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Evaluation of the vasorelaxant effect of Sugammadex on the arterial smooth muscle in rats

Mustafa Karademir[1], Gulsah Altun[2], Dilay Karademir[3]

[1]Sivas Cumhuriyet University, Faculty of Medicine, Department of Neurosurgery, Sivas, Türkiye
[2]Sivas State Hospital, Department of Internal Medicine, Sivas, Türkiye
[3]Sivas Cumhuriyet University, Faculty of Medicine, Department of Gynecology and Obstetrics, Sivas, Türkiye

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Abstract

Although NMBAs (Neuro Muscular Blocking Agents) have been used for a long time, postoperative residual curarization is still a significant problem. Nowadays, an agent named Sugammadex is used for the reversal of curarization. It has been presented as a safer agent than its predecessor, neostigmine. The main purpose of this study is to investigate the effects of Sugammadex on rat thoracic aorta and enlighten the mechanism of action and potential benefits in surgical operations with general anesthesia. Twenty Wistar albino rats were used for the experiments. Thoracic aorta segments have been removed and mounted to the organ bath. Contraction and relaxation responses were presented as a percentage of phenylephrine ($3x10^{-5}$ M) contraction. After recording contractile responses of Sugammadex (10^{-8}-10^{-4} M), relaxation responses of Sugammadex (10^{-8}-10^{-4} M) have been recorded both in the presence and absence of L-NAME ($3x10^{-5}$ M) (Potent Nitric Oxide Sentase Inhibitor). Finally, relaxation responses of sugammadex-rocuronium have been recorded. Sugammadex caused slightly noticeable and concentration-dependent contraction on isolated thoracic aorta strips. Sugammadex also caused potent and concentration-dependent relaxation on isolated rat thoracic aorta. The relaxation response caused by Sugammadex has been diminished significantly in the presence of L-NAME. Administration of rocuronium with Sugammadex did cause neither relaxation nor any additional contractile effect on isolated rat thoracic aorta strips. Sugammadex is a promising agent in reversing rocuronium-induced neuromuscular block. Although the adverse effects of this agent are not studied in detail, it seems Sugammadex is safer than neostigmine. The side effects of anesthetic agents are one of the main problems of surgical procedures, including neurosurgery, gynecology, and obstetrics. Especially acute hypotension may be fatal in neurosurgery and gynecological operations. Sugammadex should be used carefully in adjusted and individualized doses to avoid hypotension-related adverse effects.

Keywords: Cerebral perfusion, neostigmine, hypotension, sugammadex, vasodilatation, nitric oxide

Introduction

Neuromuscular blocking agents (NMBAs) are essential in modern anesthetic practice to optimize surgical conditions by suppressing voluntary or reflex muscle movements [1]. There are two main categories of neuromuscular blocking agents (NMBAs): depolarizing agents (e.g., succinylcholine) and non-depolarizing agents (such as steroid-based and benzylisoquinoline muscle relaxants). While non-depolarizing muscle relaxants generally have fewer adverse effects, except for allergic reactions during anesthesia, they are associated with a well-recognized and significant issue known as postoperative residual curarization. This condition can lead to respiratory complications [2], upper airway dysfunction [3], increased risk of aspiration [4], and, consequently, the risk of postoperative pulmonary complications [5].

The intraoperative complications caused by NMBAs might be dangerous. Especially in neurosurgical operations, a sudden increase in blood pressure may result in brain swallowing and

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Corresponding Author: Mustafa Karademir, Sivas Cumhuriyet University, Faculty of Medicine, Department of Neurosurgery, Sivas, Türkiye
Email: krdmr58@gmail.com

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limit the surgeon's ability to operate. Hypoxia, hypercapnia, blood pressure fluctuations, and heart rate variations can increase intracranial pressure. This, in turn, can lead to irreversible neurological deficits and, in severe cases, even mortality [6].

The recovery process from NMBAs relies on reducing NMBA concentration at the Neuromuscular Junction (NMJ). However, complete restoration of neuromuscular function (NMR) can vary from person to person. Inadequate management of NMR can result in awake and paralyzed patients experiencing symptoms such as sympathetic hyperactivity, elevated blood pressure, increased heart rate, weakened skeletal muscles for respiration, and weakened glossopharyngeal muscles, making it challenging to protect the airway from secretions. Achieving a rapid and effective NMR prevents these complications [7].

There are three simple ways to avoid medical problems caused by muscle relaxants. The first one is to use something other than them. The second is to wait until the muscle relaxant is metabolized and the muscle function fully recovers spontaneously. The third and most compelling one is using an agent to antagonize the residual effect of muscle relaxants [8].

Cholinesterase inhibitors are widely used to reverse neuromuscular blockade caused by neuromuscular blocking agents such as pancuronium and rocuronium. Among cholinesterase inhibitors, neostigmine is the most potent and selective one. Although cholinesterase inhibitors can reverse neuromuscular blockade, they have a burden of side effects associated with their non-selectivity to muscarinic receptors. They may cause several serious side effects, including bradycardia, QT lengthening, bronchoconstriction, hypersalivation, and increased gastrointestinal motility [9,10].

Sugammadex has been developed as a novel type of reversal agent as an alternative to neostigmine [11]. It has a different mechanism of action from anticholinesterase neuromuscular antagonists [10,12]. The mechanism of action involves the encapsulation of NMBA molecules. This encapsulation alters the concentration gradient along which the molecules are distributed, causing the muscle relaxant molecules to move away from their receptors and return to the central compartment through simple diffusion [13,14]. It encapsulates and inactivates rocuronium and selectively binds to free rocuronium molecules with an affinity in a molar ratio of 1:1 [15]. However, Sugammadex is widely considered a safer and more effective agent for reversing neuromuscular block than neostigmine [16]. Because it has no endogenous targets, it is unlikely to cause significant adverse effects, including cardiovascular outcomes [17]. In addition to its beneficial effects, Sugammadex may also exhibit several side effects, such as mild headache, nausea, injection site irritation, dry mouth, fatigue, a cold sensation at the injection site, and oral discomfort [18], QT prolongation [19], risk of bronchospasm [20], and hypotension [21].

As a gradually new agent in clinical practice, the effect of Sugammadex on the brain vessels remains unknown. Only a few studies in the literature claim the hypotensive effects of sugammadex [21]. But these studies are primarily clinical and far from explaining possible mechanisms of action. Because of the gap in the literature, we aimed to investigate the effects of Sugammadex and its mechanism of action on the vasculature system by using rat thoracic aorta strips.

Material and Methods

Animals

The present study utilized twenty male Wistar albino rats weighing 180 and 200 grams. These rats were housed under standard laboratory conditions, with a 12-hour light and 12-hour dark cycle, and provided unrestricted access to tap water and food. The experimental procedures followed the guidelines in the "Guide for the Care and Use of Laboratory Animals." The study protocol received approval from the Animal Ethical Committee of Sivas Cumhuriyet University in Turkey. Ethics committee approval was obtained with the number 65202830-050.04.04-708 dated 17.12.2021.

Preparation of thoracic aorta tissue and performing contractility studies

The thoracic aorta segment was promptly extracted and delicately cleaned, taking care not to harm the endothelium while ensuring the removal of any surrounding connective tissue. The segment was then divided into rings measuring approximately 3 mm in diameter. These rings were subsequently cut open to create separate ring segments. Four individual smooth muscle rings of the thoracic aorta from each rat were obtained and examined independently.

The aortic strips were carefully placed in a 10 mL organ bath containing Krebs solution, which consisted of the following concentrations in mmol/L: 119 NaCl, 4.7 KCl, 2.5 CaCl2, 1 MgCl2, 25 NaHCO3, 1.2 K2HPO4, and 11 glucose. One end of the strips was attached to the tissue holder, while the other was connected to the Grass FT03 force-displacement transducer. The organ bath was continuously supplied with a mixture of 95% oxygen and 5% carbon dioxide, and the temperature was maintained at 37°C with a pH level between 7.3 and 7.4.

The tissue was allowed to equilibrate for 60 minutes under a resting tension of 1 g. The Krebs solution was replaced every 15 minutes with a new one. To assess smooth muscle contractility and evaluate the contraction responses achieved with phenylephrine, a concentration of 80 mmol/L of potassium chloride (KCl) was added at the beginning of the experiments.

Following the equilibration phase, the contractile responses to various concentrations of phenylephrine ranging from 10^{-8} to 10^{-4} mol/L were recorded.

To assess the potential contractile effect of Sugammadex on arterial rings, a cumulative application of Sugammadex was performed, ranging from 10^{-8} to 10^{-4} mol/L. Following this, the tissues were thoroughly washed and pre-contracted with

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phenylephrine at a concentration of 10^{-5} mol/L, which induced a contraction equivalent to 70% to 80% of the maximum response to phenylephrine. Once the phenylephrine-induced contraction reached a stable plateau, concentration-response relationships for Sugammadex (ranging from 10^{-8} to 10^{-4} mol/L) were established by incrementally adding this compound to the organ bath.

Furthermore, relaxation responses to Sugammadex were repeated in the presence of L-NAME at a concentration of $3x10^{-5}$ mol/L. Additionally, the effects of combining Sugammadex with rocuronium were investigated. Before adding the vehicle, the tissues were washed for 15 minutes.

Drugs

The chemicals utilized in the current experiments included phenylephrine and L-NAME, both procured from Sigma (St. Louis, Missouri, USA). Sugammadex and rocuronium were obtained in commercially available forms. Distilled water was employed as the solvent for dissolving all chemicals. Notably, all drugs were freshly prepared on the day of the experiments.

Statistical analysis

The data obtained from the experiments were presented as means±standard error (SE). Statistical analysis was performed using repeated measures analysis of variance (ANOVA). A p-value of less than 0.05 was deemed statistically significant.

Results

Since there is no study investigating the effects of Sugammadex on vascular smooth muscle, we did not know whether Sugammadex has contractile or relaxant effects on vascular smooth muscle. We tasted cumulative concentrations of Sugammadex (10^{-8}-10^{-4} M) isolated rat thoracic aorta. Sugammadex caused slightly noticeable and concentration-dependent contraction on isolated thoracic aorta strips (Figures 1A and 1B). The maximum contraction caused by Sugammadex was only 22±2.8% of phenylephrine contraction. Then, to determine if Sugammadex also has vasorelaxant effects on the vasculature system, cumulative concentrations of Sugammadex have been administrated on isolated rat thoracic aorta strips, which have been previously pre-contracted by $3x10^{-5}$ M phenylephrine. Interestingly, Sugammadex caused strong and concentration-dependent relaxation on isolated rat thoracic aorta. The maximum relaxation caused by Sugammadex was 88±3.2% of phenylephrine contraction (Figure 1C and 1D).

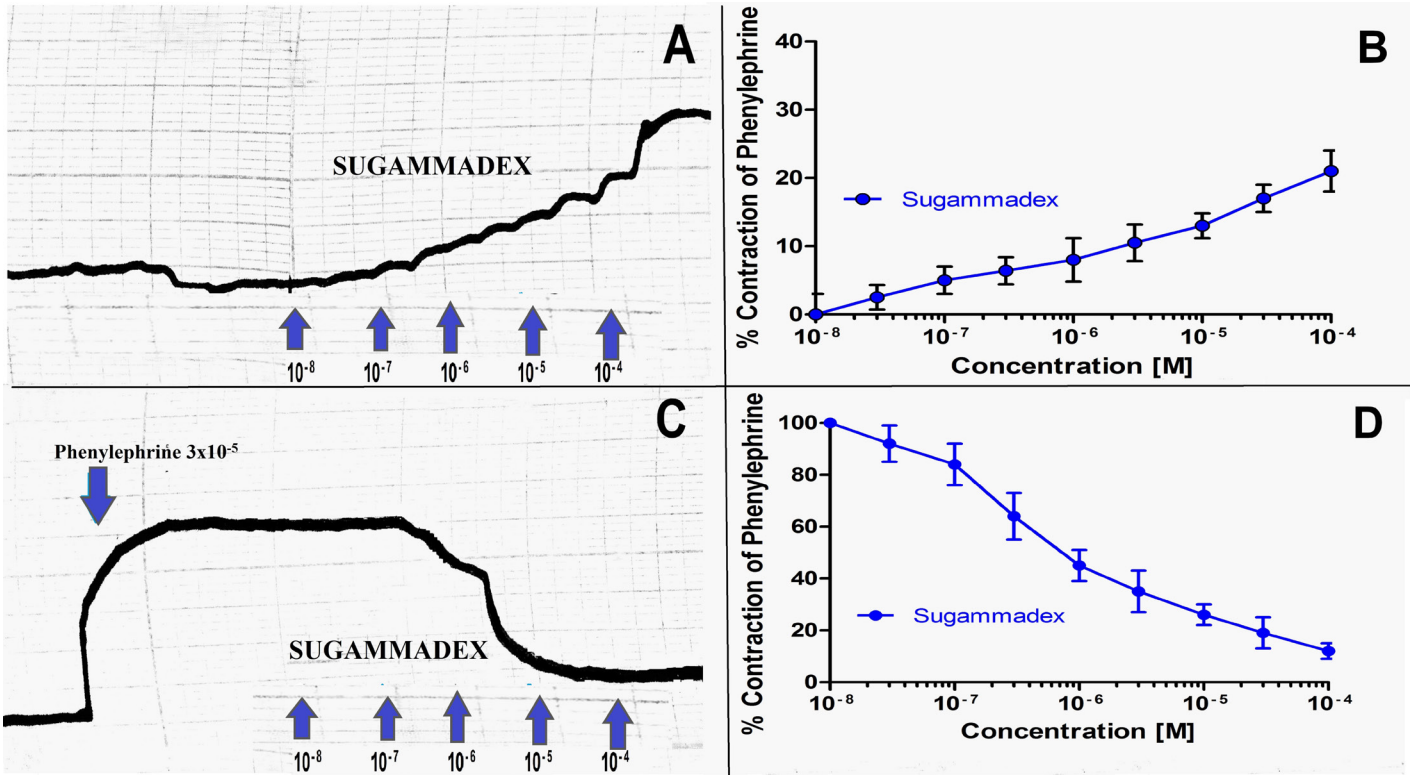

Figure 1. A. Analog record of concentration-dependent contraction of Sugammadex, **B.** Line graph of concentration-dependent contraction of Sugammadex (10^{-8}-10^{-4} mol/L), **C.** Analog record of concentration-dependent relaxation of Sugammadex (10^{-8}-10^{-4} mol/L) on isolated rat thoracic aorta strips precontracted with $3x10^{-5}$ phenylephrine, **D.** Line graph of concentration-dependent relaxation of Sugammadex (10^{-8}-10^{-4} mol/L) on isolated rat thoracic aorta strips precontracted with $3x10^{-5}$ phenylephrine

To enlighten the mechanism of action of Sugammadex and see if the nitrergic system has any role in the mechanism, relaxation responses of Sugammadex have been re-recorded in the presence of nitric oxide synthase inhibitor L-NAME. The relaxation response caused by Sugammadex has been diminished significantly in the presence of L-NAME ($p<0.05$).

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The difference in relaxation responses at 10^{-6}, 10^{-5}, and 10^{-4} M concentration was statistically different in a sugammadex+L-NAME group than in the Sugammadex-only group ($p<0.05$) (Figure 2A and 2B). Since, in clinical practice, Sugammadex would not be used without neuromuscular blocking agents like rocuronium, we tested if cumulative concentrations of rocuronium have vasorelaxant effects in the presence of Sugammadex. Administration of rocuronium with Sugammadex did not cause relaxation or any additional contractile effect on isolated rat thoracic aorta strips (Figure 2C).

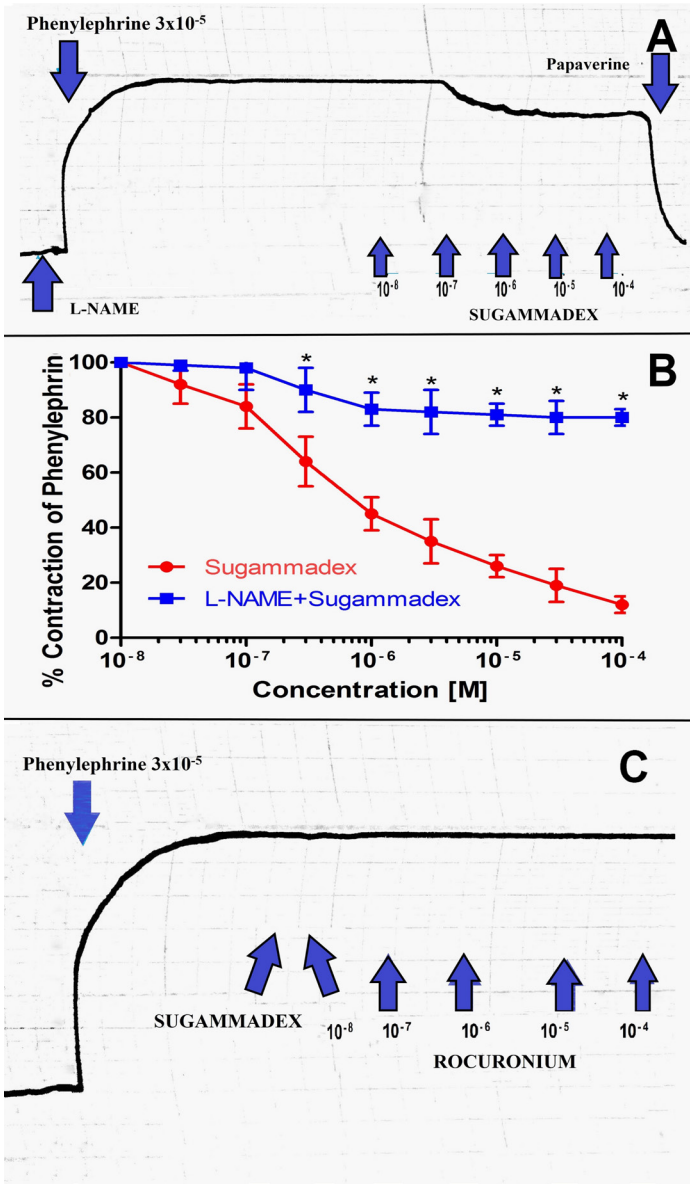

Figure 2.A. Analog record of concentration-dependent relaxation of Sugammadex (10^{-8}-10^{-4} mol/L) on isolated rat thoracic aorta strips precontracted with 3x10-5 phenylephrine, in the presence of L-NAME, **B.** Line graph of concentration-dependent relaxation of Sugammadex (10^{-8}-10^{-4} mol/L) on isolated rat thoracic aorta strips precontracted with $3x10^{-5}$ phenylephrine, in the presence and absence of L-NAME, **C.** Analog record of the effect of Sugammadex (10^{-8}-10^{-4} mol/L) in combination with rocuronium on isolated rat thoracic aorta strips precontracted with $3x10^{-5}$ phenylephrine

Discussion

NMBAs have commonly used drugs in the course of operation along with general anesthesia to facilitate tracheal intubation and optimize surgical conditions for surgeons by causing skeletal muscle relaxation [2]. Because of the diversity of their duration of action, NMBAs' residual neuromuscular blockade may cause complications in many systems, including the cardiovascular and neurovascular systems [22,23]. To reduce or avoid postoperative residual paralysis, anesthesiologists typically tend to reverse residual neuromuscular blockade with acetylcholinesterase inhibitors such as neostigmine. Growing evidence mentions that neostigmine reversal does not decrease the incidence of postoperative complications caused by NMBAs, including respiratory failure [24]. Because of these reasons, today, NMBAs are being used much less frequently than in past years [25]. This situation may change again with the increasing use of a gradually new agent named Sugammadex in clinical practice.

Although, Sugammadex is believed to be a safer and superior agent in neuromuscular block reversal when compared to neostigmine [17], there is not enough study about the adverse effects of Sugammadex, especially in the vasculature system. Since hemodynamic stability is one of the most important subjects during surgical operations, the impact of agents used in the procedure on the vasculature system is also essential, especially in neurosurgical procedures. Gursoy S. et al. [26] showed relaxant effects of pancuronium and rocuronium on rat thoracic aorta, which were pre-contracted with PG-F2α. They have also suggested that the relaxation effect of pancuronium and rocuronium was endothelium-independent because there was no significant response difference from the endothelium-denuded group. Since neuromuscular blocking agents have a vasodilator effect, the impact of Sugammadex, which natively tends to be used in combination with NMBAs, on the vasculature system is more important than ever.

Best of our knowledge, there is no direct study about the effect of Sugammadex on the vasculature system. So that reason, we investigated both the vasoconstrictive and vasorelaxant effects of Sugammadex. In the present study, we observed that Sugammadex has a weak vasoconstrictive and powerful vasorelaxant effect on isolated rat thoracic aorta. At first look, it may be more evident. But we believe that the weak vasoconstrictive effect of Sugammadex is related to its partial agonist effect against sympathetic system receptors.

There are two central systems regulating the vascular tonus. The first is the muscarinic system, and the second is the sympathetic system. Since Srivastava A et al. [27] showed in their study that Sugammadex does not directly interact with the cholinergic system. We suggest that vasocontraction caused by Sugammadex should be related to its partial agonist effect against sympathetic system receptors. This effect could find a chance to manifest itself because of the in-vitro nature of our study. In an in-vivo situation, this partial agonist effect would manifest as

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vasorelaxation because of endogen sympathomimetic agonists. The main effect of Sugammadex on isolated rat aorta was vasorelaxation. Sugammadex caused strong and concentration-dependent vasorelaxation on isolated rat aorta strips. There are only a few case reports in the literature about the hypotensive effect of Sugammadex. The first case of hypotension after Sugammadex was reported in 2006 [28]. There is only a second case in the literature presented by Kokki M et al. [21]. In both cases, hypotension occurred 10 minutes after the sugammadex injection, and in both cases, investigators did not propose a valid explanation for the vasodilation mechanism of Sugammadex.

In the present study, we performed relaxation experiments with L-NAME. L-NAME diminished relaxation responses caused by Sugammadex but did not altogether abolish. This finding may suggest that the primary mechanism in relaxation caused by Sugammadex is a nitrergic system dependent on endothelial function. On the other hand, at least one minor system contributes to the relaxation mechanism because L-NAME could not abolish relaxation caused by Sugammadex. Since using Sugammadex in the absence of NMBAs does not make sense, testing the effects of the sugammadex-rocuronium complex on rat thoracic aorta was crucial. The sugammadex-rocuronium complex did not show a vasoconstrictive or vasorelaxant effect on rat thoracic aorta strips. Although both Sugammadex and rocuronium have vasorelaxant effects on rat thoracic aorta, it seems they neutralize each other's vasorelaxant effect when they make sugammadex-rocuronium complex. This finding may seem contradictory with cases reported by Kokki M et al. and Sorgenfrei IF et al. [21,28].

We believe that while the amount of Sugammadex bounded to rocuronium would not cause any biological activity, the free, unbounded amount of Sugammadex would be responsible for hypotension. Consistent with our study, Bom A. et al. [29] showed that Sugammadex forms an inactive complex with rocuronium bromide, which has no biological activity. Avoiding excessive doses of Sugammadex would let practitioners limit the free, unbounded amount of Sugammadex and prevent Sugammadex-related hypotension. It has been mentioned in the case report of Ortiz-Gómez JR. et al. [30] that Sugammadex provides dose-dependent reversal of neuromuscular blockade (NMB) caused by rocuronium. This dose-dependent nature of deterioration supports our hypothesis.

Conclusion

In conclusion, Sugammadex is a promising agent in reversing rocuronium-induced neuromuscular block. Although the adverse effects of this agent are not studied in detail, it seems Sugammadex is safer than neostigmine. We have shown in the present study that Sugammadex has a vasorelaxant solid effect, and this effect is likely related to the nitrergic system. We also managed to show that the Sugammadex-rocuronium complex does not have a vasorelaxant effect. In surgical procedures, hypotension is dangerous because if the cerebral perfusion pressure drops, it may cause neuronal damage. On the other hand, hypertension is also hazardous because it may cause the brain to swallow. And all surgeons, including obstetricians, gynecologists, and general surgeons, may face severe intraoperative complications, including excessive bleeding. So regulating blood pressure is critical, and Sugammadex should be used carefully in adjusted and individualized doses.

Conflict of Interests
The authors declare that there is no conflict of interest in the study.

Financial Disclosure
The authors declare that they have received no financial support for the study.

Ethical Approval
Ethics committee approval was obtained with the number 65202830-050.04.04-708 dated 17.03.2023.

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