10.21608/avmj.2025.345396.1526 Assiut University web-site: www.aun.edu.eg

THE IMPACT OF REPEATED ADMINISTRATION OF SERRATIOPEPTIDASE ON ANESTHESIA

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Received: 23 December 2024; **Accepted:** 17 April 2025

ABSTRACT

Serratiopeptidase is a proteolytic enzyme originally derived from the bacterium Serratia species. It has been shown to possess a range of therapeutic effects, including anti-inflammatory, analgesic, and fibrinolytic activities. The objective of this study was to evaluate the effects of serratiopeptidase on the anesthetic response in mice, specifically focusing on the changes in oxygen saturation (SpO2), respiratory rate, and heart rate during anesthesia induction with xylazine and ketamine. Mice were administered serratiopeptidase (5, 10 or 20 mg/kg) orally for 15 days prior to anesthesia induction with xylazine and ketamine (10 and 150 mg/kg, respectively). Anesthetic parameters, including onset, duration, and recovery time, were recorded. Compared to the control group, the 5 and 10 mg/kg serratiopeptidase groups exhibited a significantly delayed onset and prolonged duration of anesthesia. Conversely, the 20 mg/kg group showed a shorter onset time, and a shorter duration of anesthesia compared to the 5 and 10 mg/kg groups. Recovery time was prolonged in the 20 mg/kg group. Compared to the control group, all serratiopeptidase-treated groups exhibited significantly higher SpO_2. Additionally, all treated groups showed a significant decrease in heart rate and a significant increase in respiratory rate. These findings suggest that serratiopeptidase exerts a limited dose-dependent effect on anesthetic response, likely through complex mechanisms involving neurotransmitter modulation and/or anti-inflammatory actions. Furthermore, serratiopeptidase may influence the physiological parameters associated with anesthesia in mice. Further research is warranted to elucidate the underlying mechanism and explore the potential clinical implications of these findings.

Keywords: Anesthesia, Serratiopeptidase, Ketamine, Xylazine, Mice

INTRODUCTION

The complex interaction between anesthetic drugs and various pharmacological agents is not well understood, and the negative and positive effects of their interaction can have serious implications for patients requiring surgery (Nestor *et al.,* 2022). Off-label drugs are commonly used during anesthesia to increase drug efficacy and reduce side effects (Rusz *et al.,* 2021; Pai *et al.,* 2022; Duarte *et al.,* 2024). Research on this phenomenon is crucial for anesthesiologists and pharmacologists. Although studies focused on the off-label

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use of anesthetics are increasing, reports on non-analgesic drugs that are still used as adjuvants are limited (Duarte *et al.,* 2024; Nagarajan *et al.,* 2024) Serratiopeptidase, a proteolytic enzyme derived from the bacterium *Serratia marcescens*, has shown promise as an adjunct to anesthesia, exhibiting anti-inflammatory and analgesic properties (Naser and Albadrany, 2024). Preclinical studies have demonstrated that administration of a single dose of serratiopeptidase can affect the function of the central nervous system and modulate some neurotransmitters like acetylcholine (Fadl *et al.,* 2013; Fadel *et al.,* 2023; Abdul Hameed and Naser, 2025). However, the impact of repeated serratiopeptidase administration on anesthesia remains largely uncharted territory. Repeated administration of any pharmacological agent, including serratiopeptidase, raises several critical questions. Will repeated doses maintain their efficacy or lead to development of tolerance (Stewart & Badiani, 1993), diminishing their impact on anesthesia outcome? Could cumulative effects of repeated serratiopeptidase administration alter anesthetic requirements, potentially leading to unintended consequences, such as prolonged recovery or increased risk of complications? Furthermore, the potential for drug interaction between serratiopeptidase and other anesthetics, as well as the long-term safety profile of repeated serratiopeptidase administration, warrant careful consideration.

Addressing these questions is crucial for several reasons. Firstly, understanding the effect of repeated serratiopeptidase administration will allow for development of safe and effective dosing regimens for potential clinical applications. Secondly, this knowledge will contribute to a deeper understanding of the mechanism by which serratiopeptidase interacts with anesthetic agents and influences physiological responses during anesthesia. Finally, this research will inform future investigations into the use of serratiopeptidase as an adjunct to anesthesia in various clinical settings. Anesthesiologists recognize that overall anesthesia is the result of a loss of consciousness, memory, immobility, and autonomic and protective reflexes (Cascella, 2020). The anesthetic actions on the central nervous system may occur via intravenous anesthetics as well as inhaled anesthetics by related neurotransmitter systems (Hao *et al.,* 2020). The primary action of such drugs is the potentiation of inhibitory synaptic current mediated through the neurotransmitter gamma-aminobutyric acid, an action that can promote sedation, hypnosis, general anesthetic effects, and loss of consciousness. Their secondary actions are blockade of excitatory tracts mediated through the neurotransmitter glutamate to produce amnesia, analgesia, immobility, and inhibition of dialogue between the cortex, reticular activating system, and thalamus to produce hypnosis (Sills & Rogawski, 2020). A clinical adjunct for producing anesthetic effect is to facilitate or prevent serotonergic and dopaminergic effects. Combining these differing independent effects or using them simultaneously, a new synthesis of CNS depressants with greater effectiveness, fewer side effects, and improved actions can be obtained (Altwal *et al.,* 2020; Gomes & Grace, 2021; Angelopoulou *et al.,* 2023). The aim of the present study was to evaluate the impact of serratiopeptidase on anesthesia indices, including onset, duration, and recovery, as well as the depth of anesthesia, respiratory rate, and heart rate, in mice anesthetized with xylazine and ketamine.

MATERIALS AND METHODS

Animals: Male albino mice (n=32) aged 8-10 weeks were obtained from the College of Veterinary Medicine/University of Tikrit. Mice were housed in standard polypropylene cages (4 mice per cage) under controlled environmental conditions (Temperature: 22± 2°C, humidity: 50-60%, 12-hour light/dark cycle). Mice were

provided with standard rodent chow and water *ad libitum.*

Ethical considerations: All experimental procedures were approved by the Institutional Animal Care and Use Committee (IACUC) of the College of Veterinary Medicine/University of Mosul (UM.VET.2024.006) and were conducted in accordance with the National Institutes of Health Guide for the Care and Use of Laboratory Animals.

Experimental Design:
Grouping: Mice were randomly divided into four groups (n= 8 per group):
First group: Received vehicle (saline) daily for 15 days.

Second group: Received 5 mg/kg serratiopeptidase orally once daily for 15 days.

Third group: Received 10 mg/kg serratiopeptidase orally once daily for 15 days.

Fourth group: Received 20 mg/kg serratiopeptidase orally once daily for 15 days.

Anesthesia: On the 16th day, all mice were anesthetized with an intraperitoneal injection of xylazine (10 mg/kg) and ketamine (150 mg/kg) (Levin-Arama *et al.,* 2016). The onset, duration, and recovery of anesthesia were recorded. The onset of anesthesia was defined as the time from injection to the loss of the righting reflex. The duration of anesthesia was measured from the onset of anesthesia to the recovery of the righting reflex. Recovery time was recorded as the time from the end of anesthesia to the full recovery of spontaneous movement and consciousness (Alves *et al.,* 2010; Naser *et al.,* 2024). The mice were warmed during anesthesia by placing them near an electric heater.

Monitoring of Physiological Parameters: Oxygen Saturation (SpO_2), respiratory rate, and heart rate were recorded using the YK-8000C Multi-Parameter Patient Monitor. After the mouse lose the body-righting reflex (Tsukamoto *et al.,* 2015) and entered the anaesthesia stage, the three electrodes of the device are placed as shown in Figure (1). First, we place the right electrode for the right forelimb and then the left electrode for the left forelimb. The second step is to place the SpO2 probe animal clip on the right leg where the vein or artery is located. The third step is to read the heart rate, respiratory rate and SpO2 from the multiparameter monitor device.

Statistical Analysis:
All data are presented as mean ± standard error of the mean (SEM). Data was analyzed using one-way ANOVA followed by Tukey's post-hoc test for multiple comparisons. Statistical significance was set at $P<0.05$.

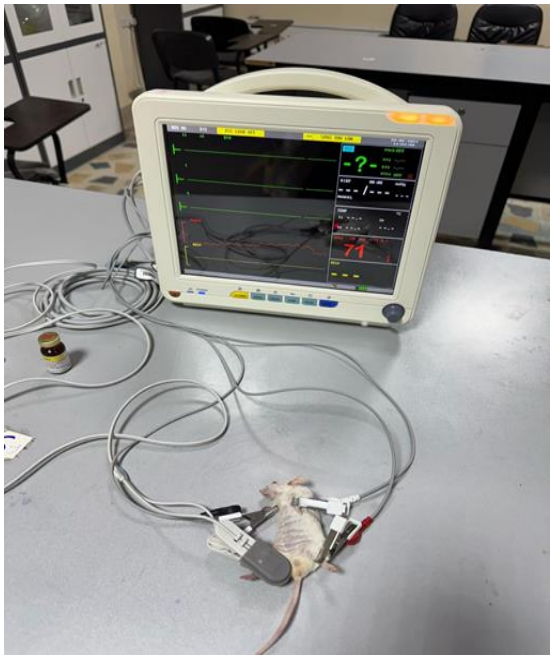

Figure 1: Multi-Parameter Patient Monitor

RESULTS

Onset of Anesthesia: The control group had the shortest onset time (72.88±13.50 seconds), and the serratiopeptidase 5 mg group exhibited a significantly longer onset time (147.4±8.13 seconds) (P=0.023) compared to the control group. The

serratiopeptidase 10 mg group also showed a significantly longer onset time (137.40± 17.72 seconds) (P=0.041) compared to the control group. The serratiopeptidase 20 mg group had a significantly shorter onset time (107.38± 8.05 seconds) compared to the 5 mg group.

Duration of anesthesia:
The serratiopeptidase 5 mg and 10 mg groups showed significantly prolonged anesthesia duration (192.25±32.81 minutes and 195.75±26.66 minutes, respectively) compared to the control group (119.50±7.22 minutes). The serratiopepti-dase 20 mg/kg group had a significantly shorter duration of anesthesia (120.50± 14.74 minutes) compared to both the 5 mg and 10 mg groups.

Recovery time: The serratiopeptidase 20 mg group exhibited a significantly longer recovery time (77.9±14.90 minutes) (P=0.048) compared to the 5 mg group (55.3±9.38 minutes).

Oxygen Saturation (SpO_2): All serratiopeptidase-treated groups exhibited significantly higher oxygen saturation compared to the control group. The SpO_2 increased in a dose-dependent manner with serratiopeptidase treatment, with the 20 mg group showing the highest SpO_2.

Respiratory rate: All serratiopeptidase-treated groups showed a significant increase in respiratory rate compared to the control group. The 20 mg serratiopeptidase group exhibited the highest respiratory rate.

Heart rate: All serratiopeptidase-treated groups displayed a significant decrease in heart rate compared to the control group (p=0.033). The 10 mg serratiopeptidase groups showed the lowest heart rate.

Table 1: The effect of 15-day oral administration of serratiopeptidase on the anesthesia indices by xylazine and ketamine.

Group / Index	Control	Serratiopeptidase (5 mg)	Serratiopeptidase (10 mg)	Serratiopeptidase (20 mg)
Onset (second)	72.88±13.50	147.40±8.13*	137.40±17.72*	107.38±8.05[A]
Duration of anesthesia (minute)	119.50±7.22	192.25±32.81*	195.75±26.66*	120.50±14.74[AB]
Recovery (minute)	59.0±5.82	55.3±9.38	64.5±9.69	77.9±14.90*
Oxygen saturation (SpO_2)	86.50 ±4.21	92.00 ±1.83	95.25*±0.81	97.50*±0.42
Respiratory rate	11.0±0.4	17.5±2.9*	15.8±1.1	19.8±2.9*
Heart rate	101.5±15.2	84.0±1.8*	82.3±5.6*	83.3±3.2*

The data are presented as the mean ± SE of 8 mice/group.
* Significantly different from the data of the control group at P≤ 0.05.
[A] significantly different from the data of group 5 mg at (P≤ 0.05).
[B] Significantly different from the data of the group of 10 mg at (P≤ 0.05).

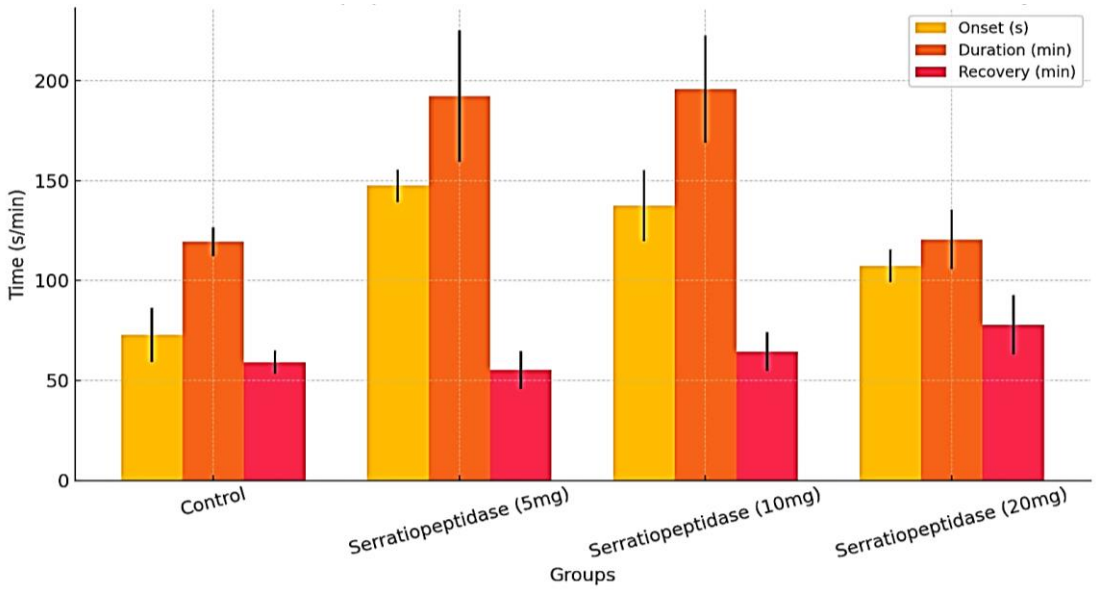

Figure 2: Effects of serratiopeptidase on Anesthesia onset, duration, and recovery

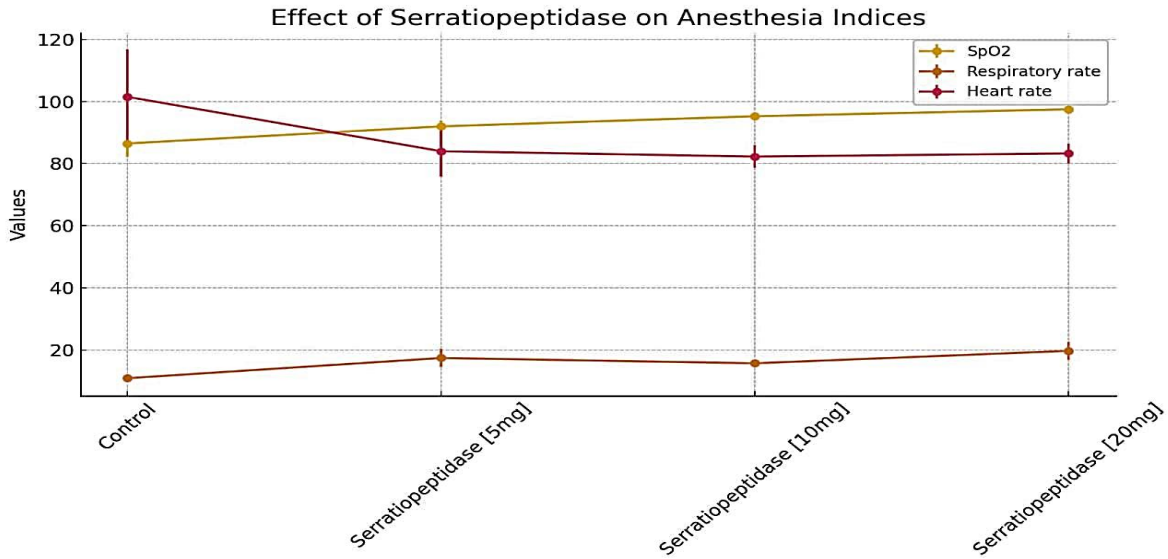

Figure 3: Effect of serratiopeptidase on anesthesia indices (Line Plot).

DISCUSSION

The study was designed to examine the properties of serratiopeptidase on anesthesia by a mixture of xylazine and ketamine in murine. Animals play a crucial role in research, contributing significantly to medical and scientific advancements. They are used to study disease, test new drugs, and understand biological processes in ways not possible with other methods (Naser *et al.,* 2020; Albadrany & Naser, 2020; Bashar & Albadrany, 2022). Anesthesia is a critical aspect of numerous medical procedures, and understanding how drugs and other substances influence its onset, duration, and recovery is important for optimizing patient care (Feldheiser *et al.,* 2016). Serratiopeptidase at 5 mg/kg and 10 mg/kg orally significantly delayed the onset of anesthesia compared to the control group. This suggests that lower doses of serratiopeptidase might augment the anesthetic agents to slow the induction of anesthesia. Serratiopeptidase may compete with the xylazine and ketamine receptors, and this can inhibit the binding and delay anesthesia (Goldman *et al.,* 2014). Serratiopeptidase can influence the concentrations of neurotransmitters participating in the

process of anesthesia, like GABA and glutamate (Azzam *et al.,* 2023). and thus influence the duration of the anesthetic action. Serratiopeptidase 10 mg and 5 mg significantly increased anesthesia duration compared to the control. This may indicate that lower doses of serratiopeptidase potentiate the anesthetic effects of xylazine and ketamine. Serratiopeptidase has anti-inflammatory activity. Anesthetic sensitivity can be modulated by inflammation. Serratiopeptidase may act because it potentially reduces inflammation, therefore enhancing the anesthetic effects and prolonging their duration (Wala, 2017; Fadel & Mustafa, 2023). Serratiopeptidase may affect the concentrations of some of the neurotransmitters relevant to general anesthesia, which includes GABA and glutamate, leading to extended duration of the action of the general anesthetics. The 20 mg dose showed a trend towards a longer recovery time, but it was not statistically significant. This suggests that higher doses of serratiopeptidase might have a greater impact on recovery time, potentially due to a stronger interaction with anesthetic agents or physiological systems. Here it should be noted that high doses of serratiopeptidase may have a stimulating effect on the nervous system through its mechanism of inhibiting the brain cholinesterase, and thus a relative increase in the concentration of acetylcholine, which is a stimulating neurotransmitter (Ahmed *et al.,* 2013; Fadl *et al.,* 2013). Therefore, high doses of serratiopeptidase led to a reduction in the period of anesthesia. All doses of serratiopeptidase led to a significant increase in SpO_2 level compared to the control group. This suggests that serratiopeptidase may improve oxygenation during anesthesia. An increase in respiratory rate could be a compensatory mechanism to maintain adequate oxygen delivery to the tissues (Shah, 2021). A deeper level of anesthesia can depress respiratory drive, and the increased respiratory rate might be an attempt to counteract this effect. Serratiopeptidase may directly influence the respiratory centers in the brainstem, leading to increased respiratory drive (Hosseini *et al.,* 2024). Xylazine and ketamine themselves can cause a decrease in heart rate (Ullah *et al.,* 2017; Afshar *et al.,* 2005). Serratiopeptidase might potentiate this effect. Serratiopeptidase could potentially stimulate the parasympathetic nervous system, leading to a decrease in heart rate.

Limitation of the study: the study was conducted on mice, and the results may not directly translate to humans. The study investigated only a limited range of serratiopeptidase doses. A wider range of doses might reveal a more nuanced dose-dependent effect. The exact mechanisms underlying the observed effects of serratiopeptidase on anesthesia are not fully understood and require further investigation.

CONCLUSION

The study provides preliminary evidence that serratiopeptidase may have some influence on anesthesia induced by xylazine and ketamine in mice. However, the findings require further validation and exploration in other animal species. The potential mechanisms underlying these effects need to be thoroughly investigated.

AUTHORS CONTRIBUTIONS

Author 1 conceived and designed the study, and author 2 performed the experiments, analyzed the data, and wrote the manuscript.

CONFLICT OF INTEREST

The authors declare that they have no competing interests.

ACKNOWLEDGMENT

The authors would like to thank the deanship of the College of Veterinary Medicine for their valuable contributions to this work.

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تأثير الجرعات المتكررة للسيراتيوبيبتداز على التخدير

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يعد السيراتيوبيبتيداز من الانزيمات الحالة للبروتينات و هو مشتق من بكتيريا السيراتيا ، وله عدة تاثيرات علاجية لامتلاكه خصائص ضادة للالتهابات و مسكنة للالام و محللة للفيبرين. هدفت هذه الدراسة في تأثير السيراتوبيبتيداز ، وهو إنزيم بروتيني، على الاستجابة للتخدير مع ملاحظة التغيرات المصاحبة له في المعايير الفسيولوجية مثل تشبع الأكسجين (SpO2) ومعدل التنفس ومعدل ضربات القلب في الفئران المخدرة بالزيلازين والكيتامين. تم إعطاء الفئران السيراتوبيبتيداز بجرعات) 5 أو 10 أو 20 ملغم / كغم (عن طريق الفم لمدة 15 يومًا قبل اجراء التخدير بالزيلازين والكيتامين (10 و 150 ملغم / كغم في الخلب على التوالي). تم تسجيل معايير التخدير بما في ذلك بدء التخدير ومدته ووقت الافاقة. بالمقارنة مع المجموعة السيطرة ، أظهرت مجاميع السيراتوبيبتيداز 5 و 10 ملغم / كغم تاخر في بدء التخدير وزيادة معنوية في فترة التخدير وعلى العكس من ذلك، أظهرت مجموعة 20 ملغم / كغم قصر وقت بدء التخدير و نقصان معنوي في فترة التخدير مقارنة بمجموعات 5 و 10 ملغم / كغم. اضافة الى زيادة فترة الافاقة في المجموعة 20 ملغم/كغم مقارنة بمجموعة السيطرة أظهرت جميع المجموعات المعالجة بالسيراتيوببتيداز زيادة في تشبع الأكسجين بشكل معنوي.بالإضافة إلى ذلك، أظهرت جميع مجموعات السيراتيوبيبتيداز انخفاضًا معنويا في معدل ضربات القلب وزيادة معنوية في معدل التنفس. تشير هذه النتائج إلى أن السيراتيوبيبتيداز يمتلك تأثيرات تعتمد على الجرعة في الاستجابة للتخدير قد تكون من خلال آليات معقدة تتضمن حدوث تغييرات في النواقل العصبية و/ أو آليته المضادة للالتهابات، علاوة على ذلك، قد يؤثر السيراتيوبيبتيداز على المعايير الفسيولوجية المرتبطة بالتخدير في الفئران. هناك حاجة إلى مزيد من البحث لتوضيح الآلية الأساسية واستكشاف الآثار السريرية المحتملة لهذه النتائج .