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Review Article

Snake bites in morocco: Progress and challenges

Abstract

Snakebites are a real health problem in Morocco because of the diversity of the ophidian fauna and the significant morbidity and mortality if treatment measures are delayed. The Moroccan Poison Control Center reports hundreds of snakebites every year.

Being aware of this problem, Morocco started to set up a specific strategy for the control of snakebites since 2008. This strategy has allowed the implementation of a specific snakebite information system, the standardized guidelines for snakebite treatment and the acquisition and distribution of an adequate antivenom. These measures have led to an increased number of snakebites with better therapeutic management but despite these efforts, snakebites remain underestimated in Morocco.

Introduction

Snake envenomation constitutes a major health problem and a common cause of injury and death in many regions of the world especially in tropical and subtropical countries where occurrences of accidental snakebites are at their highest level [1,2].

The annual frequency of snakebites is underestimated at 4.5 to 5.4 million cases worldwide with estimates of 81,000 to 138,000 deaths annually while 400 000 of them survive but keep severe and permanent functional sequels [3].

In Sub-Saharan Africa, where data is even more incomplete, up to a million people are reported as being bitten each year; 7000 to 20 000 of which lead to death [3].

In Morocco, snakebites have long remained of secondary importance behind envenomations by scorpion stings [4].

The present work aims to offer a brief overview of the ophidian envenomation problematic in Morocco.

Epidemiology of snakebites in morocco

The current annual incidence of snakebites in Morocco is estimated at 2.65 per 100,000 inhabitants with children under the age of 15 experiencing the most severe cases. The majority of bites occur in rural areas because of agricultural activities. The spring and summer are the seasons when most snake bites happen with a bit of a peak in June, resulting from a higher activity of both snakes and humans. Snakebites are mainly inflicted on the feet or ankles, most frequently during the evening when there is a greater probability of accidentally treading on a snake and sometimes at night while it is sleeping or moving [5-7].

According to the study of Chafiq, et al., the majority of victims were young, with a mean age of 26.8±17.2 years and a male/female sex ratio of 1.67 [7]. The highest annual incidence was observed in the region of Tangier-Tetouan followed by the region of Meknes-Tafilalet. These high incidences can be explained by the diverse fauna of snakes found there and a more efficient reporting of cases due to a better health system management. However, other studies reported the region of Souss-Massa-Daraa as the most affected by snakebites [5]. This region is known to be agricultural and has a large population, a diverse fauna of snakes and a semiarid to arid climate.

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Regarding mortality, the studies of both Chafiq, *et al.*, and Arfaoui, et al., revealed that the current annual mortality rate from snakebites reaches 3.9% [5,7], while a retrospective study between 1980 and 2008 revealed a higher rate of 7.2% [7]. The studies also showed that females aged more than 60 and less than 20 present a significantly higher specific lethality [5]. The region of Souss-Massa Daraa records the highest number of deaths, which reflects a deficiency in the management of snakebites, mainly in the delay of hospital management and/or unavailability of adequate antivenom if we disregard a strong under-reporting of mild cases [5,7].

Snake species in morocco

There are over 3000 snake species worldwide 200 of which are venomous and hold medical importance. Of these, the species represented in Figure 1 are considered to be the 10 most dangerous snakes in the world. Notably, the *Bitis arietans* viper and the *Naja cobra* can be found in Morocco.

In Morocco, the geographic distribution of snake species is not clearly established and most snakebites and deaths are not nationally updated. Therefore, the study of the biogeographic distribution of snakes merits being part of a global national research network involving ecologists, biochemists and clinicians.

According to Chafiq, et al. and Lallie, et al., [5,7], there are eight species of dangerous snakes in Morocco (Figure 2):

Seven of them belong to the Viperidae family,

1. *Bitis arietans*, which is widespread in the south of the Sahara (only absent from tropical rainforests) and represents isolated populations in south-western Morocco;
2. *Daboia mauritanica*, which can be found in the north of the Sahara, from Morocco to eastern Algeria, with isolated populations in arid areas;
3. *Echis leucogaster*, present in isolated populations in the center and north of the Moroccan Sahara;
4. *Cerastes cerastes*, which is widespread throughout arid areas but appears in select rocky over sandy habitats; and *Cerastes vipera* which is restricted to the sandy habitats of desert areas;
5. *Vipera latastei*, found in the Rif and Middle Atlas Mountains of Morocco;
6. *Vipera monticola*, which is restricted to the High Atlas Mountains of Morocco.

Snake species are not always identified after the bite. The snakes were identified in only 6.2% of cases with the vipers are involved in 66.6% of the bites, which reflects the general abundance of these species and the frequency of direct contact. The vast majority of bites reported are attributed to *Daboia mauritanica* (69.4%), *Bitis arietans* (16.6%) and *Cerastes* sp. (16.6%) [7].

In Morocco, the Elapidae family is represented by a single species: *Naja haje legionis*, which can mainly be found in the arid and Saharan bioclimatic zones with warm or temperate winters. Cobra bites are very rare in Morocco apart from some accidents involving snake charmers in the Jamaa Lafna place in Marrakech [5,7].

Snake venoms

Snake venoms have an important role in the snake's defense/offense against predators or prey and in the initiation of digestion.

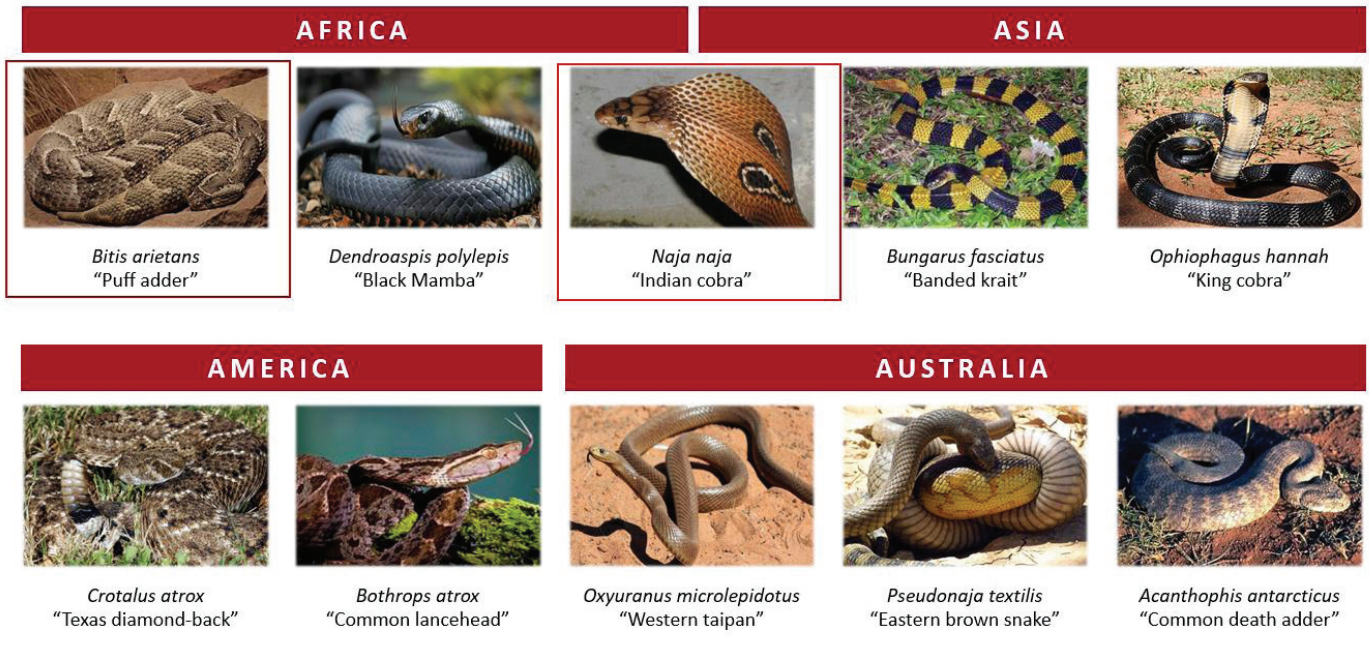

Figure 1: Ten of the most dangerous snake species in the world.

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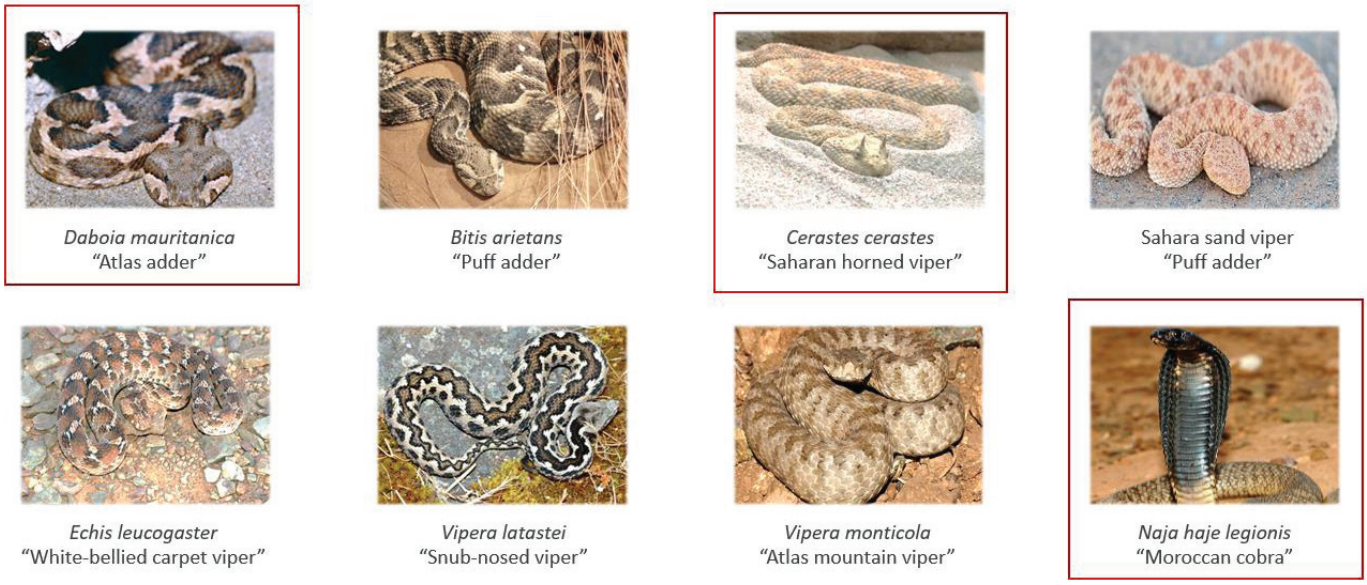

Figure 2: Snake species found in Morocco [6].

There are two types of venom: venoms rich in neurotoxins affecting the nervous system and others rich in enzymes inducing loco-regional damage and hemostasis disorders.

Snake venoms are rich sources of pharmacologically active polypeptides and proteins representing approximately 90% of their dry weight [4,8].

These components can be divided in:

Enzymatic proteins: the enzymes include phospholipases A2, proteinases, nucleotidases, phosphodiesterases, and L-amino acid oxidases. In addition to their catalytic properties that may contribute to the digestive action of the venom, these enzymes also induce various pharmacological effects including neurotoxic, myotoxic, cardiotoxic, hemorrhagic, hemolytic, procoagulant, and anticoagulant effects [4,9].

Non-enzymatic proteins: These proteins include neurotoxins, cardiotoxins, myotoxins, ion channel inhibitors, and anticoagulant proteins [4,9].

Thus, snake venom proteins, whether they are enzymatic or nonenzymatic, target several tissues, organs, and physiological systems and interfere in their normal functions when injected into a prey or victim leading to multiple organ or system failure and often death.

That said, the toxic effects of snake venoms can result from both the protein and the non-protein components and are further complicated by the inflammatory response of the victim's body.

The proteomic mapping of Moroccan cobra and viper venoms shows a complex mixture of biologically active molecules. Among these molecules, enzymes are the most widely recognized for their severe clinical spectrum of activity in envenomed victims.

The proteomic characterization of cerastes cerastes and *Daboia mauritanica* venoms from the viperidae family and *naja haje legionis* venom from the elapidae family showed a variation between the viper and cobra venoms [9,10].

About the Moroccan viper venoms, we have found that the *Cerastes cerastes* venom has a low complex proteome with six protein families: Disintegrins (8.5%), phospholipases (19%), serine proteinases (7%), type C lectins (1.7%), metalloproteinase (63%) and cysteine-rich secretory proteins (0.7%). On the other hand, *Daboia mauritanica* venom has a complex proteome with nine protein families: Disintegrins (13%), phospholipases (5%), serine proteinases (6%), type C lectins (12%), metalloproteinase (45%), cysteine-rich secretory proteins (1.2%), kunitz inhibitors (3.8%), snake venom vascular endothelial growth factor (4%) and C-type natriuretic peptide (4%) [1,6].

Hemorrhage is mainly caused by snake venom zinc-dependent metalloproteinases which digest components of the extracellular matrix (ECM) proteins resulting in bleedings [4].

As for the venom of Moroccan cobra *Naja haje legionis*, it is mainly rich in non-enzymatic proteins such as neurotoxins, cardiotoxins, myotoxins inducing a neurotoxic effect by attacking the central and peripheral nervous system causing paralysis, excitotoxic shocks and cytotoxic or cardiac effects by destroying the cells or attacking the cardiac cells and disrupting the cardiac rhythm [4,10]. Besides neurotoxicity and cardiotoxicity, *Naja haje legionis* venom was found to cause myotoxicity, cytotoxicity, hepatotoxicity and nephrotoxicity in animals and *in-vitro* studies [21–23].

The neurotoxic effects of the *Naja haje legionis* venom are attributed to the presence of highly potent alpha neurotoxins while myotoxicity and cytotoxicity are caused by phospholipase A2 enzymes and cytotoxins [23,24].

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Clinical features

Snakebites lead to various clinical pictures depending on the snake species involved and the severity of the envenomation.

In Morocco, the diagnosis depends upon recognizing specific signs of envenoming. These include local signs such as swelling, blistering, local necrosis and systemic signs, such as hemorrhage, incoagulable blood, hypovolemic shock and neurotoxic signs [8].

***Viper syndrome:** whose venoms are rich in cytotoxic and hematotoxic substances, are responsible for what is called a "viper syndrome" that associates inflammatory and hemorrhagic disorders [7,8].

Patients with the viper syndrome are generally, graded according to the following severity criteria [11].

- **Grade 0 or dry bite:** Bite without envenomations, only the presence of fang marks and moderate pain.
- **Grade 1:** Minor envenomations with local edema and severe pain.
- **Grade 2:** Moderate envenomation with regional edema or local bleeding in the affected limb, coagulopathy and/or moderate general symptoms.
- **Grade 3:** Severe envenomation with extensive edema reaching the torso and/or severe general symptoms.

The gradation of envenomation is important for the choice of the therapeutic care strategy and the use or not of antivenom [5,7].

In Morocco, several cases of snakebite were reported with different bite circumstances and different clinical features. Envenomations by *Cerastes cerastes* and *Daboia mauritanica* are clinically characterized by pain at the site of the bite, from mild to severe local effects, hypotension, coagulopathy, venous and arterial thrombosis which can lead to heart or lung infarction and affect the majority of envenomed patients in the first days after the bite [9,12-14].

The first four cases of envenomation by *Daboia mauritanica* in Morocco were in Tiznit in South Morocco: Two of the four victims presented severe clinical symptoms such as thrombocytopenia, low blood pressure, compartment syndrome, and hemorrhagic syndrome. One of the two had local necrosis of the thumb, thenar and hypothenar areas. As for the third victim, the envenomation was moderate (extensive swelling, non-life threatening systemic symptoms) and minor for the fourth victims (local swelling, no systemic symptoms) (Figures 3A,B). No antivenom with coverage of this species was available to give to any of the victims [15].

Another severe case of snake bite by *Daboia mauritanica* was later reported: The victim was a 3-year-old male toddler presented to the emergency room three hours after a snake had bitten his lower right leg. He was unconscious and agitated with symptoms of a severe envenomation, thrombocytopenia and anemia. He was intubated, ventilated and his brain scan revealed a subarachnoid hemorrhage. The only antivenom available was FAV-Afrique®, a polyvalent snake antivenom, elaborated by immunisation of horses with venom from 10 different snake species among the most dangerous in Africa and belonging to Elapidae and Viperidae families with neutralizing potency superior at 20 DL50/ml, and was given without any clinical or biological improvement. The toddler died ten days after the snakebite [16].

The envenomation of two snake charmers by *Bitis arietans* (Figure 4A) was also reported by Chafiq, et al., [17]. The first victim was a 46-year-old male who sustained a bite in the left hand while handling a *Bitis arietans*. He was admitted to the intensive care unit with significant local pain and bleeding at the bite site (Figure 4B) as well as an edema extending to the arm with ecchymosis. The symptoms improved after the administration of three vials of FAV-Afrique®. The second snake charmer was a 31-year-old bitten at the anterior area of the left leg. He presented an edema at the leg that extended to the thigh. The coagulation time was normal and the symptoms improved with symptomatic care without antivenom

Rebahi, et al., [18] reported three patients who were bitten by *Cerastes cerastes* and developed extensive local swelling and life-threatening systemic envenomations characterized by disseminated intravascular coagulopathy, and acute renal failure. These patients had either a low Glasgow Coma Scale (GCS) or developed acute ischemic cerebrovascular. One of the patients had a good clinical recovery without any neurologic deficits but the other two died.

A case of acute renal failure following the *Cerastes cerastes* bite was reported by Elkabbaj, et al. [19]. Despite the treatment with FAV-Afrique→, the patient needed prolonged hemodialysis

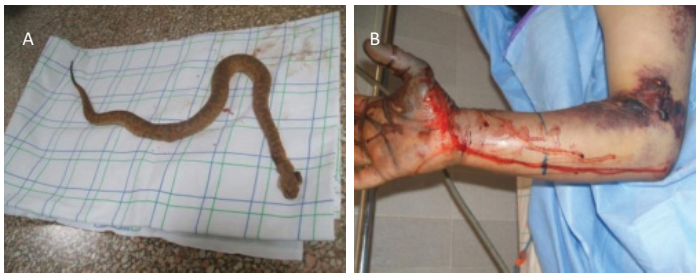

Figure 3: A: Daboia mauritanica (Courtesy of Nadia Chrouqui, Hassan Premier Hospital-Tiznit). B: Thumb and thenar eminence cyanotic, persistent bleeding in severe envenomation by Daboia mauritanica. (Courtesy of Nadia Chrouqui, Hassan Premier Hospital-Tiznit).

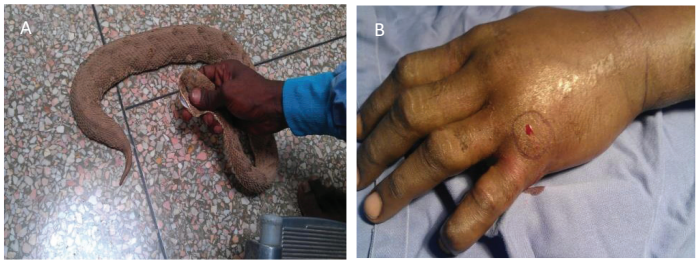

Figure 4: Bitis arietans viper. B: Envenomation of snake charmer by Bitis arietans.

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and he was discharged from the hospital after four weeks with normal renal function.

* Cobra syndrome: Cobra venoms are rich in neurotoxic compounds and responsible for a neurotoxic syndrome characterized by visual disorders, paralysis and respiratory distress [20]. Envenomation by *Naja haje* legionis causes prominent neurotoxic symptoms with local swelling and pain at the bite's site [5,7,20].

A case of cobra bite was reported by Chafiq, et al., [25]. The patient is a 35 year old man from the province of Essaouira who was bitten on the right foot. At admission, the patient was conscious with pupils being equal and reactive, but complained of dizziness and a headache and had fang marks without bleeding or edema. He was treated with FAV-Afrique® antivenom and left the hospital 24 hours after admission without sequelae.

Moroccan strategy against snakebites

Statistically, snake envenomation entails more than 5 million people bitten worldwide yearly out of whom 100,000 die and more than 300,000 are permanently disabled or disfigured. This prompted the World Health Organization to classify snake envenoming as a neglected tropical diseases.

1 million cases are annually recorded in Africa, which is the most affected continent with snake envenomation due to a lack of technical knowledge and poor medical facilities thus making envenomation cases difficult to manage.

In Morocco, a national strategy for snake envenomation control was enforced since 2012 to ensure a better management of envenomed patients starting by the implementation of a specific snakebite information system and the training of medical and paramedical personnel. Morocco also put in place standardization guidelines of snakebite treatment as well as training programs for toxicologists and doctors of the CAPM to ensure a more accurate identification of snakes.

Immunotherapy

Antivenom has remained the only specific medication for snakebites.

Since the establishment of an antivenom production chain in 1958, Morocco has relied on local antivenom production by Sanofi Pasteur until its discontinuation in 2002 due to the non-compliance of the production's infrastructures with the GMP norms.

This prompted us to initiate a collaboration with Inosan BIOPHARMA (Mexico), one of the leaders in antivenom production.

Today and since 2016, only the Inoserp® MENA (Middle East & North Africa) antivenom produced by Inosan, is available and has a spectrum of action covering the genera and species of snakes responsible for the most serious envenomations in Morocco notably *Daboia mauritanica*, *cerastes cerastes*, *Bitis arietans* and *Naja haje legionis*.

This antivenom can be stored at room temperature which is an advantage for the climate in Morocco. During 2016, 348 cases of ophidian envenomation were reported to the CCPM (Moroccan poison control center), 93 received the Inoserp® MENA antivenom. No cases of anaphylactic shock were recorded following its administration and the general lethality by snakebite showed a significant decrease which went from 3.44% in 2015 to 1.15% in 2016 [30].

Discussion & Conclusion

In conclusion, the ophidian envenomations remain a serious public health issue in Morocco. They are mostly particular by the extended geographic territory of their occurrences, a great biodiversity and the presence of two types of ophidian families responsible of two different symptomatologies (hemorrhagic and neurotoxic).

Seeing the socio-economic consequences caused by this pathology, it would be recommended to reinforce the surveillance of snake bites, especially during the hot season.

Conflict of Interest

All authors declare that this work has no financial interest nor conflict of interest.

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