Archives of Anesthesiology and Critical Care (Autumn 2024); 10(Supplement 2): 608-614.

Available online at http://aacc.tums.ac.ir

Research Article

Comparison of the Impact of Atracurium and Cisatracurium on the Neutrophil-To-Lymphocyte Ratio in Addition to Hemodynamic Changes during Anesthesia Induction

Behzad Nazemroaya[1]*, Sahand Taei[2]

[1]Department of Anesthesiology and Critical Care, School of Medicine, Isfahan University of Medical Sciences, Isfahan, Iran.

[2]School of Medicine, Isfahan University of Medical Sciences, Isfahan, Iran.

ARTICLE INFO

Article history:
Received 07 April 2024
Revised 30 April 2024
Accepted 16 May 2024

Keywords:
Neuromuscular blocking agents;
Neutrophil-to-Lymphocyte ratio;
General anesthesia;
Demargination;
Migration

ABSTRACT

Background: Muscle relaxants are used for two general purposes. One is to ease endotracheal intubation, and the other is provide surgical relaxation.
This study has been designed with the aim of assessing the impact of atracurium and cisatracurium on patients at the anesthesia induction and the neutrophil to lymphocyte ratio.

Methods: This is a randomized clinical trial that was performed in 2022-2023 in Kashani hospital in Isfahan, Iran on patients that were candidates for elective surgery under general anesthesia by atracurium or cisatracurium. A total number of 80 patients entered and were randomized into two group's one receiving group atracurium 0.5mg/kg, and other group received cisatracurium 0.15mg/kg over 60 seconds as NMB. Blood sample were taken base time, after 3, and 20 minutes following intubation. Qualitative data is reported as frequency with percentage. And quantitative data as average with standard deviation. Statistical analysis was done using SPSS version 25. Qualitative data were analyzed using chi-square tests and quantitative data using independent T test. Significance level was defined as p value <0.05.

Results: Overall, 80 patients were enrolled in this study. 40 of them belonged to the cisatracurium group and 40 to the atracurium group. Average age of the participants was 42.86 (±14.52) years old. Mean arterial pressure (MAP) in cisatracurium group dropped significantly following intubation (p<0.005), while it rose significantly in the atracurium group (p<0.05). However neutrophil to lymphocyte ratio (NLR) was significantly higher in the cisatracurium group following intubation (P<0.05).

Conclusion: While the use of atracurium in patients is still safe, is yet more correlated with pronounced hemodynamic instability compared to cisatracurium.

Introduction

Anesthesiologists play a major role in any surgery; however, their main objective is to provide and maintain a patent airway. Rapid and safe endotracheal intubation is of extreme importance in general anesthesia. Muscle relaxants are used for two general purposes. One is to ease endotracheal intubation, and the other is provide surgical relaxation [1-2]. Suxamethonium, a depolarizing neuromuscular blocking (NMB) agent is the "gold standard" for tracheal intubation [3] in most cases. However as it comes with a variety of complications and side effects such as muscle pain-related discomfort and rare potentially lethal multi-organ complications [4], anesthesiologists have been looking for other solutions. Atracurium and Cisatracurium are two non-depolarizing NMB agents

The authors declare no conflicts of interest.

*Corresponding author.
E-mail address: behzadnazemroaya797@gmail.com

with intermediate duration of action [5]. Cisatracurium is the R-cis isomer of atracurium and is 3-4 times more potent than atracurium. It is also associated with a lower tendency to cause histamine release and a longer onset of action [6]. Furthermore, atracurium could cause hemodynamic instability particularly in patients with a previous cardiovascular problem. Except this difference, most other characteristics of the two drugs are similar.

Considering that histamine is a vasoactive substance, it could cause hypotension and tachycardia in patients. It also facilitates phagocyte chemotaxis and migration across the vascular wall [5-6]. Histamine not only causes hemodynamic instability, it is also a potent messenger for inflammation and causes cell apoptosis [7-8], severely hampering the recovery period both during and after a surgery. Moreover, a histamine release and the subsequent inflammation during the surgery can severely impact the course of the surgery by causing bronchospasms and spikes in blood pressure and heart rate [9-10]. on the other hand, given the many functions neutrophils bring to the inflammatory process, the tightly regulated recruitment of these cells has been a major subject of research for many years. Recruitment of neutrophils to the site of inflammation (Forward migration) follows several specific patterns [11]. The demargination process is an event that has not been well characterized or explored. What is known about circulating neutrophils (demarginated neutrophils) is that this process is prevalent following strenuous exercise, smoking, stress, and ingestion of food. Even though the mechanism of demargination is not completely understood, certain factors such as stress hormones, in particular glucocorticoids and catecholamines can alter the different stages of the adhesion cascade [11].

Objectives

Minimizing inflammation and ensuring a smooth course for surgery is an important part of the anesthesiologist role. This study has been designed with the aim of assessing the impact of atracurium and cisatracurium on patients at the anesthesia induction.

Methods

Trial design and setting

This was a double blinded randomized controlled trial conducted in Isfahan, Iran between 2022 and 2023 on patients undergoing general surgery with the goal of assessing the safety profile and effect on hemodynamic stability and lymphocyte to neutrophil ratio of atracurium and cisatracurium. The trial protocol was approved by medical university of Isfahan committee of ethics (IR.MUI.MED.REC.1401.230) and, was in concordance with the CONSORT (consolidated standards of reporting trials) 2010 guidelines (IRCT20160307026950N48). Two different investigators prepared and analyzed the trial database independently. Both the authors involved and the patients were unaware of their grouping and after the data were collected were made aware. Sample size was calculated as 80 patients in total, divided in two groups. Inclusion criteria was patients the patient being between 18 to 65 years old, the patient being classified in American society of anesthesiologist (ASA) Physical Status Classification System group I or II, i.e. The patient also had to be a candidate for general anesthesia by atracurium or cisatracurium. Exclusion criteria was allergy to the medications used (atracurium or cisatracurium), a BMI of over 30, history of asthma, myocardial infarction or brain stroke in the past six months, atrial or ventricular fibrillation or flutter, and antihistamine or corticosteroid usage within one week of surgery.

Intervention

Patients who met the inclusion criteria were then asked to fill out a consent form. Afterwards they were divided in two groups using a random number generator. Patients were entered into the operation room and were under standard monitoring (blood pressure, electrocardiography, respiratory and heart rate, pulse oximetry). Standard general anesthesia proceeded for all patients. First blood sample was taken after the patient was eased into the bed and their stress was reduced. Afterwards induction was started. All of the patients received 1mg midazolam as pretreatment. General anesthesia was induced using thiopental sodium IV 5mg/kg as sedative, afterwards patients in group A received atracurium 0.5mg/kg, and patients in group B received cisatracurium 0.15mg/kg over 60 seconds as NMB. All of the patients also received fentanyl 100µg as analgesic. Second blood sample was taken just after drug administration. After 3 minutes of manual ventilation, intubation and mechanical ventilation using a mixture of 65% nitrous oxide and oxygen was used and the third sample was taken. Blood sample were again taken after 3-, 5-, 10- and 20-minutes following intubation. NMB dosage was repeated based on the type of surgery every 20 to 40 minutes. Patients in group A received 0.1mg/kg atracurium and group B received 0.03mg/kg cisatracurium. All of the patients also received propofol (0.1-0.2 mg/kg.hr) infusion during the surgery. NMB reversal was done using a mixture of neostigmine (0.04mg/kg) and atropine (0.2mg/kg).

Outcome

Demographic information of the patients (including age, weight and comorbidities) was recorded. Systolic and diastolic blood pressure (SBP, DBP), neutrophil and lymphocyte count were taken during the surgery and recorded. Complications such as nausea, vomiting, hypotension (blood pressure <30% of base), bradycardia (pulse rate <60), hypertension or tachycardia (increase of >30% in either), laryngospasm or respiratory depression were recorded.

Statistical analysis

Qualitative data is reported as frequency with percentage. And quantitative data as average with standard deviation. Statistical analysis was done using SPSS version 25 (SPSS Inc., Chicago, IL, USA). Qualitative data were analyzed using chi-square tests and quantitative data using independent T test. Significance level was defined as p value <0.05.

The frequency of hypotension and bradycardia during the surgery were significantly higher among patients that received 4 mg/min labetalol (P= 0.002, P= 0.001 respectively). During recovery, the patients that received 4 mg/min labetalol had significantly higher frequencies of nausea/vomiting (P= 0.006), total surgical complications (P< 0.001) and total complications during recovery (P< 0.001)

We had no complications such as nausea or laryngospasms in our study, we also had no cases of hypotension, bradycardia, tachycardia or hypertension. Average time until patients regained breathing was 10 (±5.21) minutes in the atracurium and 14.86 (±9.92) in the cisatracurium group with this difference being statistically significant (p=0.015, 95%CI = [-4.86 – 1.93]). Average recovery time following anesthesia was 56.28 (±14.35) minutes in the atracurium group and 62.44 (±19.14) in the cisatracurium group. While average recovery time was higher in the cisatracurium group, there was no statistically significant difference between the two (p>0.05).

Results

Overall, 80 patients were enrolled in this study. 40 of them belonged to the cisatracurium group and 40 to the atracurium group (Figure 1).

Average age of the participants was 42.86 (±14.52) years old; gender distribution was nearly 1:1, with 29 (44.6%) male and 31 (55.4%) female. Demographic characteristics of the patients was not significantly different (Table 1).

Average base SBP of the patients was 124.33 (±16.87) in the atracurium and 144.32 (±20.88) in the cisatracurium group (p<0.05) (Figure 2).

Average DBP of the patients was 71.97 (±14.21) in atracurium and 91.2 (±14.7) in cisatracurium group (p<0.05) (Figure 3).

Blood pressure in cisatracurium group dropped significantly following intubation (p<0.005, 95%CI= [8.98 – 27.46]), while it rose significantly in the atracurium group (p<0.05, 95%CI= [(-16.66) – (-4.68)]). Heart rates were similar between groups, with an average of 83 (±13.97) in atracurium group and 81.08 (±13.46) in cisatracurium group (p>0.05). the patients in cisatracurium group showed a significant drop in diastolic blood pressure following intubation (p<0.05, 95%CI= [6.76 – 17.39]), and the patients in atracurium group showed a significant increase in blood pressure (p<0.01, 95%CI= [(-13.53) – (-2.06)]. While the patients in atracurium group showed a small spike in heart rate and patients in cisatracurium group showed a drop in heart rate, there was no statistical significance (p>0.05).

Average neutrophil count was 56.32 (±7.44) % in our study with the atracurium group having 58.56 (±7.83) % neutrophil and cisatracurium having 62.99 (±13.75) %. This number was 55.62 (±7.12) % in the atracurium group 20 minutes following intubation and 64.51 (±11.59) in the cisatracurium group. There was no statistically significant difference between the groups before surgery, however neutrophil to lymphocyte ratio (NLR) was significantly higher in the cisatracurium group following intubation (P<0.05) (Table 2).

The frequency of hypotension and bradycardia during the surgery were significantly higher among patients that received 4 mg/min labetalol (P= 0.002, P= 0.001 respectively). During recovery, the patients that received 4 mg/min labetalol had significantly higher frequencies of nausea/vomiting (P= 0.006), total surgical complications (P< 0.001) and total complications during recovery (P< 0.001)

We had no complications such as nausea or laryngospasms in our study, we also had no cases of hypotension, bradycardia, tachycardia or hypertension. Average time until patients regained breathing was 10 (±5.21) minutes in the atracurium and 14.86 (±9.92) in the cisatracurium group with this difference being statistically significant (p=0.015, 95%CI = [-4.86 – 1.93]). Average recovery time following anesthesia was 56.28 (±14.35) minutes in the atracurium group and 62.44 (±19.14) in the cisatracurium group. While average recovery time was higher in the cisatracurium group, there was no statistically significant difference between the two (p>0.05).

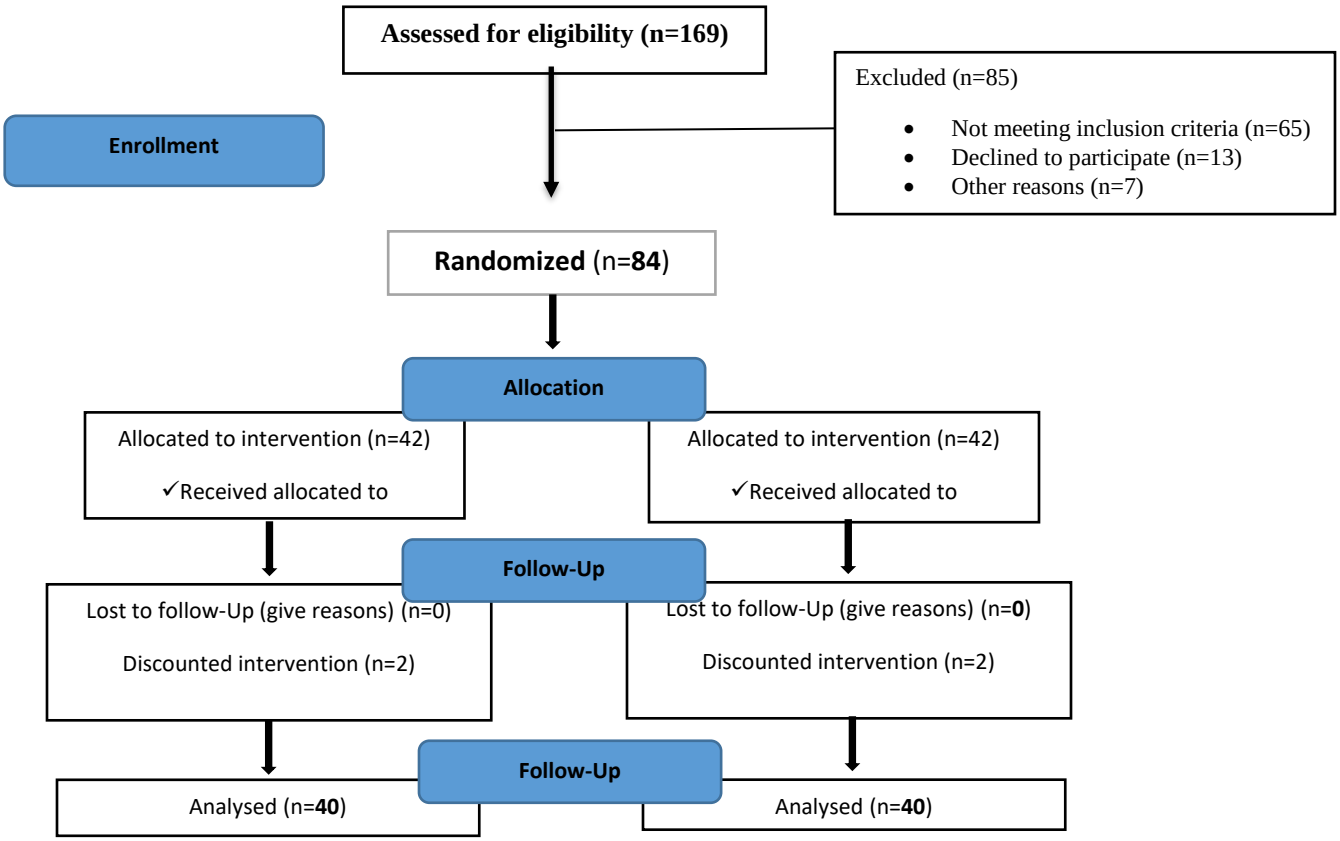

Figure 1- Study flow diagram

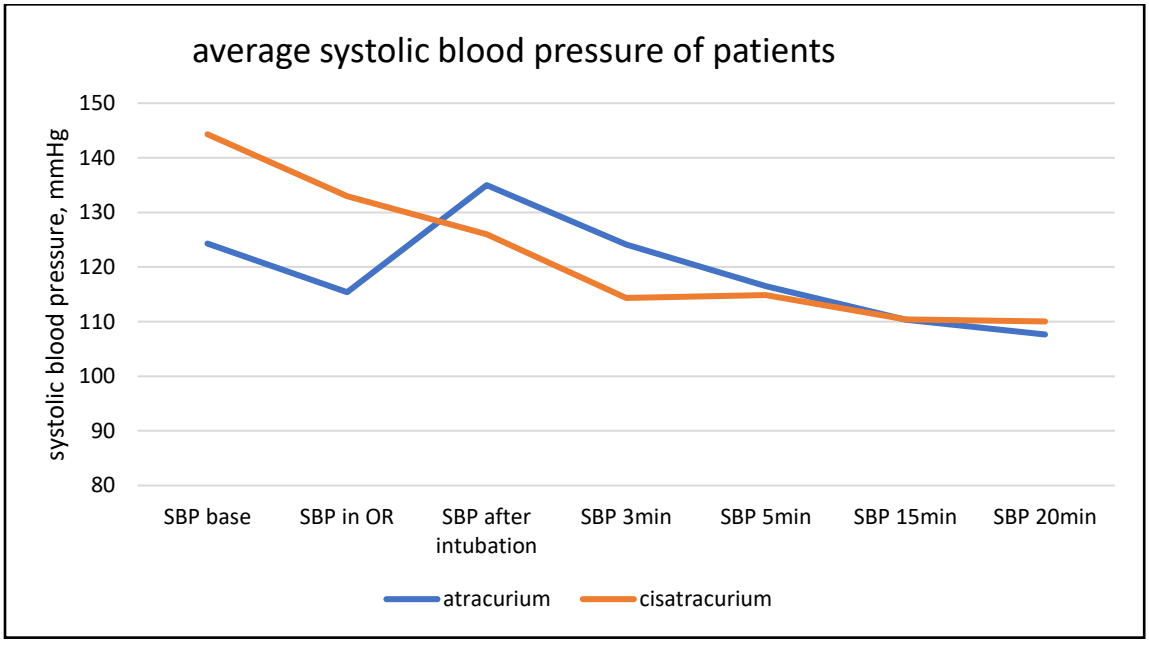

Figure 2- Mean systolic blood pressure of the patients before and during the surgery

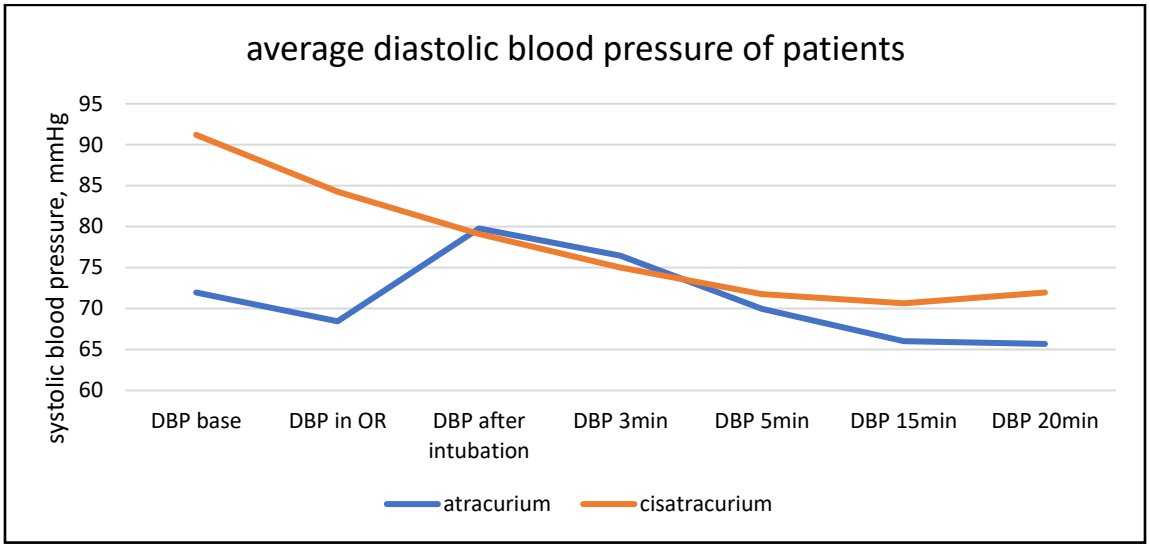

Figure 3- Mean diastolic blood pressure of the patients before and during the surgery.

Table 1- Demographic and preoperative characteristics of the patients.

Variable		Atracurium, n=40	Cisatracurium, n=25	P value
Age, mean years (±SD)		42.95 (±13.85)	41.32 (±15)	0.332
Gender, n(%)	Male	17 (42.5%)	12 (48%)	0.557
	Female	23 (57.5%)	13 (52%)	
BMI, mean kg/m2 (±SD)		24.07 (±3.89)	26.06 (±4.62)	0.076

p value was calculated using chi square and independent T test. Significance is defined as $p<0.05$.

Table 2- Neutrophil, lymphocyte and Neutrophil to Lymphocyte ratio of the patients before and during surgery.

Variable		Base	3min	20min	P value
Atracurium, average % (±SD)	Neutrophil	58.56 (±7.83)	53.33 (±7.64)	55.62 (±7.12)	0.742
	Lymphocyte	31.32 (±6.17)	36.59 (±7.26)	33.44 (±5.78)	0.335
	NLR	2 (±0.7)	1.56 (±0.59)	1.75 (±0.57)	0.025
Cisatracurium, average % (±SD)	Neutrophil	62.99 (±13.75)	64.91 (±12.72)	64.51 (±11.59)	0.425
	Lymphocyte	29.68 (±12.15)	28.29 (±11.27)	29.16 (±11.2)	0.458
	NLR	2.26 (±1.29)	2.69 (±1.56)	2.63 (±1.53)	0.038
P value		0.303	<0.01	<0.01	

Discussion

This was a study focused on the effect of cisatracurium and atracurium as NMB agents used in general anesthesia on patient vital signs, neutrophil and lymphocyte count. We found that patients in the atracurium group showed a significant spike in systolic and diastolic blood pressure following intubation, while the patients in the cisatracurium group witnessed a drop in systolic and diastolic blood pressure. However, after intubation and in the subsequent measurements, there was no significant difference between the two groups. Showing that while the patients in the cisatracurium group had a significantly higher base blood pressure, the effects of cisatracurium on blood pressure can show a significant reduction in blood pressure, while atracurium, increases the blood pressure of the patients after administration. This opposite effect of the two drugs, was the reason that the patients showed a similar blood pressure following induction. Heart rates also followed a similar trend to blood pressure in the patients. The difference was that the patients had similar base heart rates, and while there was again a spike in the atracurium group and a drop in the cisatracurium group, the differences were not significant. Base neutrophil and lymphocyte counts in patients were similar in two groups, however the similarities ended there. We found that cisatracurium showed a significant increase in NLR, while it was reduced in the atracurium group. Furthermore, while the base NLR was similar between the two groups, following the administration of the drug, it was significantly higher in the cisatracurium group and while the difference was lower after 20 minutes, it was still significant. Atracurium and cisatracurium are both non-depolarizing NMB agents that act by antagonizing the neurotransmitter action of acetylcholine. One expected side effect of both drugs is a drop in blood pressure following induction [11-12].

While this was seen in the cisatracurium group, the atracurium group showed a marked increase in blood pressure following intubation, a result that was unexpected. In our study, the cisatracurium group was shown more hemodynamic stability, compared to the atracurium group. Comparable to the study by Paśko-Majewska et al. who reported similar findings [13]. MAP increase following atracurium administration has been shown in other studies as well [14-15]. However other studies have shown MAP decrease following atracurium administration, probably due to histamine release [16-17]. Overall, it seems that there are contradictory findings about the immediate effect of atracurium on blood pressure and heart rate. We suggest more studies be done on this matter. While previous studies have found signs of histamine release in patients undergoing anesthesia with atracurium [15, 18-19], in our study we found no such signs. There was no laryngospasm, no blood pressure drops, or erythema of the skin. In our study we found that patients who have undergone anesthesia with atracurium showed a reduced NLR compared to cisatracurium. Preliminary studies have shown that NMB, cisatracurium specially, could inhibit inflammatory pathways in the lungs and epithelial cells by binding to the acetylcholine receptor and reduce neutrophil migration [20-21].

Conclusion

However, the evidence is still slim and the results are inconclusive. In our study we found no signs of histamine release following the bolus injection of atracurium, however neutrophil demargination and migration following intubation could still have occurred, resulting in a lowered NLR that began to normalize quickly after a short period of time. Overall, we suggest more studies be done on NLR and neutrophil behavior following anesthesia induction by any of the NMB agents to better prepare for long term complications of continuous infusion of such drugs and for better understanding of the interplay between these drugs and the immune system.

In conclusion, atracurium, while still safe to use in patients, is yet more correlated with pronounced hemodynamic instability compared to cisatracurium.

Assistance with the study: we would like to thank the nursing staff on the operating room, especially Mrs. Mozhgan Namaki. Similarly, we would like to honour our study patients in this project.

References

[1] Chang HC, Liu SY, Lee MJ, Lee SO, Wong CS. Sugammadex reversal of muscle relaxant blockade provided less Post-Anesthesia Care Unit adverse effects than neostigmine/glycopyrrolate. J Formos Med Assoc. 2022; 121(12):2639-43.

[2] Priebe H-J. Should anesthesiologists have to confirm effective facemask ventilation before administering the muscle relaxant? J Anesth. 2016; 30(1):132-7.

[3] Plaud B, Baillard C, Bourgain J-L, Bouroche G, Desplanque L, Devys J-M, et al. Guidelines on muscle relaxants and reversal in anaesthesia. Anaesth Crit Care Pain Med. 2020; 39(1):125-42.

[4] Mazur B, Greguła A, Stachyrak K, Mika D, Kłos A, Turek K, et al. Safety and side effects of suxamethonium in clinical practice – literature overview. J Education, Health and Sport. 2024; 52:11-24.

[5] Farooq K, Hunter JM. Neuromuscular blocking agents and reversal agents. Anaesthesia & intensive care medicine. 2017; 18(6):279-84.

[6] Bhagat M, Haque E, Mishra A. Safety Comparison of Cisatracurium And Atracurium In Patients Undergoing General Anaesthesia. J Anesth Clin Res. 2023; 14(3):e123-e129.

[7] Zhou DR, Eid R, Miller KA, Boucher E, Mandato CA, Greenwood MT. Intracellular second messengers mediate stress inducible hormesis and Programmed Cell Death: A review. Biochim Biophys Acta Mol Cell Res. 2019; 1866(5):773-92.

[8] Dib K, Perecko T, Jenei V, McFarlane C, Comer D, Brown V, et al. The histamine H4 receptor is a potent inhibitor of adhesion-dependent degranulation in human neutrophils. J Leukoc Biol. 2014; 96(3):411-8.

[9] Baldo BA. Toxicities of opioid analgesics: respiratory depression, histamine release, hemodynamic changes, hypersensitivity, serotonin toxicity. Arch Toxicol. 2021; 95(8):2627-42.

[10] Ghorbanlo M, Mohaghegh MR, Yazdanian F, Mesbah M, Totonchi Z. A comparison between the hemodynamic effects of cisatracurium and atracurium in patient with low function of left ventricle who are candidate for open heart surgery. Medical Archives. 2016; 70(4):265.

[11] Dahdah A, Johnson J, Gopalkrishna S, Jaggers RM, Webb D, Murphy AJ, et al. Neutrophil Migratory Patterns: Implications for Cardiovascular Disease. Front Cell Dev Biol. 2022; 10:795784.

[12] Schramm WM, Papousek A, Michalek-Sauberer A, Czech T, Illievich U. The Cerebral and Cardiovascular Effects of Cisatracurium and Atracurium in Neurosurgical Patients. Anesth Analg. 1998; 86(1):123-7.

[13] Paśko-Majewska M, Owczuk R, Wujtewicz M. [Comparison of atracurium, cisatracurium and vecuronium during anaesthesia for laparoscopic surgery]. Anestezjol Intens Ter. 2011; 43(1):9-13.

[14] El-Kasaby AM, Atef HM, Helmy AM, El-Nasr MA. Cisatracurium in different doses versus atracurium during general anesthesia for abdominal surgery. Saudi J Anaesth. 2010; 4(3):152-7.

[15] Khobragade N, Sonwane RB. Comparative study of atracurium and cisatracurium for intubating conditions under general anaesthesia. IOSR J Dent

Med Sci. 2020; 19(2):52-6.
[16] Miller RD, Eriksson LI, Fleisher LA, Wiener-Kronish JP, Cohen NH, Young WL. Miller's anesthesia e-book: Elsevier Health Sciences; 2014.
[17] Guggiari M, Gallais S, Bianchi A, Guillaume A, Viars P, editors. Hemodynamic effects of atracurium in man. Annales Francaises D'anesthesie et de Reanimation; 1985.
[18] Kale J, Mahadik HA, Korde PM. A comparative study of Atracurium and Cisatracurium for assessment of intubating conditions. IJMA. 2020; 3(3):24-7.
[19] Kaur H, ATTRI JP, Chatrath V, KAur H, Kaur J. Recovery Profile of Atracurium versus Cisatracurium. Journal of Clinical & Diagnostic Research. 2018; 12(2).
[20] Kadry RW, Adil MS, Newsome AS, Somanath PR. Cisatracurium attenuates LPS-induced modulation of MMP3 and junctional protein expression in human microvascular endothelial cells. BioScience Trends. 2021; 15(1):50-4.
[21] Fanelli V, Morita Y, Cappello P, Ghazarian M, Sugumar B, Delsedime L, et al. Neuromuscular blocking agent cisatracurium attenuates lung injury by inhibition of nicotinic acetylcholine receptor-α1. Anesthesiology. 2016;124(1):132-40.