Original Article

Evaluation of the three different doses of cisatracurium during general anaesthesia: A prospective randomized study

Prashant Kumar, Jyoti Vats, Kiranpreet Kaur, Jyoti Sharma[1], Sanjay Johar

Department of Anaesthesiology and Critical Care, Pt. B.D. Sharma PGIMS, Rohtak, Haryana, [1]Department of Anaesthesiology, AIIMS Bhatinda, Punjab, India

Abstract

Background and Aims: The present study was conducted to determine the optimal dose of cisatracurium for intubating conditions and onset and offset of neuromuscular blockade. Data in Indian population are scarce, and hence, the present study was planned to evaluate different doses of cisatracurium.

Material and Methods: The prospective randomized double-blind study was conducted on 180 patients of either sex in the age group of 20-60 yrs., having physical status class I to III, scheduled for surgery under general anesthesia. After exclusion 154 patients were randomly divided into three groups comprising 52, 51, and 51, respectively, in Group A, Group B, and group C. They received 0.1 $mgkg^{-1}$, 0.2 $mgkg^{-1}$, and 0.3 $mgkg^{-1}$ of cisatracurium, respectively, to facilitate endotracheal intubation. Time of onset, intubating conditions, hemodynamic parameters, signs of histamine release, and recovery time were noted.

Results: Mean time to onset was maximum in group A (4.37 ± 0.48 minutes) and minimum in group C (2.33 ± 0.43 minutes). Intubating conditions were found excellent in 88% patients in group. Change in HR was found to be non-significant at all time periods, but decrease in MAP was found between 2 and 10 minutes in group C. Duration of action was longest in group C.

Conclusion: We conclude that cisatracurium in dose of 0.2 $mgkg^{-1}$ and 0.3 $mgkg^{-1}$ provides good-to-excellent intubating conditions within less than 3 minutes.

Keywords: Cisatracurium, neuromuscular blockers, stereoisomer

Introduction

Cisatracurium is a new non-depolarizing, benzylisoquinoline intermediate-acting neuromuscular blocking agent. It is a purified form of 1 of the 10 stereoisomers of atracurium and is three times more potent than atracurium. Compared with atracurium, lower doses of cisatracurium are required to achieve the adequate neuromuscular block (NMB). Laudanosine concentrations following cisatracurium are approximately a third of an equipotent dose of atracurium.[1] Studies have shown that histamine release with cisatracurium is less compared with that after atracurium treatment. Thus, anaphylactoid responses are rare. Wheezing, bronchospasm, rash, and itching following cisatracurium administration are also found to be rare.[2]

Cisatracurium and atracurium have similar pharmacodynamic profiles, except that cisatracurium leads to a slower onset; however, higher doses of cisatracurium may shorten onset time.[3] Cisatracurium provided superior hemodynamic stability in many studies.[4] Cisatracurium has an intermediate duration of action and onset. The average ED_{95} of cisatracurium is 0.05 $mgkg^{-1}$ in adults receiving opioid, nitrous oxide, and oxygen anesthesia. Opinions regarding the optimal dose of

Address for correspondence: Dr. Kiranpreet Kaur, 9J/52 Medical Campus, Rohtak, Haryana, India.
E-mail: Kiranpreet72@rediffmail.com

Access this article online

Quick Response Code:

Website: https://journals.lww.com/joacp

DOI: 10.4103/joacp.joacp_253_22

How to cite this article: Kumar P, Vats J, Kaur K, Sharma J, Johar S. Evaluation of the three different doses of cisatracurium during general anaesthesia: A prospective randomized study. J Anaesthesiol Clin Pharmacol 2024;40:69-74.

Submitted: 16-Jul-2022 **Revised:** 22-Oct-2022
Accepted: 09-Dec-2022 **Published:** 14-Mar-2024

cisatracurium are varied. Few studies have suggested 3 × ED_{95} as a recommended dose for intubation, and others have advocated higher doses. We evaluated different cisatracurium doses to determine the optimal dose for intubating conditions and onset and offset of the NMB. The present study was planned on Indian population because results may vary in different population settings because of variation in genetic factors. Moreover, it can also gather information about drug's safety on different inhabitants.

Material and Methods

This prospective randomized double-blind study was conducted in 180 patients of either sex, aged 20–60 years, belonging to the American Society of Anesthesiologists (ASA) physical status I–III scheduled for surgery under general anesthesia (GA) after approval from the institutional ethical committee (IEC/Th/18/Anst16) and registration with the trial registry [CTRI/2019/01/016873 (recruitment closed in April 2019)]. Informed consent was obtained from all the participants. Patients with a difficult airway, receiving drugs known to interact with NM-blockers such as aminoglycosides and phenytoin, and allergic to the study drug were excluded from the study. A total of 154 patients were included and randomized into Group A (n = 52), Group B (n = 51), and Group C (n = 51) by using computer-generated randomization [Figure 1 CONSORT]. The patients were examined preoperatively, and all required investigations were performed. Before the induction of anesthesia, surface electrodes were placed over the ulnar nerve at the wrist for neuromuscular monitoring using a train-of-four (TOF) watch. GA was induced in all patients with intravenous injection of fentanyl (2 μgkg^{-1}) and propofol (2 $mgkg^{-1}$). Group A, Group B, and Group C received 0.1, 0.2, and 0.3 $mgkg^{-1}$ of cisatracurium respectively, to facilitate orotracheal intubation. It is already proved in previous studies that dose 0.1 $mgkg^{-1}$, 0.2 $mgkg^{-1}$, and 0.3 $mgkg^{-1}$ corresponds to $2ED_{95}$, $4ED_{95}$, and $6ED_{95}$, respectively. The study drugs were diluted with normal saline to make a total volume of 10 mL by an anesthesiologist not involved in study and were injected as a bolus over 5 s. An anesthesiologist not involved in the data collection and analysis assessed the TOF response on a nerve stimulator. Anesthesia was further maintained using O_2 in 50% N_2O and sevoflurane.

Time of onset was recorded as the time taken to achieve TOF = 0 and was noted through stimulation every 12 s. Tracheal intubation was performed with an endotracheal tube of size 7.0 mm in females and 8.0 mm in males by consultant anesthesiologists who were aware of the protocol to minimize inter observer variation. Intubating conditions were assessed as excellent, good, poor, and inadequate depending on mouth opening, vocal cord movement, position of the vocal cord, and presence or absence of bucking. Intubating conditions were graded as follows:[5] Excellent: Easy passage of the tube without coughing and vocal cords relaxed with no movement and abducted. Good: Passage of the tube with slight coughing or bucking and vocal cords relaxed and abducted. Poor: Passage of the tube with moderate coughing or bucking and vocal cords moderately adducted. Inadequate: Vocal cords not relaxed and tightly adducted. The changes in hemodynamic parameters, that is, mean arterial pressure (MAP) and heart rate (HR), were assessed as secondary outcomes. Recordings were made every 1 min until 5 min after administering the muscle relaxant and every 5 min until the next 30 min thereafter. Signs of histamine release were observed, and the recovery time from

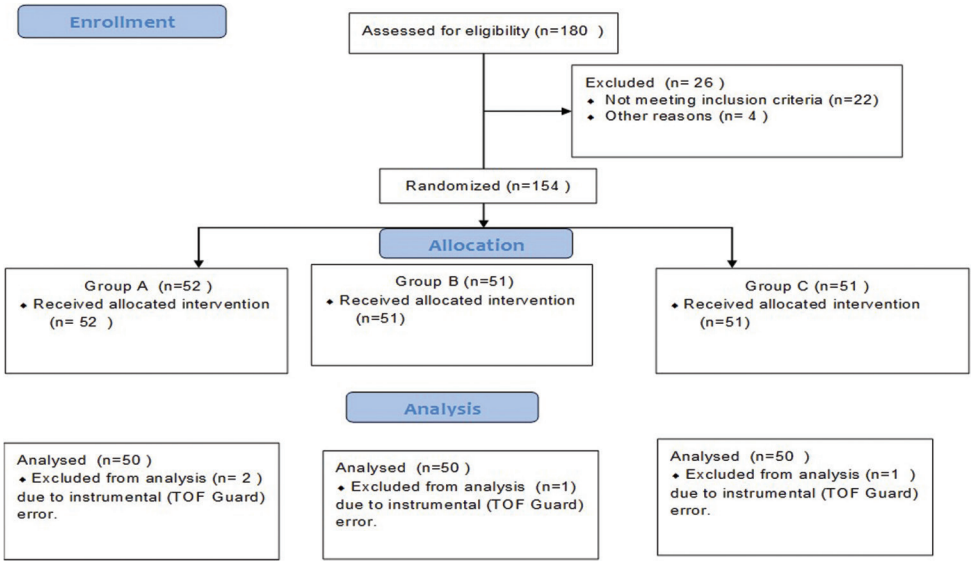

Figure 1: CONSORT

the loading dose of the neuromuscular blocking agent was noted as time to achieve TOF = 2.

Statistics

The primary objective of the study was to assess the efficacy of different doses of cisatracurium. The sample size calculation was based on the time of onset (time to maximal suppression of T1%). With reference to study by El Kasaby *et al.*,[5] a sample size of 47 per group was calculated on the basis of a difference of 1 in patients' mean onset time between any two groups, with a standard deviation of 1.5, a two-sided alpha of 0.05, and a power of 90%.

Statistical testing was conducted with the statistical package for the social science system version SPSS 17.0. Continuous variables were presented as mean ± SD or median interquartile range (IQR) for non-normally distributed data. Categorical variables were expressed as frequencies and percentages. The normally distributed continuous variables were compared between the groups using analysis of variance. Nominal categorical data between the groups were compared using either the Chi-square test or Fisher's exact test. The non-normally distributed continuous variables were compared using the Kruskal–Wallis test, and further paired comparisons were performed using the Mann–Whitney U test. For all statistical tests, a *P* value of less than 0.05 was considered to indicate a significant difference.

Results

The demographic data of the patients were comparable in all the three groups [Table 1]. Time of onset, intubating conditions, and recovery time are presented in Table 2. Mean time to onset was maximum in Group A (4.37 ± 0.48 min) and minimum in Group C (2.33 ± 0.43 min). Intergroup comparison revealed that the time to reach TOF = 0 was highly significant among all groups ($P < 0.001$). Intubating conditions were assessed and were excellent in 88% patients in Group C, followed by 84% in Group B and least (76%) in Group A. The difference in intubating conditions was statistically non-significant. Variation in the mean HR and MAP between the groups is graphically represented in Figures 2 and 3. Change in HR was non-significant at all time periods, but a decrease in MAP was observed at 2, 3, 4, 5, and 10 min in Group C and was significant compared with that in Group B ($P < 0.05$). No patient showed any positive evidence of histamine release in all the groups. Group C subjects had the longest duration of action among the three groups. Intergroup comparison revealed that the duration was highly significant between all the groups ($P < 0.001$).

Table 1: Demographic data

	Group A	Group B	Group C	*P*
Age (yrs)	36.06±12.92	40.88±12.84	38.80±12.95	0.177
Sex				
M	30 (60.0%)	34 (68.0%)	31 (62.0%)	0.765
F	20 (40.0%)	16 (32.0%)	19 (38.0%)	
Weight (kgs)	56.96±5.67	57.46±5.51	58.54±6.09	0.377
Height (cms)	162.36±8.04	163.3±5.75	164.52±7.19	0.311

Discussion

An anesthesiologist should endeavor to achieve three objectives when selecting a neuromuscular blocking agent to facilitate tracheal intubation, namely rapid adequate muscle relaxation, hemodynamic stability, and optimal duration with complete return of skeletal muscle function. Cisatracurium has the ability to produce NMB similar to atracurium, without the side effect of histamine release at high doses and laudanosine accumulation in the plasma. Its decomposition occurs in the blood plasma and extracellular fluid, and it is little affected by liver or kidney diseases. Despite these benefits, cisatracurium has limited use as it exhibits a slower onset and less satisfactory intubating conditions compared with other neuromuscular blocking agents when used in equipotent doses.[1,2] Hence, we evaluated different doses of cisatracurium to assess its onset, intubating condition, and total duration of action.

Time of onset was determined using different cisatracurium doses, and Group C demonstrated earlier onset of NMB than Group B and Group A. Our results indicated that the onset of NMB with cisatracurium, such as other non-depolarizing agents, is more rapid with higher doses. Doubling the initial dose decreased the time of onset time by approximately 1.5 min. Similar findings were observed by El-Kasaby *et al.*[5] who recorded time of onset as 4.37 ± 0.46, 2.9 ± 1.4, and 2.2 ± 1.2 min for 0.1, 0.2, and 0.3 mgkg^{-1}, respectively, which was nearly comparable to the time noted in our study. Variation in time duration was noted by few investigators. Carroll *et al.* recorded 2.42 ± 0.41 min with 0.1 mgkg^{-1} cisatracurium, and

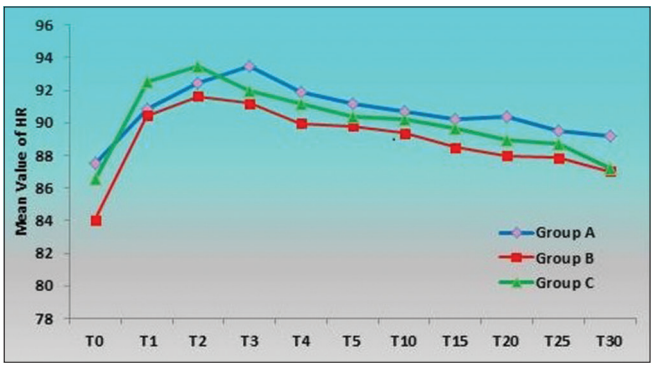

Figure 2: Variation in heart rate in different groups

Table 2: Time of onset & recovery and intubating conditions

Variables	Observations	Group A	Group B	Group C	*P*
Time of onset (min)		4.37±0.48*	2.96±0.41*	2.33±0.43*	<0.001*
Intubating conditions					
Mouth opening	Easy	50 (100%)	50 (100%)	50 (100%)	
VC movement	No	46 (92.0%)	46 (92.0%)	46 (92.0%)	
	Yes	4 (8.0%)	4 (8.0%)	4 (8.0%)	1.000
Vocal cord position	Abducted	47 (94.0%)	48 (96.0%)	48 (96.0%)	
	Adducted	1 (2.0%)	0	0	0.733
	Intermediate	2 (4.0%)	2 (4.0%)	2 (4.0%)	
Bucking	Bucking	7 (14.0%)	7 (14.0%)	5 (10.0%)	
	No	43 (86.0%)	43 (86.0%)	45 (90.0%)	0.786
Grading of intubation	Excellent	38 (76.0%)	42 (84.0%)	44 (88.0%)	
	Good	10 (20.0%)	7 (14.0%)	5 (10.0%)	0.613
	Poor	2 (4.0%)	1 (2.0%)	1 (2.0%)	
Time of recovery (min)		42.6±3.6*	60.55±5.97*	67.65±7.76*	<0.001*

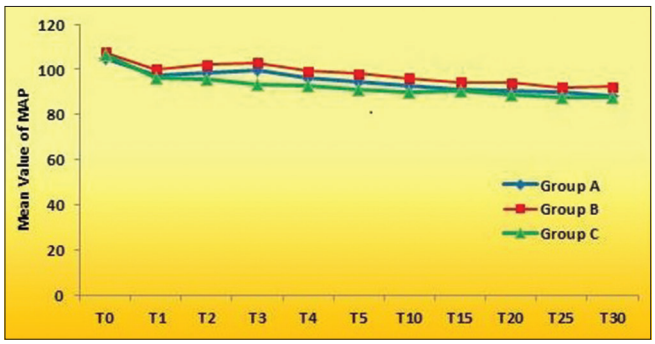

Figure 3: Variation in mean arterial pressure in different groups

Teymourian *et al.* recorded 1.6 ± 3.6 min with 0.3 mgkg^{-1} cisatracurium, which was a shorter time of onset than our observation.[6,7] Bluestein *et al.* suggested that an increasing dose of cisatracurium (from 0.1 to 0.2 mgkg^{-1}) decreases the mean time of onset (from 4.6 to 2.8 min, respectively).[8] Although a contrasting time of onset was observed by few authors, all the authors inferred that a higher dose of cisatracurium exhibits significantly less onset time compared with lower doses. Results on the time to TOF 0 are different in different publications, as this can vary depending upon genetic factor, skin resistance, type of stimulus, current, and sensor.[9]

Speed of onset of a neuromuscular blocker is influenced by factors such as the rate of delivery of the drug to the neuromuscular junction, receptor affinity, and plasma clearance.[10] Laryngeal adductors were found to be more resistant to the action of cisatracurium than adductor pollicis (AP) muscles; thus, recovery of NMB was faster at the larynx. Our results demonstrated that the onset of NMB was rapid in the AP muscle at a higher dose of cisatracurium. A high ED_{95} is predictive of rapid onset of the effect and vice versa. For the aforementioned reasons, we speculated that 6 ED_{95} (0.3 mgkg^{-1}) of cisatracurium provides the rapid onset of action in our subjects.[7]

The overall percentage of excellent intubating conditions was maximum in Group C. Other investigators also noted a similar finding that excellent intubating conditions exceeded beyond 80% when using 0.3 mgkg^{-1} cisatracurium.[5,7] Cisatracurium at a dose of 0.3 mgkg^{-1} provided appropriate muscle relaxation in the diaphragm and the AP and laryngeal muscles after 90 s. However, satisfactory intubating conditions were achieved by Bluestein and Rimaniol *et al.* with 0.2 mgkg^{-1} cisatracurium.[8,11]

The current study and other authors found that a better intubating condition was attained at higher doses. This may be explained by an inverse relationship between the potency of NMBs and their onset times. Cisatracurium is known to be a highly potent NMB agent. Although maximum block was achieved clinically with the use of a TOF guard at 4.37, 2.96, and 2.33 min by using 0.1, 0.2, and 0.3 mgkg^{-1} of cisatracurium, the intubating condition was still not excellent in few patients despite TOF = 0. Clinicians postulate that this may be because the vocal cords are more resistant to NMBs than the AP muscle; therefore, after 3 min of administering 0.1 mgkg^{-1} cisatracurium to these patients, vocal cord paralysis was less marked than AP. This is concurrent with the finding that 0.3 mgkg^{-1} cisatracurium produces satisfactory intubating conditions. The correlation between intubating conditions and the degree of NMB has not been studied much in the literature due to difference in NMB sensitivity and muscle flow at the AP and vocal cords or diaphragm. If the dose is increased sufficiently to quickly suppress the transmission at central muscle receptor sites, laryngoscopy and tracheal intubation can be successfully accomplished before peripheral twitch is abolished.[7,12] Thus, it was supposed that 2ED_{95} (0.1 mgkg^{-1}) does not create satisfactory intubating conditions, whereas 4ED_{95} (0.2 mgkg^{-1}) and 6ED_{95} (0.3 mgkg^{-1}) have nearly the same effect in providing appropriate conditions for intubation with rapid onset.

No significant change was established in the HR at any time period. All doses of cisatracurium induced the same trend of HR until the study was accomplished. Statistically non-significant tachycardia was observed after intubation in all groups probably due to the stress response of laryngoscopy and intubation. El-Kasaby *et al.*[5] noted a significant increase in HR with higher doses of cisatracurium ($4ED_{95}$ and $6ED_{95}$), which was observed 120 s after cisatracurium administration and following intubation. The increase in HR was ascribed to the stress response of intubation and inadequate relaxation of the patients. This finding was concurrent with a study by Schramm *et al.* and Jammer *et al.* who did not perceive any noteworthy changes in HR too and inferred that the maximum HR changes were small and non-significant.[13,14] The overall change in HR and MAP in the study was minimal, perhaps attributable to the use of N_2O, barbiturate, and fentanyl that masked the hemodynamic changes associated with histamine release, making it more difficult to recognize the clinical signs of this phenomenon. El Kasaby *et al.* and Larijani *et al.* observed an increase in MAP following intubation, which may be due to the intubation pressor response, whereas others recorded hypotension and tachycardia, which may be a response to thiopental administration.[5,15] However, other investigators, i.e., Teymourian *et al.*, Schramm *et al.* and Doenicke *et al.*, observed no significant hemodynamic changes in concordance to the present study.[7,13,16]

No signs of histamine release such as flushing, erythema, and itching were noted in any of the study groups. Other studies had a similar observation with no evident sign of histamine release.[7,16] The authors inferred that cisatracurium doses as high as 6–8 ED_{95} can be safe and have no histamine-mediated cardiovascular effect or cutaneous flushing.

The duration of action is designated as the time from the end of injection of the drug until 25% recovery of T_1. Group C had the longest duration of action among the groups, followed by Group B and Group A. Doubling the dose of cisatracurium from 0.1 to 0.2 $mgkg^{-1}$ prolonged the duration of action by approximately 19 min. In contrast to our study findings, Jammer *et al.* found that the time of recovery for 0.2 mgk^{-1} cisatracurium was 44.42 ± 3.14 min, which was significantly shorter than that observed in our study.[11] The current study largely confirms the finding of El-Kasaby *et al.*, Carroll *et al.*, Bluestein *et al.*, and Larijani *et al.* that increasing the dose of cisatracurium increases the mean time of recovery.[5,6,8,15]

The duration of action depends on the drug potency and the drug dose used. Non-depolarizing neuromuscular blockers of high potency such as cisatracurium have fewer molecules to diffuse from the central compartment into the effect compartment. Buffered diffusion occurs in a highly potent drug and causes repetitive binding and unbinding to receptors, which keeps potent drugs nearer to the effectors sites and lengthens the duration of effects.[7] Increasing the dose from $2ED_{95}$ to $4ED_{95}$ prolongs the duration of blockade. Doubling the dose results in additional NM block, which may be helpful in surgeries exceeding 1 h.

Our study had a few limitations. All participants were healthy adults of ASA class I and II. Our study had a small sample size and was limited to one geographical area only. Although fluid was transfused as the standard protocol, and laryngoscopy was limited by an experienced consultant anesthesiologist to minimize the confounding effects, further comparative multicenter studies with a larger study group are required to obtain global results.

Conclusion

Cisatracurium in dosages of 0.2 and 0.3 $mgkg^{-1}$ was observed to minimize the time of NMB onset and offer good-to-excellent intubating conditions within less than 3 min but prolongs the period of spontaneous recovery. The onset of cisatracurium, however, is delayed at 0.1 $mgkg^{-1}$. The main benefit of cisatracurium is the absence of histamine release, which offers good hemodynamic stability. Cisatracurium is therefore a more promising alternative NMB in clinical practice due to its fast onset and longer duration of action at the doses 4ED95 or 6ED95, which also provides greater cardiovascular stability and predictable recovery.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form, the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

References

1. Bryson HM, Faulds D. Cisatracuriumbesilate. A review of its pharmacology and clinical potential in anaesthetic practice: Drugs 1997;53:848-66.
2. Soukup J, Doenicke A, Hoernecke R, Qass J. Cisatracurium is the stereoisomer an “ideal” relaxant? Histamine liberation and

tryptase determination after bolus administration of cisatracurium: A comparison with vecuronium. Anaesthesist 1997;46:486-91.
3. Lee H, Jeong S, Choi C, Jeong H, Lee S, Jeong S. Anesthsiologist's satisfaction using between cisatracurium and rocuronium for the intubation in the anaesthesia induced by remifentanil and propofol. Korean J Anesthesiol 2013;64:34-9.
4. Hemmerling TM, Russo G, Bracco D. Neuromuscular blockade in cardiac surgery: An update for clinicians. Ann Card Anaesth 2008;11:80-90.
5. El-Kasaby AM, Atef HM, Helmy AM, Abo El-Nasr. Cisatracurium in different doses versus atracurium during general anaesthesia for abdominal surgery. Saudi J Anaesth 2010;4:152-7.
6. Carroll MT, Mirakhur RK, Lowry D, Glover P, Kerr CJ. A comparison of the neuromuscular blocking effects and reversibility of cisatracurium and atracurium. Anaesthesia 1998;53:744-8.
7. Teymourian H, Samet MA, Mohajerani SA, Jafari A. Comparison of modified and high dose of cisatrcurium for rapid sequence intubation. Asian J Pharm, Nurse Med Sci 2014;2:2321-3639.
8. Bluestein LS, Stinson LW, Lennon RL, Quessy SN, Wilson RM. Evaluation of cisatracurium, a new neuromuscular blocking blocking agent, for tracheal intubation. Can J Anaesth 1996;43:925-31.
9. Naguib M, Brull SJ, Johnson KB. Conceptual and technical insights into basis of neuromuscular monitoring. Anaesthesia 2017;72:16-37.
10. Donati F, Meistelman C. A kinetic-dynamic model to explain the relationship between high potency and slow onset time for neuromuscular blocking drugs. J Pharmacokinet Biopharm 1991;19:537-52.
11. Rimaniol JM, Kersuzan Y, Duvaldestin. Intubating conditions using cisatrcurium after induction of anaesthesia with thiopentone. Anaesthesia 1997;52:998-1014.
12. Kirov K, Motamed C, Decailliot F, Behforouz N, Duvaldestin P. Comparison of the neuromuscular blocking effect of cisatracurium and atracurium on the larynx and the adductor pollicis. Acta Anaesthesiol Scand 2004;48:577-81.
13. Schramm WM, Jesenko R, Bartunek A, Gilly H. Effect of cisatrcurium on cerebral and cardiovascular hemodynamics in patients with severe brain injury. Acta Anaesthesiol Scand 1997;41:1319-23.
14. Jammar P, Pathak DG, Begum I, Chauhan RC. A clinical comparative study of two intubating doses of cisatracurium during general anaesthesia for gynaecological surgery. Int J Basic Clin Pharmacol 2017;6:1206-10.
15. Larijani GE, Gratz I, Silverberg M, Jacobi AG. Clinical pharmacology of the neuromuscular blocking agents. DICP 1991;25:54-64.
16. Doenicke A, Soukup J, Hoernecke R. The lack of histamine release with cisatracurium: A double-blind comparison with vecuronium. Anesth Analg 1997;84:623-8.