind clinical study was carried out to compare 3xED95 dose atracurium with that of cisatracurium in adult patients undergoing abdominal laparoscopic surgical procedures under general anaesthesia.

MATERIALS AND METHODS

The study was conducted in the Department of Anaesthesiology after due clearance from the hospital ethical committee (IEC code no: 013IP-20). The trial was registered before patient enrollment with Clinical Trials Registry- India (CTRI/2019/01/017370). This manuscript adheres to the applicable CONSORT guidelines. After taking written informed consent, 50 patients (ASA grade 1 and 2), between 18-60 years of age undergoing laparoscopic abdominal surgery were randomly divided into two groups according to a computer-generated random number list based on the NMBD they received.

- Group A: (n =25) received cisatracurium 0.15mg/kg
- Group B: (n =25) received atracurium 0.6mg/kg.

Patients who refused to participate in the study, with neuromuscular diseases, taking aminoglycosides and tetracycline, anticipated difficult intubation, requiring rapid sequence induction, pregnant females, obese individuals (BMI > 35), history of asthma, atopic and allergic tendencies and patients requiring emergency surgery were excluded from the study.

After a thorough pre-anaesthetic evaluation, written informed consent was obtained and the anaesthetic procedure was also explained to each of the patients. No premedication was prescribed. On the day of surgery, upon completion of the safety checklist, the patients were taken inside the operation theatre and baseline vitals (ECG, heart rate, SpO₂, and NIBP) were recorded. Electrodes for neuromuscular monitoring were placed over the ulnar nerve on the ventral aspect of the wrist. All the patients were pre oxygenated with 100% oxygen for 3 min. Intravenous induction of anaesthesia was carried out with fentanyl

2 mcg/kg and propofol 2mg/kg along with 100% oxygen. Once the patient became unconscious, neuromuscular monitoring was commenced by stimulating the ulnar nerve with TOF measurement with 50mA current every 15 seconds. After ensuring adequate bag-mask ventilation and stable haemodynamic parameters, muscle relaxant was administered as per group allocation. All the patients of group A received cisatracurium 0.15mg/kg while group B patients, atracurium 0.6mg/kg. The time of injection of muscle relaxant was noted. Bag-mask ventilation was performed until adequate muscle relaxation was achieved (TOF 0). Time from completion of injection of muscle relaxant till TOF 0 was noted as onset time. Upon achieving TOF 0, a senior anaesthesiologist blinded to the study drug, performed direct laryngoscopy and intubation with appropriate size endotracheal tube, and classified intubating conditions (Mitra, S. et al., 2015) as follows:-

- Excellent: no coughing/bucking. Vocal cords relaxed and abducted
- Good: slight coughing and/or bucking. Vocal cords relaxed and abducted
- Poor: moderate coughing and/or bucking vocal cords moderately adducted
- Not possible: Vocal cords not relaxed, tightly adducted.

Anaesthesia was continued with a mixture of O₂/Air/Sevoflurane and a minimum alveolar concentration (MAC) of 0.8 to 1 was maintained in the intraoperative period. The core temperature of all the patients was monitored by placing a temperature probe into the esophagus. Top up dose of the muscle relaxant (with atracurium 0.1mg/kg and cisatracurium 0.03mg/kg) was given at the appearance of

1st TOF after the initial intubating dose. Patients were monitored for any signs of histamine release clinically by observing skin changes that were graded as flush (if redness lasted > 120 seconds), erythema, or wheals and presence of any haemodynamic changes or bronchospasm for the first 10 minutes after NMBD injection. Intraoperatively patients were put on mechanical ventilation and normocapnia was maintained. The core temperature of all the patients was maintained at 35.5 to 37.5 C with the help of a forced-air warming blanket (Bair Hugger™).

From the time of injection of NMBD, the patient's heart rate, systolic, diastolic and mean arterial blood pressure were monitored at 1, 3, 6, and 10 minutes after intubation, and then every 5 minutes thereafter throughout the surgery. The core temperature was recorded every half-hourly. The patient's vitals, immediately after intubation, were noted. Any fall in blood pressure (i.e. greater than 20% from baseline) was treated with a bolus dose of Ephedrine 3 mg and bradycardia (heart rate < 50 /min) was managed with Atropine 0.6mg i.v.

At the end of the surgery, the reversal of neuromuscular blockade was achieved by administration of 0.05 mg/kg neostigmine and 10mcg/kg glycopyrrolate mixture through slow i.v. injection after the appearance of TOF 2. Time taken from TOF 2 to TOF 4 was recorded as recovery time. The trachea was extubated after confirmation of adequate neuromuscular recovery. Patients were shifted to the recovery room for postoperative monitoring.

The following parameters were evaluated and are defined as

- Onset - Time taken from the end of initial muscle relaxant injection until TOF score becomes "0".
- Intubating conditions - Graded by senior anaesthesiologist who was blinded to the study
- Duration- Time taken from the end of initial muscle relaxant injection until TOF score was "1".
- Recovery- Interval from the time of Reversal of blockade at TOF 2 (after the last dose) till TOF 4
- Side effects- Skin rashes/erythema, bronchospasm and sudden changes in patient's haemodynamics

The sample size was calculated using G Power statistical software (3.0.10) and was based on the reference study (El- Kasaby, A. M. et al., 2010), using onset time as the primary outcome. In the current study, power analysis on the assumption of a type I error of 0.05 and power of study as 0.90 revealed a sample size of eighteen patients in each group and a total of 36 patients. However, we had recruited 25 patients in each group. The data is tabulated

in MS Excel and analysis performed using Statistical Package for Social Sciences (SPSS) version 16.0 software. Quantitative variables are expressed in terms of mean ± sd and compared between groups using unpaired t-test and within groups across follow-ups using

paired t-test. Qualitative variables are expressed as frequency/percentage and compared between groups using Chi-square/Fisher's exact test. A p-value < 0.05 is considered statistically significant

RESULTS

Demographic data (age, sex, weight, height, and BMI) were comparable between the groups. The majority of the patients underwent laparoscopic cholecystectomy. Type of surgery, mean duration of anaesthesia, and 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 (Table- 1). The preoperative vitals i.e. heart rate, blood pressure (systolic, diastolic, and mean), SpO2, were also comparable between the two groups.

Table 1: Demographic Data

		GROUP A	GROUP B	P- VALUE
AGE (YEARS)		40.96 ± 13.03	42.52 ± 12.73	0.335
GENDER (M: F)		11:14	11:14	
BMI (kg/m ²)		27.57 ± 2.75	28.90 ± 3.08	0.058
	CHOLECYSTECTOMY	19	22	
	INGUINAL HERNIA REPAIR	5	3	
	VENTRAL HERNIA REPAIR	1	0	
DURATION OF SURGERY		68.36 ± 11.71	65.84 ± 6.11	0.172
DURATION OF ANAESTHESIA		74.32 ± 12.67	71.32 ± 7.28	0.155
INTRAOP FLUID USED		804 ± 116.3	774 ± 7.03	0.128
TEMPERATURE		36.77 ± 0.03	36.66 ± 0.04	0.012

The onset time was significantly longer in the cisatracurium (p<0.001) in comparison to atracurium (4.44 ± 0.45 vs. 3.14 ± 0.23 minutes, p<0.001). Cisatracurium took 41% more time to achieve TOF 0 in contrast to atracurium. But, the duration of action was longer in the cisatracurium group to that of the atracurium group (50.09 ± 5.3 vs. 41.03 ± 1.69 minutes) which was highly significant (p<0.001) (Table 2, figure 2). Grading of intubating conditions was carried out by the senior anaesthesiologist (blinded to the study), showed excellent intubating conditions in all the patients from both drug groups.

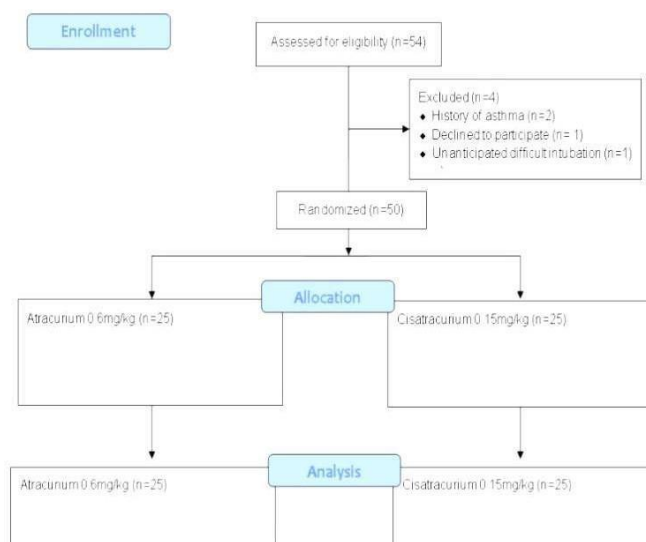


Fig 1: CONSORT flow diagram of the study

Table 2: Neuromuscular Blocking Properties of Cisatracurium (Group A) and Atracurium (Group B)

	GROUP A		GROUP B		p-value
	MEAN	± SD	MEAN	± SD	
ONSET	4.44	0.45	3.14	0.23	<0.001
DURATION	50.09	5.3	41.03	1.69	<0.001
RECOVERY	2.84	0.23	3.68	0.21	<0.001

NUMBER OF PATIENTS RECEIVING TOP-UP DOSE	6		8		
--	---	--	---	--	--

ABBREVIATIONS

BMI: Body mass index; ECG: Electrocardiogram; ED: Effective dose ; MAC: Minimum alveolar concentration
 NIBP: Non-invasive blood pressure; NMBD: Neuromuscular blocking drug; NMJ: Neuromuscular junction; TOF: Train-of- four

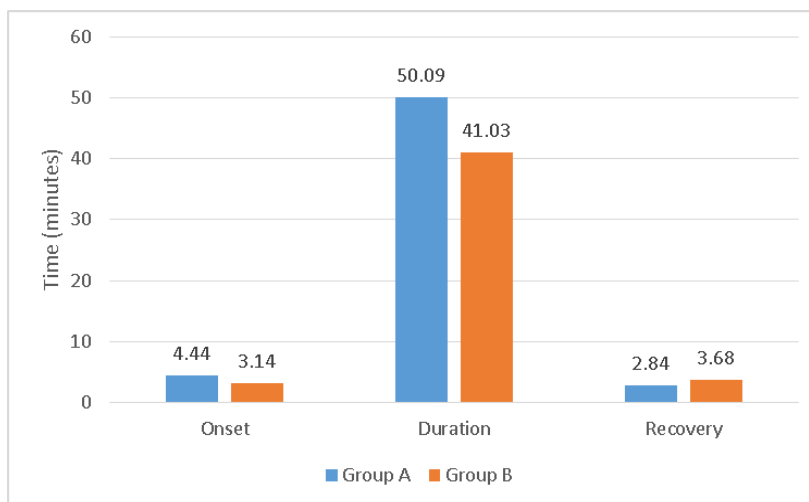


Fig 2: Neuromuscular blocking properties of cisatracurium (Group A) and atracurium (Group B). This bar diagram compares the mean onset time, duration of action and recovery time between the two groups.

There was a decrease in mean pulse rate, systolic, diastolic, and mean blood pressure after administration of the muscle relaxant in comparison to the baseline values in both the groups. All these haemodynamic parameters increased following intubation (figure 3). There was neither any apparent signs of histamine release nor any episode of bradycardia or hypotension or hypertension in any patient. Recovery time after administration of cholinesterase inhibitors (from TOF2 to TOF4) was faster in the cisatracurium group in comparison to atracurium group (2.84 ± 0.23 vs. 3.68 ± 0.21 minutes, p < 0.001).

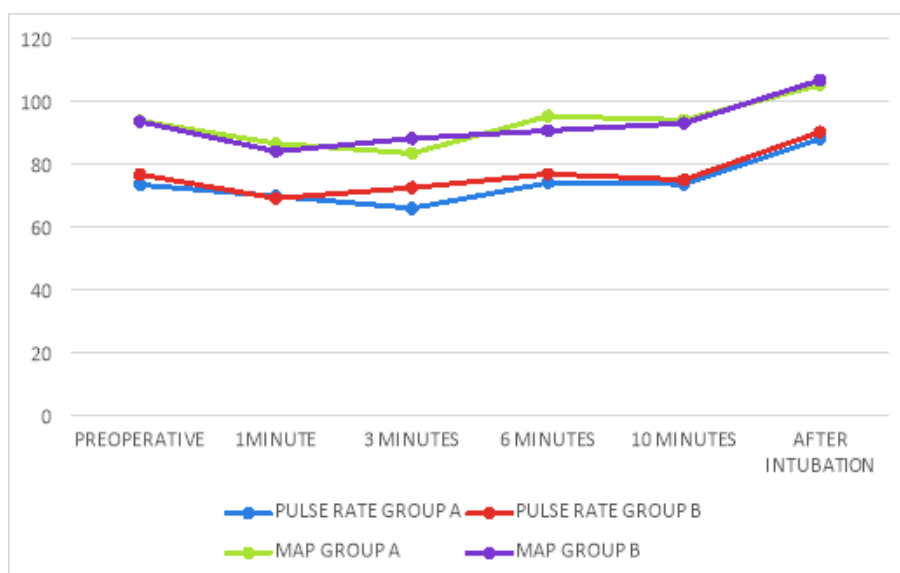


Fig 3: Haemodynamic changes following injection of cisatracurium (Group A) or atracurium (Group B). This figure depicts changes in pulse rate and mean arterial pressure (MAP) in both the groups at 1, 3, 6, 10 minutes and after intubation as compared to baseline (preoperative) values.

DISCUSSION

Traditionally, 2xED95 dose is considered to be the ideal intubating dose for most non-depolarizing muscle relaxants (Farooq, K., & Hunter, J. M. 2011). However,

cisatracurium, at 2xED95, fails to provide satisfactory intubating conditions (Jeong, H. J. et al., 2012). Various researchers (Lee, H. et al., 2013; & Kirov, K. et al., 2004) have recommended 3xED95 dose of cisatracurium for

intubation. A dose-response study (Mandal, P. 2002) was carried out to discover the ideal intubating dose of cisatracurium by comparing 3xED95(0.15mg/kg), 4xED95(0.20mg/kg) and 5xED95(0.25mg/kg) doses and author had concluded, 4xED95 dose of cisatracurium provided very good to excellent intubating conditions in 90 seconds in all the patients in comparison to 3xED95 dose of cisatracurium. However, 5xED95 dose of cisatracurium provided very good to excellent intubating conditions after 75 and 90 seconds. But, in that study, the author had assessed the intubating condition clinically without any neuromuscular monitoring. Recently, Kaur et al., (2018) had compared 2xED95 dose of atracurium and cisatracurium and observed, prolonged onset time following administration of both the drugs by using neuromuscular monitoring (TOF).

The literature search did not reveal any studies comparing 3xED95 dose of both the drugs. In this clinical trial, we have compared the equivalent intubating dose (3xED95) 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 (3xED95) ($p < 0.001$). 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 2xED95 dose in contrast to atracurium (El-Kasaby, A. M. et al., 2010; & Kaur, H. et al., 2018). This is attributed to the fact that there is an inverse relationship between the onset time and potency of NMBDs (Maheshwari, M. et al., 2019) and cisatracurium is approximately three times more potent than atracurium (Kim, Y. B. et al., 2017). Both the drugs provided excellent intubating conditions which may be due to the higher dose used (3xED95) and several studies have found comparable intubating conditions (very good to excellent) between the two. [12,15] The duration of action was longer in the cisatracurium group in contrast to atracurium. Our observations are in line with the findings of other researchers (El-Kasaby, A. M. et al., 2010; & Bakhshi, R. G. et al., 2016). Heart rate and mean blood pressure which were measured every minute following administration of cisatracurium and atracurium till intubation and then every five minutes thereafter throughout the surgery were comparable in both the group of patients. We did not observe any erythema, flushing, urticaria, sudden changes in haemodynamics and bronchospasm following administration of any of the NMBDs and during maintenance of anaesthesia. Haemodynamics and safety profile of both the drugs were comparable. Movafegh and colleagues had studied 100 patients for cost analysis and safety comparing equipotent doses (3xED95) of cisatracurium and atracurium in patients undergoing general anaesthesia and concluded that atracurium and cisatracurium had similar safety profile and both the drugs can be used safely during anaesthesia (Movafegh, A. et al., 2013). Another interesting observation we had, the recovery time after administration of cholinesterase inhibitors (from TOF2 to TOF4) which was faster in the

cisatracurium group, ensuring rapid recovery from neuromuscular blockade at the end of surgery. This observation of ours is in sharp contrast to the study done by Rocca and colleagues (Della Rocca, G. et al., 2003) to compare the cumulative index, the recovery, the onset, and the duration of action, of atracurium, cisatracurium, vecuronium, and rocuronium. In our study, the average duration of surgery was around 70 minutes. Only six patients in the cisatracurium group and eight patients in the atracurium group needed a single top-up dose. We could not study the duration of action of top-up dose as the surgery got over. To summarize, the equipotent dose of cisatracurium had longer onset time, and duration of action was significantly prolonged than atracurium. Both the drugs are safe as regards to cardiovascular parameters and there were no signs of histamine release in any patient of both the 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. We conclude that cisatracurium is a better drug in terms of neuromuscular blocking properties in comparison to atracurium. Both drugs have comparable haemodynamic parameters and safety profile

CONCLUSION

Equipotent dose of atracurium had faster onset than cisatracurium. But, the duration of action was longer in cisatracurium as compared to atracurium. The recovery profile of cisatracurium was faster and better than atracurium. Both the drugs have comparable haemodynamic parameters, intubating conditions, and safety profile..

REFERENCES

1. Khan, Z. H., Hajipour, A., Zebardast, J., & Alomairi, S. R. (2018). Muscle Relaxants in Anesthesia Practice: A Narrative Review. *Archives of Anesthesiology and Critical Care*, 4(4), 547-552.
2. Dewachter, P., & Mouton-Faivre, C. (2015). Anaphylaxis incidence with rocuronium, succinylcholine, and atracurium: how risk communication can influence behavior. *Anesthesiology: The Journal of the American Society of Anesthesiologists*, 123(3), 735- 736.
3. Szakmany, T., & Woodhouse, T. (2015). Use of cisatracurium in critical care: a review of the literature. *Minerva Anestesiologica*, 81(4), 450-460.
4. Dieye, E., Minville, V., Asehnoune, K., Conil, C., Georges, B., Cougot, P., ... & Conil, J. M. (2014). Pharmacodynamics of cisatracurium in the intensive care unit: an observational study. *Annals of intensive care*, 4(1), 1-5.
5. Mitra, S., Purohit, S., Bhatia, S., Kalra, P., & Sharma, S. P. (2015). A comparative study of effect of sevoflurane on intubating conditions with rocuronium in neurosurgical patients. *Indian journal of anaesthesia*, 59(12), 774.

6. El-Kasaby, A. M., Atef, H. M., Helmy, A. M., & El-Nasr, M. A. (2010). Cisatracurium in different doses versus atracurium during general anesthesia for abdominal surgery. *Saudi journal of anaesthesia*, 4(3), 152.
7. Farooq, K., & Hunter, J. M. (2011). Neuromuscular blocking agents and reversal agents. *Anaesthesia & Intensive Care Medicine*, 12(6), 266-270.
8. Jeong, H. J., Lee, S. H., Kim, H. J., & Kwak, S. H. (2012). Effects on intubating conditions of pretreatment with remifentanyl before administration of cisatracurium. *Chonnam medical journal*, 48(2), 96-102.
9. Lee, H., Jeong, S., Choi, C., Jeong, H., Lee, S., & Jeong, S. (2013). Anesthesiologist's satisfaction using between cisatracurium and rocuronium for the intubation in the anesthesia induced by remifentanyl and propofol. *Korean journal of anesthesiology*, 64(1), 34.
10. Kirov, K., Motamed, C., Decailliot, F., Behforouz, N., & Duvaldestin, P. (2004). Comparison of the neuromuscular blocking effect of cisatracurium and atracurium on the larynx and the adductor pollicis. *Acta anaesthesiologica scandinavica*, 48(5), 577-581.
11. Mandal, P. (2002). Intubating conditions after cisatracurium administration: a dose response study in adults. *J Anaesth Clin Pharmacol*, 18, 147-51.
12. Kaur, H., ATTRI, J. P., CHAtrAtH, V., KAur, H., & Kaur, J. (2018). Recovery Profile of Atracurium versus Cisatracurium. *Journal of Clinical & Diagnostic Research*, 12(2).
13. Maheshwari, M., Sanwatsarkar, S., & Katakwar, M. (2019). Pharmacology related to paediatric anaesthesia. *Indian journal of anaesthesia*, 63(9), 698.
14. Kim, Y. B., Sung, T. Y., & Yang, H. S. (2017). Factors that affect the onset of action of non-depolarizing neuromuscular blocking agents. *Korean journal of anesthesiology*, 70(5), 500.
15. Bakhshi, R. G., Nagaria, A., Mohite, S. N., & Ahluwalia, G. (2016). Comparison of Neuromuscular Blockade and Recovery Characteristics of Cisatracurium Besylate versus Atracurium Besylate in Adult Surgical Patients. *differences*, 1(2), 3.
16. Movafegh, A., Amini, S., Sharifnia, H., Torkamandi, H., Hayatshahi, A., & Javadi, M. (2013). Cost analysis and safety comparison of Cisatracurium and Atracurium in patients undergoing general anesthesia. *Eur Rev Med Pharmacol Sci*, 17(4), 447-450.
17. Della Rocca, G., Pompei, L., Coccia, C., Costa, M. G., Cecchini, V., Vilardi, V., & Pietropaoli, P. (2003). Atracurium, cisatracurium, vecuronium and rocuronium in patients with renal failure. *Minerva anesthesiologica*, 69(7-8), 605