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Review

VENOMOUS SNAKEBITES IN CROATIA, CLINICAL PRESENTATION, DIAGNOSIS AND TREATMENT

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SUMMARY – Venomous snake bites are recognized as a major public health problem, affecting mostly poor, underdeveloped areas in the tropical and subtropical areas. Every year, more than three million bite cases and about 100,000 deaths are registered worldwide. Over the past years, 632 people have been hospitalized in Croatia with only 3 deaths due to venomous snake bites. Favorable geographic position, warm climate and great biodiversity of Croatia have resulted in the development of a total of 15 species of snakes, of which only 3 are venomous: horned viper (*Vipera ammodytes*), the common European viper (*Vipera berus*) and meadow viper (*Vipera ursinii macrops*). Snake venom envenomation is called ophidism (greek ofis=snake). Snake venoms are complex mixtures of proteins and toxins that have a wide range of toxic effects. The clinical presentation of ophidism is due to hematotoxic, neurotoxic, myotoxic (cardiotoxic) and cytotoxic effects of venom. There is currently no test to identify patients with a systemic spread of the venom, the diagnosis is made by a combination of diagnostic tests, clinical symptoms and sings of systemic envenomation. Ophidism is a medical condition that requires urgent treatment. Following first aid given at the scene, the patient should be transported to the closest medical facility to assess the severity of the clinical presentation in a timely manner and take the necessary treatment measures.

Keywords: Croatia, *ophidism, epidemiology, diagnostics of ophidism, treatment*

Introduction

Venomous snake bites are emergencies that pose a clinical challenge due to a possible rapid fatal outcome. The group of venomous snakes with the highest medical importance, as defined by the World Health Organization includes species that are widespread in densely populated geographical areas where they cause bites resulting in high morbidity, disability and mortality, as well as species that are understudied but provide a strong indication of this that they could pose a significant risk to humans, and finally species whose bites, although rare, in principle result in severe and life-threatening systemic envenomation[1]. 2,500 to 3,000 species of snakes have been explored till now, and approximately 375 different species are considered venomous, of which 250 can cause severe systemic envenomation in humans[2,3]. Venomous snake bites are recognized as a major public health problem, affecting mostly poor, underdeveloped areas in tropical and subtropical regions.[4,5]. For this reason, the World Health Organization included venomous snake bite as a neglected tropical disease in June 2017, and in May 2019 launched a plan to double the reduction in number of deaths and disabilities by 2030, with particular emphasis on antidote development and their adequate availability in the most vulnerable countries[6]. Worldwide, the venomous snake bites more than three million people each year, while approximately 125,000 die[1]. In Europe, including the European part of Russia and Turkey, about 7,500 snake bites have been reported annually, 1,000 cases of severe clinical presentation of

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systemic envenomation with an average of four deaths[2,3]. According to statistics of the Croatian Institute of Public Health, a total of 632 people were hospitalized due to venomous snake bites in the period from 1998 to 2019. The highest number of hospitalizations was in 2001-58; 2000 - 57; 2018 - 40; 2019 - 18. In the last 20 years, only 3 snake bites deaths were recorded in the Republic of Croatia, in 2006, 2007 and 2013. Analyzed for this period, the mortality rate from venomous snake bites in Croatia is 0.2% per year[2,7]. It is believed that the number of snake bites is much higher because not all injured people seek medical help due to unavailability of health care or turn to the methods of traditional medicine. The number of venomous snake bites is on the rise, partly due to climate change, and due to the growing trend of keeping exotic venomous snakes as pets.

Species and geographic distribution of venomous snakes

We distinguish four families of venomous snakes: *Colubridae* (colubrids), *Elapidae* (elapids), *Viperidae* (vipers), and *Atractaspidae* (sub-terranean snake venoms of Africa and the Middle East). During evolution, *Colubridae* lost their venomous glands and only a few specimens are dangerous to humans. Their fangs are located at the back of the upper jaw, which prevents them from successfully biting their prey. The fangs of the Elapidae group are located in front of the upper jaw and cannot rotate or move. The vipers (*Viperidae*) have hollow venomous teeth that are located in front and through which the venom is expelled when bitten. The vipers (*Viperidae*) are divided into true vipers (*Viperinae*) and rattlesnake (*Crotalinae*)[8]. On all continents, except Australia, the number of non-venomous snake species is higher than the number of venomous snakes[7]. The most venomous snake species are in the tropical and subtropical zone, India, the Malay Archipelago, Brazil, Central America, the southern United States, and some parts of Africa. Among the few families of venomous snakes in Europe, only vipers (*Viperidae*), mainly the subspecies of the true viper (*Viperinae*). From the rattlesnake subfamily (*Crotalinae*), only Ancistrodon halys inhabits the extreme southeast of Europe. There are areas in the world where there are no venomous snakes at all. In Europe, these are Ireland, Iceland, the Balearics, Corsica and Sardinia[9]. Croatia is the area with the most widespread venomous snakes throughout Europe[10].

Snakes in Croatia

Favorable geographical position, warm climate and a great biodiversity of Croatia have conditioned the development of a total of 15 species of snakes, of which only 3 belong to the venomous ones. These are horned viper (*Vipera ammodytes*), the common European viper (*Vipera berus*) and meadow viper (*Vipera ursinii macrops*). Two species belong to the semi-venomous category, dragon (*Malpolon insignitus*) and the European ratsnake (*Telescopusfallax*), which cannot bite humans hard enough to inject venom, while the remaining species are non-venomous and harmless. In the south of Croatia, snakes are active from late winter to late autumn[6].

The horned viper (*Vipera ammodytes*) is the most dangerous European venomous snake, also the most important snake in Croatia, given the severity of the systemic envenomation it can cause and the outcome of which can be fatal[8]. Despite the complex taxonomic status and insufficiently uniform division of this species, two subspecies are considered significant: *Vipera ammodytes ammodytes* and *Vipera ammodytes meridionalis*[11]. In Croatia, the subspecies *Vipera ammodytes ammodytes* predominates, which is particularly common in Dalmatia, as it lives more often in dry and rocky areas than in lowland areas[8]. Its length reaches up to 90 cm, the head is extended at the nape of the neck, and at the tip of the nose is a soft horn covered with scales. It is ash gray in color that turns yellowish-brown and reddish-brown in some specimens, and both black and white specimens were found. A dark winding line extends along the entire body in the middle of the back. On the underside, the horned viper is whitish with black dots. The horned viper inhabits dry, rocky areas with bushes. It is mostly active at night. In cold areas, it goes into hibernation (winter sleep). In mountainous areas, it can be found at an altitude of 2500 m. It is widespread from South Tyrol and Carinthia to Asia Minor, and it is also found on larger Croatian and Greek islands[12]. In venom glands, adult specimens of horned viper have 10-45 mg of venom, and one bite can excrete as much as 20 mg of venom, which can be a lethal dose for a healthy adult, especially children, and chronically ill patients.

The common European viper (*Vipera berus*) is the most widespread snake in the world. There are two subspecies in Croatia: *Vipera berus berus*, in the area of Gorski Kotar, and *Vipera berus bosniensis*, in the area of floodplain meadows along the Sava, Drava and Danube river, and the mountains Triglav and Dinara. The length ranges from 60 to 80 cm, and large females reach up to 90 cm. The head is broad and triangular, the torso rounded, narrowed in the neck area. A characteristic sinuous dark line stretches in the middle of the back of the body. It is variable in color, from ashy gray to black (melanistic shape), but can also be reddish without a characteristic pattern and greenish. The common European viper bites are much rarer than the horned viper bites and are rarely fatal to a healthy adult[12].

The meadow viper (*Vipera ursinii macrops*) is our smallest and rarest venomous snake, about 50 cm long. It is light gray to yellow with a dark dashed pattern on the back[12]. Its bites are much rarer in our areas than the horned viper and the common European viper bites[10]. It is found on the southern, grassy slopes of Velebit, Dinara and Kamešnica[12]. The common European viper and meadow viper are strictly protected domestic species, while the horned viper is currently only a protected domestic species. In recent years, the number of venomous snakes in Croatia has increased significantly both in the Zagreb Zoo and among private individuals[13].

Snake venom

Snake venom envenomation is called ophidism (greek ofis=snake). Of all the venoms of natural origin, those produced by venomous snakes are considered the most complex, containing more than a hundred different bioactive molecules of variable toxicity and pathophysiological effects, acting individually and/or combined. From a biochemical point of view, snake venoms are complex mixtures of proteins and polypeptides that make up more than 90% of the total dry matter of the entire venom, and low molecular weight organic molecules, including amines, free amino acids and lipids, carbohydrates, citrates, nucleosides, and various inorganic ions. primarily sodium, zinc, and calcium[14,15]. According to the clinical symptoms of poisoning, the division of snake venoms into those with neurotoxic, hematotoxic, cytotoxic and myotoxic (cardiotoxic) effects is common. Snakes from the family *Viperidae* have venom of predominantly hematotoxic and necrotoxic effects, while snakes from the family *Elapidae* have primarily neurotoxic venom. Depending on the site of action, the components of venom can be divided into those with local and systemic action[14]. Snake venoms contain enzymatic and non-enzymatic proteins and peptides that are classified into different families according to their structure and function[16]. Enzymatically active proteins in snake venoms are: phospholipases A2 (PLA2), zinc-dependent metalloproteinases, serine proteinases, L-amino acid oxidases and acetylcholinesterases. Proteins isolated so far without enzymatic activity are three-finger toxins, α-neurotoxins, disintegrins, C-type lectins, natriuretic peptides, myotoxins, cysteine-rich secretory proteins, neuronal and vascular endothelial growth factors, cystatins and Kunitz-type protease inhibitors[16,17].

Previous research indicates that differences between snake venoms are due to the variable presence of protein components that exhibit (no) enzymatic activity and that the composition of snake venom can vary within genera and even species due to ontogenesis, geographic distribution, which can significantly change the clinical presentation and the course of symptom development and further complicate the treatment of venomous snake bites[18,19]. Snake venom PLA2 is one of the most researched components showing heterogeneous pharmacological effects, of which the most important are neurotoxic and myotoxic[20,21]. Three venomous phospholipases called amoditoxins have been found in vipers, the most venomous European snakes. Most PLA2 acts like β-neurotoxins, by binding to specific receptors on the presynaptic membrane irreversibly inhibits the release of acetylcholine in the neuromuscular junction, thus causing a complete disruption of signal transduction in motoneurons. Neurotoxicity is also manifested by phospholipase activity and blocking of voltage-dependent potassium channels[17,22]. In addition, PLA 2 can cause mitochondrial membrane disorders in respiratory muscles due to the hydrolysis of phospholipids[23,24], leading to acute neuromuscular weakness, followed by flaccid paralysis[25]. Snake venom PLA2 is known to cause local or systemic skeletal muscle necrosis. The myotoxic effect essentially manifests itself in the form of rapid, drastic and irreversible biophysical changes of the sarcolemma, which are attributed to disruption of its integrity, depolarization and finally, an increase in

permeability followed by loss of cytoplasmic markers, e.g. myoglobin, creatine kinase, and lactate dehydrogenase[16].

Zinc-dependent metalloproteinases account for about one-third of the total protein composition of the venom and are considered major toxins responsible for local tissue damage at the site of the bite. They are a common component of snake venom from the *Viperinae* family. Metalloproteinases have the ability to directly activate cells and release endogenous bioactive components directed to basement membrane proteins, coagulation factors, platelets, endothelial and anti-inflammatory cells[16,17,22].

Metalloproteinases and PLA2 are known to cause venom-induced expendable coagulopathy, which can be complicated by life-threatening bleeding. The procoagulant action of metalloproteinases, mediated by their repeated activation of coagulation factors, is most likely to be manifested as a marked depletion of available plasma fibrinogen concentrations which are required for efficient blood clotting in blood vessel injury[8]. PLA2 inhibits the process of blood clotting and platelet aggregation by hydrolysis of platelet phospholipids and thus acts on the sites where coagulation complexes are formed[26,27].

Some snake venoms have been researched in detail due to common envenomation that over time have led to the production of antidotes. Some components of the venom have been identified as beneficial due to their mechanism of action on the human body which has been used in the pharmaceutical industry for the production of drugs[15]. The first drugs produced on the basis of snake venoms were the antihypertensives captopril and enalapril, the antiplatelet drugs tirofiban and eptifibatide (Integrilin ®)[28].

The role of snake venom in the treatment of certain diseases has been intensively investigated in recent years, as the components of snake venom have been shown to have antitumor, anti-inflammatory and immunomodulatory properties.[30]

Clinical presentation of ophidism

The purpose of a snake bite is for food or defense, so we distinguish two types of bites, a bite for food or a bite for defense, based on the amount of venom injected into a victim or attacker[16,29]. In a snake whose purpose is to bite for food, the intention is to kill the victim, the snake bites the victim and injects a large amount of venom, and the prey is swallowed only after killing it. By biting in order to defend, the snake injects a smaller amount of venom into the victim because it tries to escape and thus defend itself. A bite in which the venom does not empty the venom glands is called a dry bite[29]. The dose of venom injected into the human body depends on the size of the snake, the location of the bite and the characteristics of the victim. Because of their relatively lower body weight, children receive a higher dose of venom per unit body weight. Although venomous snake bites in adults and children present a similar clinical presentation, the severity of the envenomation clinical presentation is more severe in children and complications of snake envenomation are more common in childhood[30,31].

The clinical presentation of ophidism is due to hematotoxic, neurotoxic, myotoxic cardiotoxic and cytotoxic effects of venom.

The common classification of snake bite envenomation which is often used in everyday clinical practice to show the severity of the clinical presentation of envenomation, is:

- Very mild reaction - the appearance of local edema, without general signs and symptoms, except the patient's fear
- Mild reaction - the appearance of local or widespread edema, with or without gastrointestinal signs and symptoms, but without the appearance of general symptoms
- Moderate reaction - the appearance of extensive edema, shock lasting less than two hours, and the appearance of other signs and symptoms of moderate envenomation
- Severe reaction - the appearance of shock lasting more than two hours or recurrent shock and the appearance of other signs and symptoms of severe systemic envenomation
- Fatal outcome - obvious signs of systemic envenomation ending in death[10,32].

The diagnostics of ophidism

Achieving timely diagnosis, and thus treatment of ophidism, is a challenge facing physicians around the world[33]. For years, much effort has been put into development of new diagnostic tools that would facilitate

the rapid diagnosis of venomous snake bites, particularly in rural areas of the tropics. Studies have shown that early treatment of patients after venomous snake bites is associated with faster recovery and shorter hospital stays[34,35]. On the other hand, delayed treatment has been found to increase the risk of severe and life-threatening complications (acute renal failure, respiratory muscle paralysis, bleeding due to consumable coagulopathy, cardiac arrhythmias) leading to prolonged hospital stays and increased treatment costs[36,37]. There is currently no test to identify patients with systemic envenomation, the diagnosis is made by a combination of available diagnostic tests and clinical symptoms of systemic envenomation. The availability of diagnostic tests available to clinicians varies from country to country, and the level of experience in diagnosing and treating venomous snake bites varies greatly among clinicians from different hospitals. To date, diagnostics has been based on techniques ranging from immunological tests (usually an ELISA test), through enzyme activity tests, to forensic genetic methods. Tests are used to detect the venom in the blood, to evaluate the effectiveness of the antidote used to neutralize the venom, to determine the type of snake. The downside is that most of the available tests last at least 3-4 hours and are not suitable for clinical use, but are used only for research purposes. Since venomous snake bites are an emergency where toxins are present within minutes, it would be useful to have a diagnostic device for clinical use that operates on a timescale of minutes rather than hours and is stable over a wide range of temperatures and ambient conditions[38].

The basic diagnosis of ophidism includes a detailed history of the patient, targeted examination and appropriate laboratory tests. Collection of a detailed medical history includes examining the circumstances of the bite (e.g. geographic area, time of the bite, number of bites), details of the snake (if seen, photographed), clinical manifestations of the venom (including onset time), first aid and previous illnesses (eg comorbidities, allergies, previous snake bites, medications)[38]. Laboratory tests include evaluation of the coagulation profile to check for venom-induced coagulopathy by repeated measurements of the international normalized ratio (INR) of blood coagulation, activated partial thromboplastin time (aPTT), D-dimer and/or fibrinogen degradation products. An acute decrease in hemoglobin and hematocrit may indicate internal bleeding, and a decrease in fibrinogen levels may indicate coagulopathy. Blood levels of creatine kinase, electrolytes, urea, and creatinine are also measured, which can be used along with analysis of urine (hematuria, proteinuria, urea levels, and urine excretion) to assess venom-induced rhabdomyolysis and associated complications, such as acute renal failure caused by myoglobulinemia, polyuria, oliguria, or anuria[39].

Treatment of ophidism

Epidemiological researches have shown that mortality from snake bites is not a major concern, and hospitalization and rapid diagnosis are crucial to determine the proper use of antidotes which is the only specific treatment for venomous snake bites[38]. Ophidism is a medical condition that requires urgent treatment. At the time of the bite, the victim should rest, the bite site should be cleaned, and in the case of a limb bite, the limb should be immobilized. No other form of alternative and local lay help or self-help is recommended on the ground. When providing first aid at the scene, the patient should be transported to the nearest medical facility to assess the severity of the clinical presentation in a timely manner and to take the necessary treatment measures[10]. In a hospital setting, the patient is monitored and in case of progression of local and/or general symptoms, symptomatic and specific treatment is applied. When a snake bites, the amount of venom injected may not be significant, and such a bite may not require the administration of an antidote. Therefore, constant monitoring of patients is required.

The use of anti-viper serum (antidote) is recommended in our area for the moderate and severe clinical presentation of envenomation, especially in children and pregnant women, as they represent a group with an increased risk of developing complications. Pregnant women are at risk for both mother and child, and in 50% of cases, intrauterine bleeding and/or miscarriage occurs[2,10,40]. The antidote is hyperimmune globulin obtained from an animal previously immunized with snake venom. It prevents or reverses the effect of snake venom[2]. It can be monovalent or polyvalent, depending on whether it is effective for the bite of one or more species of venomous snakes. The antidote for venomous snakes in Croatia was produced at the Immunological Institute in Zagreb. It is a polyva-

lent antidote that effectively neutralizes the venom of all three venomous snakes in our area[13]. As the last batch produced expired on November 30, 2019, currently, the supply of anti-viper serum in Croatia is provided by imports[10,41].

The antitoxin should be administered according to the manufacturer's instructions. It is used exclusively in hospital conditions because its use can cause serious reactions (allergic reaction, anaphylactic shock, serum sickness)[41]. After anti-viper serum, protection against tetanus should be given depending on the immune status of the tetanus patient. The prophylactic use of antibiotics is not recommended, only in cases of proven infection (based on the isolated causative agent and its sensitivity to the antibiotic). Corticosteroids are used only in the treatment of allergic reactions to serum, while some authors recommend the use of corticosteroids in "compartment" syndrome. If the patient is severely disturbed or in shock, treatment is carried out in the intensive care unit using crystalloid solutions, blood products, sedatives, anticonvulsants, mechanical ventilation, hemodialysis and other necessary measures. Surgical intervention is sometimes required for incision of a hemorrhagic bulla or abscess, necrectomy, fasciotomy, or amputation of part or all of the limb. It is very important to recognize the development of "compartment" syndrome in time, which requires urgent fasciotomy[42].

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Sažetak

UGRIZI ZMIJA OTROVNICA U HRVATSKOJ, KLINIČKA SLIKA , DIJAGNOSTIKA I LIJEČENJE

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Ugrizi zmija otrovnica značajan je javnozdravstveni problem koji uglavnom pogađa siromašna, nerazvijena područja u tropskim i suptropskim krajevima. Svake godine u svijetu bilježi se više od tri milijuna slučajeva ugriza i oko 100.000 smrtnih slučajeva. U zadnjih 20 godina zbog ugriza otrovnih zmija u Hrvatskoj hospitalizirano je 632 osobe sa samo 3 smrtna ishoda. Povoljan geografski položaj, topla klima i velika bioraznolikost Hrvatske uvjetovao je razvoju ukupno 15 vrsta zmija od kojih samo 3 pripadaju otrovnicama: poskok (*Vipera ammodytes*), riđovka (*Vipera berus*) i planinska riđovka tj. planinski žutokrug (*Vipera ursinii macrops*). Otrovanje zmijskim otrovom naziva se ofidizam (grč. ofis-zmija). Zmijski otrovi su složene smjese proteina i toksina koji imaju širok raspon toksičnih djelovanja. Klinička slika ofidizma posljedica je hematotoksičnog, neurotoksičnog, miotoksičnog (kardiotoksičnog) i citotoksičnog djelovanja otrova. Trenutačno ne postoji test kojim bi identificirali bolesnike kod kojih je došlo do sustavnog širenje otrova, dijagnoza se postavlja kombinacijom dijagnostičkih testova i kliničkih simoptoma sustavnog otrovanja. Ofidizam je medicinsko stanje koje zahtijeva hitno zbrinjavanje. Nakon pružene prve pomoći na mjestu događaja, bolesnika treba prevesti u najbližu zdravstvenu ustanovu kako bi se na vrijeme procijenila težina kliničke slike i poduzele potrebne mjere liječenja.

Ključne riječi: *Hrvatska, ofidizam, epidemiologija, dijagnostika ofidizma, liječenje*