PROCEEDINGS OF THE YEREVAN STATE UNIVERSITY

Chemistry and Biology 2026, **60**(1), p. 61–70

Biology

SPLENIC HISTOPATHOLOGICAL CHANGES IN *MACROVIPERA LEBETINA OBTUSA* ENVENOMATION. EVALUATION OF INHIBITOR EFFECTS

G. A. AVAGYAN [1,2*]

[1] *"Yeolyan" Hematology and Oncology Center, Armenia*
[2] *Chair of Human and Animal Morphology and Physiology, YSU, Armenia*

This study aimed to evaluate splenic histopathological alterations induced by *Macrovipera lebetina obtusa* venom and to assess the protective effects of enzyme inhibitors. Experiments were conducted on mice under controlled conditions using venom alone and in combination with marimastat and varespladib. The results showed that venom exposure led to edema, vascular congestion, and moderate hemorrhagic foci, indicating significant microvascular damage. In contrast, marimastat effectively preserved splenic architecture and prevented hemorrhage, whereas varespladib provided only partial protection with mild hemorrhagic changes persisting. It should also be noted that lymphoid follicles remained relatively preserved across all groups, suggesting lower susceptibility of the immune component to acute injury. These findings indicate the dominant role of metalloproteinases in venom-induced vascular damage and highlight the potential of targeted inhibition strategies for improving snakebite treatment outcomes.

https://doi.org/10.46991/PYSUB.2026.60.1.061

***Keywords*:** snakebite envenomation, spleen, histopathology, marimastat, varespladib.

Introduction. Snakebite envenomation remains a significant global public health concern, particularly in tropical and subtropical regions, where it contributes markedly to morbidity, mortality, and long-term disability. The World Health Organization estimates that more than five million snakebites occur annually, resulting in approximately 2.7 million envenomation cases and between 81 000 and 138 000 deaths worldwide [1, 2]. In addition to fatal outcomes, many survivors develop permanent complications, including severe tissue injury and limb amputations. Due to its considerable global impact, snakebite envenoming has been designated as a neglected tropical disease requiring urgent attention [3]. Viperidae snakes are among the most clinically important causes of envenomation due to the pronounced hemotoxic and tissue-damaging effects of their venoms. The blunt-nosed viper, *Macrovipera lebetina obtuse* (*M. l. obtusa*), is among the most

* E-mail: drgevavagyan@gmail.com

medically important venomous species in the South Caucasus and Middle Eastern Regions. Its broad distribution and frequent presence near human settlements increase the likelihood of human–snake encounters and subsequent envenomation events [3].

In Armenia, 22 snake species have been documented, including four venomous vipers. Two species – *Vipera eriwanensis* and *Vipera darevskii* – are relatively small and rare, producing limited venom and posing minimal risk to humans. The Armenian viper, *Montivipera raddei*, although venomous, is infrequently encountered due to its restricted habitat and protected status. In contrast, *M. l. obtusa* is the most dangerous species in the country, being widely distributed across Armenia, including urban areas and the capital [4, 5]. Owing to its extensive geographical range, this species is also a major contributor to snakebite incidence across the South Caucasus and parts of the Middle East.

Snake venoms are highly complex biological secretions composed predominantly of proteins and peptides, which constitute approximately 90–95% of their dry weight [6]. These components belong to several major toxin families that play key roles in the pathophysiological effects of envenomation and serve as important therapeutic targets. The most significant among them include phospholipases A_2 (PLA_2), snake venom metalloproteinases (SVMP), snake venom serine proteases (SVSP), and three-finger toxins (3FT×s) [7]. Clinically, snake envenomation typically manifests through three main syndromic patterns. Hemotoxic effects are characterized by hemorrhage and disruptions of the coagulation system; neurotoxic effects lead to impairment of neuromuscular transmission and muscle paralysis, and cytotoxic effects result in localized tissue injury, often progressing to necrosis [8, 9].

Hemotoxic effects are a defining feature of envenomation by snakes of the *Viperidae* family. In such cases, the pathological manifestations are largely driven by the activity of key venom enzymes, including metalloproteinases, serine proteases, and phospholipases A_2 [10, 11]. Among these, SVMPs play a central role due to their potent hemorrhagic properties and their capacity to disrupt multiple components of the hemostatic system, leading to both systemic bleeding and defective clot formation in affected organisms [12, 13]. The hemorrhagic action of SVMPs is understood as a sequential, multistep process [14, 15]. Initially, these enzymes target and degrade essential structural components of the basement membrane and proteins involved in endothelial cell-extracellular matrix interactions, thereby weakening the integrity of capillary vessels. This is followed by detachment and thinning of endothelial cells, which lose their anchorage to the underlying matrix. As structural damage progresses, the vessel wall becomes increasingly fragile, ultimately leading to capillary rupture and blood leakage into adjacent tissues. Beyond their direct proteolytic effects, SVMPs further exacerbate bleeding by interfering with the coagulation cascade, thereby amplifying overall hemostatic dysfunction [16].

In recent years, small-molecule enzyme inhibitors have attracted considerable interest as potential adjunctive or alternative treatments for snakebite envenomation. In particular, metalloproteinase inhibitors such as marimastat have been shown to effectively inhibit SVMP activity and mitigate hemorrhagic injury in experimental

settings [17]. Likewise, varespladib, an inhibitor of PLA_2, has demonstrated broad-spectrum activity against venom PLA_2 enzymes and has exhibited protective effects in various animal models of envenomation [18, 19].

In the present study, we aimed to investigate the effects of *M. l. obtusa* venom on splenic structure in order to better understand the pathological processes triggered by envenomation. Particular attention was given to the identification of histo-pathological alterations within the spleen, reflecting both tissue injury and adaptive responses following venom exposure. In addition, the study evaluated how these splenic changes are influenced by enzyme inhibitors, providing insight into their potential protective role. By characterizing these alterations, the findings of this study may contribute to a deeper understanding of venom-induced organ damage and support the development of more effective therapeutic strategies for snakebite envenomation caused by *M. l. obtusa.*

Materials and Methods.

***Snake Venom, Animal Ethics and Maintenance*.** Crude venom of *M. l. obtusa* was sourced from specimens housed in the serpetarium of the Orbeli Institute of Physiology, National Academy of Sciences (Armenia), vacuum-dried at ambient temperature, and stored in the dark at 4℃ until use. Experimental animals (nonlinear gray 12-week-old adult mice weighing 20–25 *g*) were acclimatized for a minimum of one week before experimentation, with their health monitored daily. All experimental animals were maintained under controlled conditions: a 12-hour light/dark cycle (07:00 to 19:00), stable temperature, and standard feeding. Animals were euthanized after venom injection in compliance with ethical standards. All experimental procedures were conducted in accordance with the principles of laboratory animal care as approved by the Bioethics Committee of Yerevan State University. The study complied with the Directive 2010/63/EU of the European Parliament and of the Council of 22 September 2010 on the protection of animals used for scientific purposes.

***Animals for in vivo Assays*.** The mice were divided into four groups for spleen histological analysis:

a) healthy control;

b) mice injected intravenously with freshly diluted *M. l. obtusa* venom at a lethal dose of 5 LD_{50} ($5 \times 18.4\ \mu g$);

c) each mouse received an intravenous injection via the tail vein of *Macrovipera lebetina obtusa* venom (MLO) at a dose of 2.5 LD_{50}, pre-incubated with 60 μg of marimastat;

d) the same concentrations as marimastat were used for varespladib. Incubation was performed at 37℃.

The mixture was subsequently centrifuged at $3000 \times g$ for 5 *min*, and the supernatant was injected. The venom was dissolved in physiological saline, while marimastat and varespladib were dissolved in DMSO. The final concentration of DMSO in the injected mixture did not exceed 2.5%. Each mouse received 0.3 *mL* of the prepared solution containing 2.5 LD_{50} of MLO pre-incubated with the respective inhibitor.

Tissue Processing and H&E Staining for Histopathological Evaluation. During dissection and tissue preparation, standard histological techniques were applied to obtain morphological sections. Spleen samples were carefully excised and dissected, then embedded in paraplast. The paraffin-embedded tissues were sectioned at 2.5 μm using a rotary microtome and subsequently mounted on glass slides for histological examination. Histopathological assessment of splenic tissue from animals was conducted according to conventional protocols.

At the conclusion of the experimental period (1 and 7 days), surviving animals were euthanized, and spleen tissues were collected and fixed in 10% buffered formalin. Following fixation, samples were dehydrated through a graded ethanol series (70%, 80%, 90%, 95%, and 100%), cleared in xylene, and embedded in paraffin. Tissue sections were then stained with hematoxylin and eosin (H&E). Microscopic evaluation and image acquisition were performed at ×100 and ×400 magnifications using an Olympus BX43 light microscope ("Olympus", Japan).

Results and Discussion. Splenic tissue sections obtained from the control group exhibited a normal histological appearance. The overall structure of the spleen was well preserved, with clear demarcation between the white and red pulp. The capsule remained intact, represented by a thin, continuous layer of connective tissue without signs of disruption or thickening. The white pulp showed well-defined and appropriately developed lymphoid follicles with preserved cellularity. The red pulp demonstrated normal architecture with mild to moderate physiological blood filling. No evidence of hemorrhage or structural damage was observed in the perifollicular regions. Stromal vessels appeared structurally intact with partial, but normal blood content (Fig. 1, A and B).

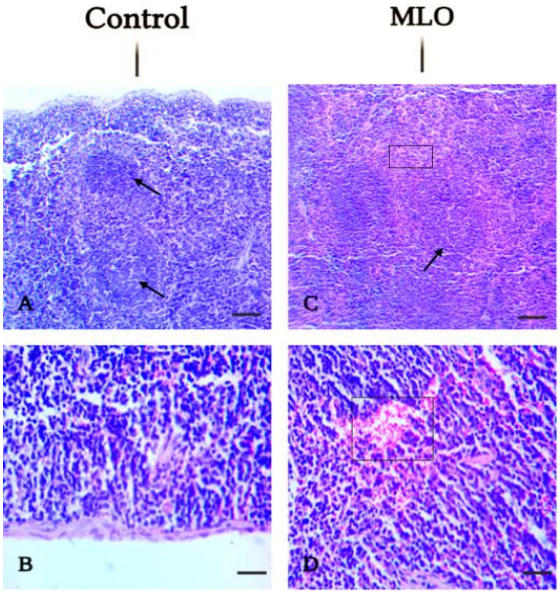

Fig. 1. Histopathological changes in the spleen after injection of PBS (Control) and *Macrovipera lebetina obtuse* venom (MLO). The representative field images were acquired with Olympus BX43. Upper row: magnification 100, scale bar 250 μm. Lower row: magnification ×400, scale bar 100 μm. Arrow indicates lymphoid follicle hyperplasia. Square marks areas of hemorrhage.

In contrast, splenic sections from the venom-treated group revealed notable pathological alterations. The tissue showed edema, contributing to partial distortion of the normal splenic architecture. Although the general architecture of the spleen

was still recognizable, structural integrity was compromised in several areas. Lymphoid follicles remained identifiable and relatively preserved, though subtle changes in their organization were evident. The red pulp showed increased vascular congestion compared to controls, indicating enhanced blood accumulation. Importantly, the perifollicular regions exhibited moderately pronounced hemorrhagic foci (moderate ++), reflecting disruption of microvascular integrity. Stromal vessels were markedly congested, supporting the presence of circulatory disturbances. Despite these changes, the splenic capsule remained intact and was still represented by a thin connective tissue layer (see Table and Fig. 1, C and D).

In the marimastat-treated groups (day 1 and day 7), splenic tissue sections demonstrated preservation of normal histological architecture. The overall organization of the spleen remained intact, with clearly defined white and red pulp compartments. Lymphoid follicles were well developed, indicating maintained structural integrity of the immune component. The red pulp exhibited moderate physiological congestion without evidence of excessive blood accumulation. Importantly, no hemorrhagic foci were observed in the perifollicular regions. Stromal vessels appeared partially filled with blood, but showed no signs of pathological dilation or damage, suggesting effective protection against venom-induced vascular injury (see Table and Fig. 2, A–D).

In the varespladib-treated group at day 1, splenic tissue exhibited mild histopathological alterations. The vasculature showed hyperemia, indicating increased blood flow and vascular activation. Small foci of hemorrhage (mild +) were observed within the splenic tissue. Despite these findings, the overall splenic architecture remained preserved, with no evidence of significant structural disruption (see Table and Fig. 2, E and I).

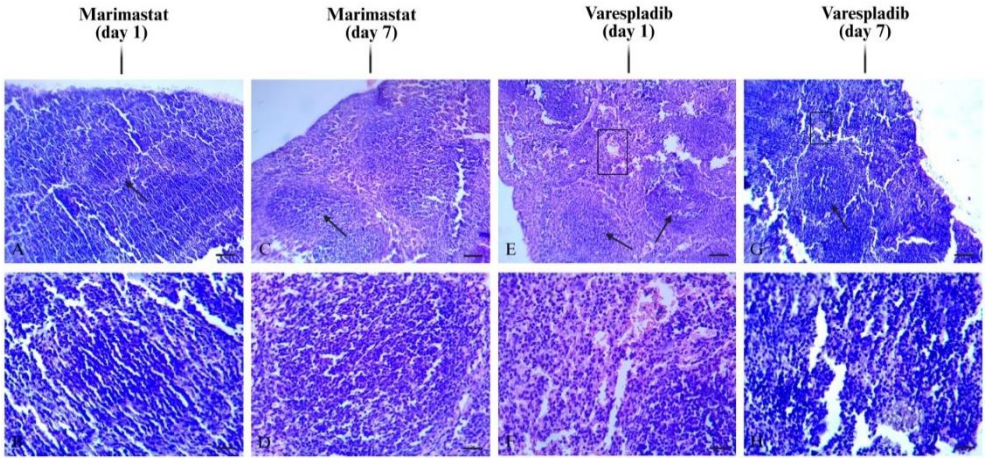

Fig. 2. Histopathological changes in spleen after administration of MLO + Marimastat and MLO + Varespladib. The representative field images were acquired with Olympus BX43. *Upper row*: magnification ×100, scale bar 250 *μm*. *Lower row*: magnification ×400, scale bar 100 *μm*. Arrow indicates lymphoid follicle hyperplasia. Square marks areas of hemorrhage.

At day 7, similar changes were observed in the varespladib-treated group. The splenic vessels remained hyperemic and small foci of mild hemorrhage (+)

persisted within the tissue. However, the overall organization of the spleen remained intact, and no progression toward severe tissue damage or architectural disintegration was detected (see Table and Fig. 2, G and H).

Tissue damage in spleen treated by venom only and MLO venom pre-incubated with inhibitors: + (mild), ++ (moderate)

Group	*Lymphoid Follicle Hyperplasia*		*Hemorrhage*	
Control	–		–	
Venom	–		++	
MLO + Marimastat	Day1 –	Day7 +	Day1 +	Day7 –
MLO + Varespladib	Day1 –	Day7 +	Day1 –	Day7 +

The present study provides detailed insight into splenic histopathological alterations induced by envenomation with *M. l. obtusa* and highlights the differential effects of enzyme inhibition on these changes. The spleen, as a highly vascularized organ with essential immunological and hematological functions, represents a sensitive target for venom-induced systemic disturbances [16]. Our findings demonstrate that envenomation leads to prominent microvascular damage, manifested by edema, increased red pulp congestion, and perifollicular hemorrhagic foci, indicating disruption of vascular integrity. These observations are consistent with the established pathophysiological mechanisms of viperid venoms, which are rich in snake venom metalloproteinases and other proteolytic enzymes. SVMPs are known to degrade key structural components of the basement membrane and to disrupt endothelial cell–matrix interactions. This results in weakening of capillary walls, endothelial detachment, and ultimately vessel rupture, leading to hemorrhage. The moderate hemorrhagic foci observed in the perifollicular regions in our study strongly support this mechanism and reflect localized microvascular injury within the splenic tissue. In addition, the pronounced congestion of the red pulp suggests impaired blood flow and erythrocyte pooling, likely secondary to both vascular leakage and disturbances in hemostasis.

An important observation in this study is the relative preservation of lymphoid follicles across all experimental groups, including venom-treated animals. This suggests that the lymphoid compartment of the spleen is less susceptible to acute venom-induced injury compared to vascular and stromal components. Given the central role of the spleen in immune surveillance, this preservation may reflect intrinsic protective mechanisms or delayed immunological involvement. However, subtle alterations in follicular organization may indicate early functional changes that are not yet morphologically pronounced, warranting further investigation using immunohistochemical or molecular approaches.

The differential effects observed following inhibitor administration provide important mechanistic insights into the contribution of specific venom components. In the marimastat-treated groups, both at day 1 and day 7, splenic architecture remained largely comparable to that of the control group. The absence of hemorrhagic foci and maintenance of normal vascular morphology strongly

indicate that inhibition of SVMP activity effectively prevents microvascular damage. These findings reinforce the central role of metalloproteinases in mediating hemorrhagic pathology and are consistent with previous studies demonstrating that metalloproteinase inhibitors can significantly reduce venom-induced tissue injury.

In contrast, varespladib provided only partial protection against splenic damage. Although the overall architecture of the spleen remained preserved, mild hemorrhagic foci and persistent vascular hyperemia were observed at both evaluated time points. This indicates that inhibition of PLA_2 activity alone is insufficient to fully prevent vascular injury. PLA_2 enzymes are primarily associated with membrane disruption, inflammatory responses, and cytotoxic effects, rather than direct degradation of vascular structural components. Therefore, while varespladib may attenuate certain aspects of venom toxicity, it does not effectively counteract SVMP-mediated microvascular damage. The persistence of mild hemorrhagic changes in the varespladib groups at day 7 suggests that partial inhibition of venom activity may delay, but not completely prevent, pathological processes. This finding underscores the complex and synergistic nature of snake venom, in which multiple toxin families contribute to overall toxicity. Consequently, targeting a single enzymatic pathway may not be sufficient for comprehensive protection, and combined therapeutic approaches inhibiting multiple toxin classes may offer greater efficacy.

From a broader physiological perspective, the spleen serves as a key organ involved in blood filtration, immune regulation, and erythrocyte turnover. The observed histopathological changes therefore, likely reflect systemic alterations in vascular permeability and hemostasis rather than isolated local injury. The sensitivity of splenic tissue to microvascular injury highlights its potential as a marker organ for assessing the severity of envenomation and the effectiveness of therapeutic interventions. Despite the strengths of this study, several limitations should be considered. The analysis was limited to histopathological assessment, and functional evaluation of splenic activity was not performed. Additionally, only two time points were examined, which may not fully capture the temporal progression of injury and recovery. Furthermore, while the use of specific inhibitors provides mechanistic insight, their translational applicability and potential interactions with conventional antivenom therapy require further investigation.

Conclusion. *Macrovipera lebetina obtusa* venom induces significant splenic alterations primarily through mechanisms involving microvascular damage and hemorrhage. Inhibition of snake venom metalloproteinases with marimastat effectively preserves splenic architecture and prevents hemorrhagic injury, whereas phospholipases A_2 inhibition with varespladib provides only partial protection. These findings emphasize the dominant role of metalloproteinases in venom-induced vascular pathology and support the development of targeted, potentially combined therapeutic strategies to improve the management of viper envenomation.

Received 06.04.2026
Reviewed 27.04.2026
Accepted 29.04.2026

REFERENCES

1. *Snakebite Envenoming – a Strategy for Prevention and Control*. World Health Organization (2019). Available from: https://www.who.int/publications/i/item/snakebite-envenoming
2. *Target Product Profiles for Animal Plasma-derived Antivenoms: Antivenoms for Treatment of Snakebite Envenoming in Sub-Saharan Africa* (1st ed.). Geneva, World Health Organization (2023). Available from: https://www.who.int/publications/i/item/9789240079229
3. Williams D.J., Faiz M.A., et al. Strategy for a Globally Coordinated Response to Snakebite Envenoming. *PLoS Neglected Tropical Diseases* **13** (2019), e0007059. https://doi.org/10.1371/journal.pntd.0007059
4. Brown N., Landon J. Antivenom: The Most Cost-effective Treatment in the World? *Toxicon*. **55** (2010), 1405–1407. https://doi.org/10.1016/j.toxicon.2010.02.012
5. de Silva H.A., Ryan N.M., de Silva H.J. Adverse Reactions to Snake Antivenom, and Their Prevention and Treatment. *Br. J. Clin. Pharmacol.* **81** (2016), 446–52. https://doi.org/10.1111/bcp.12739
6. Tasoulis T., Isbister G.K. A Review and Database of Snake Venom Proteomes. *Toxins (Basel)* **9** (2017), 290. https://doi.org/10.3390/toxins9090290
7. Escalante T., Shannon J.D., et al. Novel Insights Into Capillary Vessel Basement Membrane Damage by Snake Venom Hemorrhagic Metalloproteinases: A Biochemical and Immuno-histochemical Study. *Arch. Biochem. Biophys.* **455** (2) (2006), 144–153. https://doi.org/10.1016/j.abb.2006.09.018
8. Slagboom J., Kool J., et al. Haemotoxic Snake Venoms: Their Functional Activity, Impact on Snakebite Victims and Pharmaceutical Promise. *Br. J. Haematol.* **177** (2017), 947–959. https://doi.org/10.1111/bjh.14591
9. Ferraz C.R., Arrahman A., et al. Multifunctional Toxins in Snake Venoms and Therapeutic Implications: from Pain to Hemorrhage and Necrosis. *Front. Ecol. Evol.* **7** (2019), 218. https://doi.org/10.3389/fevo.2019.00218
10. Hall S.R., Rasmussen S.A., et al. Repurposed Drugs and Their Combinations Prevent Morbidity-inducing Dermonecrosis Caused by Diverse Cytotoxic Snake Venoms. *Nat. Commun*. **14** (1) (2023), 7812. https://doi.org/10.1038/s41467-023-43510-w
11. Siigur J., Aaspõllu A., Siigur E. Biochemistry and Pharmacology of Proteins and Peptides Purified from the Venoms of the Snakes *Macrovipera lebetina* Subspecies. *Toxicon*. **158** (2019), 16–32. https://doi.org/10.1016/j.toxicon.2018.11.294
12. Markland F.S.Jr., Swenson S. Snake Venom Metalloproteinases. *Toxicon.* **62** (2013), 3–18. https://doi.org/10.1016/j.toxicon.2012.09.004
13. Ayvazyan N., Ghukasyan G., et al. The Contribution of Phospholipase A_2 and Metalloproteinases to the Synergistic Action of Viper Venom on the Bioenergetic Profile of Vero Cells. *Toxins (Basel)* **14** (2022), 724. https://doi.org/10.3390/toxins14110724
14. Gutierrez J.M., Rucavado A., et al. Hemorrhage Induced by Snake Venom Metalloproteinases: Biochemical and Biophysical Mechanisms Involved in Microvessel Damage. *Toxicon.* **45** (2005), 997–1011. https://doi.org/10.1016/j.toxicon.2005.02.029
15. Escalante T., Rucavado A., et al. Key Events in Microvascular Damage Induced by Snake Venom Hemorrhagic Metalloproteinases. *J. Proteomics* **74** (2011), 1781–1794. https://doi.org/10.1016/j.jprot.2011.03.026
16. Fox J.W., Gutierrez J.M. *Snake Venom Metalloproteinases* (1st ed.). Basel (Switzerland), MDPI (2017).

17. Fischer T., Senn N., Riedl R. Design and Structural Evolution of Matrix Metalloproteinase Inhibitors. *Chemistry* **25** (2019), 7960–7980.
https://doi.org/10.1002/chem.201805361
18. Lewin M., Samuel S., et al. Varespladib (LY315920) Appears to be a Potent, Broad-Spectrum, Inhibitor of Snake Venom Phospholipase A_2 and a Possible Pre-Referral Treatment for Envenomation. *Toxins* **8** (2016), 248.
https://doi.org/10.3390/toxins8090248
19. Lewin M.R., Gutirrez J.M., et al. Delayed Oral LY333013 Rescues Mice from Highly Neurotoxic, Lethal Doses of Papuan Taipan (*Oxyuranus scutellatus*) Venom. *Toxins (Basel)* **10** (10) (2018), 380.
https://doi.org/10.3390/toxins10100380
20. Bronte V., Pittet M.J. The Spleen in Local and Systemic Regulation of Immunity. *Immunity* **39** (2013), 806–818.
https://doi.org/10.1016/j.immuni.2013.10.010
Erratum in: *Immunity* **56** (2023), 1152.
https://doi.org/10.1016/j.immuni.2023.04.004

Գ. Ա. ԱՎԱԳՅԱՆ

MACROVIPERA LEBETINA OBTUSA-Ի ԹՈՒՆԱՎՈՐՄԱՆ ՄԵՋ ՓԱՅԾԱՂԻ ՀՅՈՒՍՎԱԾԱԲԱՆԱԿԱՆ ՓՈՓՈԽՈՒԹՅՈՒՆՆԵՐ: ԻՆՀԻԲԻՏՈՐԱՅԻՆ ԱԶԴԵՑՈՒԹՅՈՒՆՆԵՐԻ ԳՆԱՀԱՏՈՒՄ

Այս ուսումնասիրության նպատակն էր գնահատել փայծաղի հիստոպաթոլոգիական փոփոխությունները, որոնք առաջանում են *Macrovipera lebetina obtusa* օձի թույնի ազդեցության արդյունքում, ինչպես նաև ուսումնասիրել ֆերմենտային ինհիբիտորների պաշտպանիչ ազդեցությունը: Փորձերը իրականացվել են մկների վրա՝ վերահսկվող պայմաններում, կիրառելով թույնը առանձին և համակցված՝ մարիմաստատի և վարեսպլադիբի հետ: Արդյունքները ցույց տվեցին, որ թույնի ազդեցությունը հանգեցնում է այտուցի, անոթային կանգի և միջին աստիճանի արյունազեղումների, ինչը վկայում է արտահայտված միկրոանոթային վնասման մասին: Ի հակադրություն, մարիմաստատի կիրառումը արդյունավետորեն պահպանել է փայծաղի կառուցվածքը և կանխել արյունահոսությունների զարգացումը, մինչդեռ վարեսպլադիբի կիրառումը ապահովել է միայն մասնակի պաշտպանություն՝ պահպանելով թեթև արյունազեղման փոփոխությունները: Պետք է նաև նշել, որ լիմֆոիդ ֆոլիկուլները բոլոր խմբերում մնացել են համեմատաբար պահպանված, ինչը վկայում է իմունային բաղադրիչի ավելի ցածր զգայունության մասին սուր վնասման նկատմամբ: Ստացված տվյալները ցույց են տալիս մետաղպրոտեինազների գերակշռող դերը թույնով պայմանավորված անոթային վնասման մեջ և ընդգծում են թիրախային գործոնների կարևորությունը օձի խայթոցի բուժման արդյունավետության բարելավման համար:

Г. А. АВАГЯН

ГИСТОПАТОЛОГИЧЕСКИЕ ИЗМЕНЕНИЯ СЕЛЕЗЕНКИ ПРИ ОТРАВЛЕНИИ ЯДОМ *MACROVIGERA LEBETINA OBTUSA*. ОЦЕНКА ДЕЙСТВИЯ ИНГИБИТОРОВ

Данное исследование было направлено на оценку гистопатологических изменений селезенки, вызванных ядом *Macrovipera lebetina obtusa*, а также на изучение защитного эффекта ферментных ингибиторов. Эксперименты проводились на мышах в контролируемых условиях с использованием яда отдельно и в комбинации с маримастатом и варespладибом. Результаты показали, что воздействие яда приводило к развитию отека, сосудистой конгестии и умеренных геморрагических очагов, что свидетельствует о значительном микрососудистом повреждении. В отличие от этого, введение маримастата эффективно сохраняло архитектонику селезенки и предотвращало развитие кровоизлияний, тогда как введение варespладиба обеспечивало лишь частичную защиту, при которой сохранялись легкие геморрагические изменения. Следует также отметить, что лимфоидные фолликулы оставались относительно сохранными во всех группах, что указывает на меньшую восприимчивость иммунного компонента к острому повреждению. Полученные данные свидетельствуют о ведущей роли металлопротеиназ в развитии сосудистых повреждений при отравлении ядом и подчеркивают потенциал таргетной ингибиторной терапии для улучшения исходов лечения укусов змей.