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TOXICITY AND DRUG MANAGEMENT OF VENOMOUS SNAKEBITE; ARE CHILDREN AND ADULTS EQUAL IN RISK OF DEATH?

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ABSTRACTS

Snakebite and envenomation are silent public health issues and constitutes a major public health challenge in many parts of the world. According to World Health Organization (WHO), 4.5-5.4 million people a year are bitten by snakes, 1.8-2.7 million of them develop clinical illness (envenomation) after snakebite, and death toll could range from 81,000 to 138,000. Four families of venomous snakes are found in Nigeria. They are *Viperidae*, *Elapidae*, *Colubridae*, and *Actraspididae*. Previous works and research findings on this subject were accessed through Google Search, PubMed, and Wikipedia websites. In addition standard textbooks on Pharmacology were consulted. All these sources provided necessary information for this review. There are different categories of snake venom. They are cytotoxins, hemorrhagins, anti-clotting agents, myotoxins, and neurotoxins. Signs and symptoms of snakebite vary according to the species responsible for the bite, size, age, and the amount of venom injected. A venomous snakebite usually leaves two clear puncture marks. Some of the symptoms are: vomiting, nausea, dizziness, weakness, prostration, bleeding, shock, hypotension, myalgia, stiffness, dark-colored urine, and paralysis. The mainstay of treatment is the use of antivenom (monovalent or polyvalent). Other treatment options involve antitetanus toxin administration, analgesics, and antibiotics. While adults are more occupationally exposed to more bites/envenomation, children are more at risk of death due to hypovolaemia, shock, paralysis and other effects of endotoxins.

KEYWORDS: Snakebite, Antivenom, Adults, Children, Envenomation. Toxicity.

INTRODUCTION

Snakebite envenomation constitutes a major health challenge in many parts of the world and distribution of envenoming and mortality worldwide is variable. It is numerically lowest in Europe, Australia, and North America. On the other hand, it is highest in sub-Saharan Africa, South Asia, and South-East Asia(Ochola *et al*., 2018).

According to World Health Organization, 4.5-5.4 million people a year are bitten by snakes while 1.8-2.7 million of them develop clinical illness (envenomation) after snakebite and death toll could range from 81,000 to 138,000 (WHO, 2019).

Available epidemiological data are estimates and cannot be regarded as true values as most victims do not attend health centers or hospitals instead rely on traditional treatments. The degree of under-reporting may be greater than 70% in most African countries especially in rural areas with poor health and other infrastructures. Most young doctors and hospitals may also not be adequately equipped to handle venomous snake bites (Ghosh *et al*., 2018; Ndu *et al*., 2019).

A study in Mali showed that 49.7% of victims sought initial treatment from traditional sources, and in Nepal 56% of victims reported to traditional medicine as primary health-seeking behavior, while in Kenya the figure is at least 68%. Reliance on traditional medicine not only affects the outcomes of snakebite envenoming negatively, it contributes to the poor visibility of snakebite cases in conventional measurements of disease burden (WHO, 2019). It must however be stated that snakebikes in most non-urban communities in Nigeria are successfully treated by traditional medicine healers and of course with good outcomes.

The social and economic consequences of snakebite are known to be high in communities with high prevalence (Valyapuri *et al*., 2013; Kularatne *et al*., 2014). Despite its consequences, it has largely been neglected in global health. The WHO has though re-added snakebite to the list of neglected tropical diseases in 2017, (Gulland,

2017; Bhaumick *et al*., 2018), snakebites and envenomation remain a silent killer especially among children. In Kenya alone the most affected age bracket was the under 15years of age (Ochola *et al*., 2018).

In parts of the Nigerian savanna, snakebite victims may occupy over 10% of hospitals' beds. In the Middle Belt of the country the estimated incidence is as high as 497 per 100,000 per year with 10 to 20% comprising untreated fatalities (Pugh and Theakston, 1980). Cattle herders working barefoot are vulnerable to snakebites. Other high-risk groups include poor rural dwellers, agricultural workers, fishermen, hunters who usually move at nights, working children(10-14), people living in poorly constructed housing and people with limited access to education and healthcare (Habib, 2013; WHO, 2019).

In Nigeria, four families of venomous snakes are found. They include:*Viperidae*, *Elapidae*, *Colubridae, and Actraspididae.* Three species: carpet viper (*Echisocellatus*), black-necked spitting cobra (*Najanigricollis*), and puff adder (*Bitisarietans*) belonging to the first two families, are the most important snakes associated with envenoming in Nigeria. Carpet viper venom contains a prothrombin-activating procoagulant, hemorrhagin, and cytolytic fractions which cause hemorrhage, incoagulable blood, shock and local reactions/necrosis (Habib *et al*., 2001).

Neurotoxicity has been reported following Egyptian cobra (*Najahaje*) bites in certain parts of the country. Occasionally, snakebite may lead to important complications such as amputation, blindness resulting from spitting cobra (*Najanigricollis*) venom, opthalmia, fetal loss and wound infection, tetanus, and scarring (Abubakar *et al*., 2010).

Snakes bite either to capture prey or in self-defense. Snakes that are poisonous voluntarily, emit venom when they bite and because snakes can control the amount of venom they discharge, some bites are 'dry' and only 50%-70% of venomous snakebites result in envenoming, or poisoning. Be this as it may, it is safer to treat all snakebites as medical emergency unless one is certain it was a non-venomous snake. Any delay in treatment following the bite of a venomous snake could result in death or serious injury (Cleveland clinic, 2019).

There are different categories of venom. They include:

- **Cytotoxin**. This type of venom causes swelling and tissue damage in the area of the bite.
- **Hemorrhagins**. They cause disruption of blood vessels.
- **Anti-clotting agents**. Venoms that prevent the blood from clotting.
- **Neurotoxins**. They cause paralysis or other damage to the nervous system.
- **Myotoxins**. They are venoms that breakdown muscles (Cleveland clinic, 2019).

Classification of Venomous Snakes in Nigeria

The two groups of venomous snakes in Nigeria are:

- ***Elapidae*** (cobra family). This family includes cobra, king cobra, kraits, coral snake, and sea snakes. *Elapidae* are relatively long, thin, with large smooth symmetrical scales (plates) on the top (dorsum) of the head. They have relatively short fixed front fangs. There is no loreal scale between the pre-ocular and nasal scales. Some, notably cobras, raise the front part of their body off the ground and spread and flatten the neck to form a hood. Their venom is mainly neurotoxic but it can also harm body tissues or blood cells. Death from paralysis of the heart and lungs can occur quickly. Most sea snakes have flattened pad-like tails and their ventral scales are greatly reduced in size or absent (MOHM, 2019). See figure 1.

Fig. 1: *A typical cobra*; (WHO, 2019).

Fig. 2 *Echis ocellatus* (*Nigerian Carpet Viper*) (WHO, 2019).

Fig. 3. The Malayan pit viper (*Calloselasmarhodostoma*). Source (WHO, 2019).

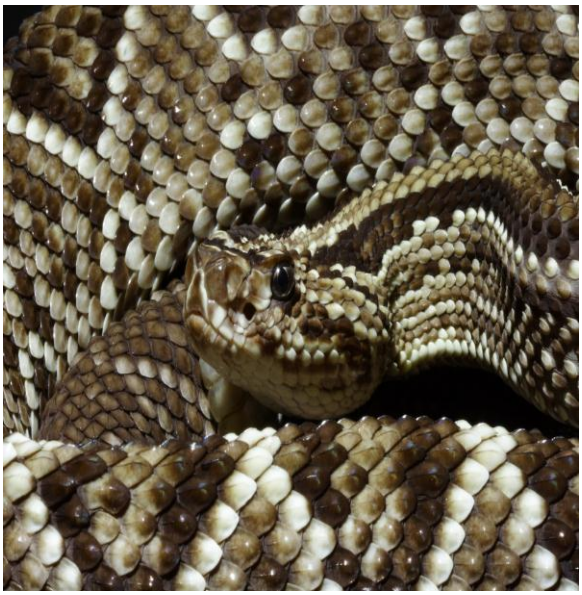

Fig. 4. Rattlesnake, from South America. (*Crotalusdurissus*). Source, (WHO, 2019).

- ***Viperidae.*** This comprises two sub-families: true viper or Old World vipers (*viperinae*) and pit vipers (*crotalinae*). They have relatively long fangs which are normally folded against the upper jaw and are erect during a bite. The *crotalinae* have a special sense organ, the loreal pit organ, to detect their warm-blooded prey. This is situated between the nostril and the eye. Pit vipers are from the *crotalinae* subfamily. Examples are: rattlesnakes, copperheads, water moccasins, or cottenmouths. Old World vipers are also called adders (Cleveland clinic, 2019). See figures 2 and 3.

Snake venom is a mixture of variety of proteins, peptides, enzymes, toxins, and non-proteins. An average venom may contain Phospholipases, metalloproteinases, serine proteinases, Three-finger Toxins, Arginine esterases, Bradykinin-potentiating peptides, C-type lectins, Cysteine-rich secretory proteins, Disintegrins, Hyaluronidases, L-amino acid oxidase, Myotoxins, Nerve growth factors, Phosphodiesterases, Prothrombin activators, Purines and pyrimidines, Saratoxins (JRex, 2017; (Ferraz et al., 2019).

Positively, snake venom is also employed in medicine and cosmetics as useful remedies. Examples include Captopril, an ACEi, Integrillin, an anti cardiac ischemic agent, Waglerins, an anti wrinkle/aging in cosmetics, Crotalphine and Mambalgin as analgesic agents, Actiflagelin as novel drug in infertility, diabetes and coagulation disorders (Cushman and Ondetti, 1999, Lauer *et al*., 2001, Debono *et al*., 2017, Bressen *et al*., 2016, Diochot *et al*., 2012; Utikin, 2019).

Evaluation and management of snakebites and envenomation

Symptoms and signs vary according to the species responsible for the bite, size, age, and the amount of venom injected. If the biting species is unknown, patient should be observed closely for at least 24 hours to allow recognition of the emerging pattern of symptoms, signs and results of laboratory tests. Together with history, this may help in identification of the snake species responsible for the attack.

The following are some of the signs and symptoms that can be observed:

- Two puncture wounds. A venomous snakebite will usually leave two clear puncture marks. In contrast, a nonvenomous bite tends to leave two rows of teeth marks (Eske, 2018).
- General: nausea, vomiting, dizziness, malaise, abdominal pain, weakness, drowsiness, prostration. These symptoms are nonspecific.
- Cardiovascular: fainting or light-headedness, collapse, shock, hypotension, cardiac arrhythmias and pulmonary edema. These symptoms are nonspecific.
- Bleeding and clotting disorders. Prolonged bleeding from bitten site, site of venipuncture, conjunctiva, oral cavity, petechial rashes or bleeding from occult sites. Bleeding from occult sites include gastrointestinal, urinary and intracranial bleeding i.e. hematoma, antepartum hemorrhage in pregnant women.
- Musculoskeletal and Renal. Generalized severe myalgia, stiffness, tenderness, dark colored urine, and oliguria/anuria (MOHM, 2019).
- Neurological. Patients present with a descending type of paralysis. The early sign is ptosis. Other signs are external opthalmoplegia, paralysis of facial muscles and other muscles innervated by cranial nerves. The patient may have a nasal voice, aphonia or dysphagia, regurgitation through the nose, difficulty in swallowing secretions leading to respiratory and generalized flaccid paralysis.
- Others are convulsions, excessive sweating, numbness of the face, especially in the mouth (Eske, 2018).

Clinical Assessment

This starts with a good history taking. It is important to establish whether a venomous snake has actually bitten the patient. Look for fang marks and signs of local envenomation. If the patient or his/her relative has brought the snake identification of the species should be carried out carefully, since crotalids can envenomate even while dead. Bringing a live or killed snake into the emergency department should be discouraged. Questions should be asked to determine the time elapsed since the snakebite and a brief medical history should be obtained (e.g. date of last tetanus immunization, , use of any medication, presence of any systemic disease, history of allergy).

Assessment of Severity of Envenomation

- **No envenomation**. Absence of local or systemic reactions.Fang marks (+/–).
- **Mild envenomation**. Fang marks (+), moderate pain, minimal local edema, erythema (+), ecchymosis (+/–), no systemic reactions (hemoglobin, platelet, protein, fibrinogen are normal).
- **Moderate envenomation**. Fang marks (+), severe pain, moderate local edema, erythema and ecchymosis (+), systemic weakness, sweating, syncope, nausea, vomiting, anemia or thrombocytopenia.
- **Severe envenomation**. Fang marks (+), severe pain, severe local edema, erythema and ecchymosis (+), hypotension, paresthesia, coma, pulmonary edema, respiratory failure (QMoPH, 2018).

Physical Examination

- During the initial evaluation the bite site should be examined for signs of local envenomation (edema, petechiae, bullae, oozing from the wound, etc) and the extent of swelling.
- The bite and at least other more proximal, locations should be marked and the circumference of the

bitten limb should be measured every 15-30min thereafter, until the swelling is no longer progressing. Serial measurement of circumference helps in estimating spread for venom and effect of antivenom. Lymph nodes draining the limb should be palpated and the presence of lymphangitic lines noted.

- ❖ Distal pulse should be checked and monitored if there is presence of gross swelling. The presence of a pulse does not rule out compartment syndrome. However, compartment pressure should be measured directly if there is concern that a compartment syndrome is developing.
- ❖ Evidence of severe snake envenomation should be sought. They consist of the following: (i) Rapid early extension of local swelling from the site of the bite. (ii) Early tender enlargement of local lymph nodes, indicating spread of venom in the lymphatic system. (iii) Early spontaneous systemic bleeding (especially bleeding from the gums. (iv)Passage of dark brown urine (QMoPH, 2018).

Investigations

The following investigations are required for management in suspected snakebite and the treatment of snake envenomation.

- Full blood count (FBC) including a blood film. A blood film is used to look for associated red cell fragmentation which would indicate thrombotic microangiopathy. Thrombocytopenia will also occur in thrombotic microangiopathy. A non-specific leukocytosis and lymphopenia is often associated with systemic envenomation. Platelet count may be decreased in victims of envenoming by vipers. Serial FBC will reveal a drop in hemoglobin if there is significant bleeding.
- Coagulation studies. Serial measurement of prothrombin time, hemoglobin, and platelet count are recommended for all pit viper victims. Fibrinogen is a more sensitive measurement of venom-induced defibrination than prothrombin time, and should be followed, if obtainable.
- Renal profile. Serum creatinine is necessary to rule out renal failure. It is also necessary to detect electrolyte imbalance in patients with repeated vomiting. Early hyperkalemia may be seen following extensive rhabdomyolysis in sea snakebites.
- Creatine kinase. It is for early detection of rhabdomyolysis. Serial monitoring is used to monitor trend.
- Urinalysis. It is used to assess for myoglobinuria, hematuria, and proteinuria.
- Liver function test. Mild hepatic dysfunction is reflected in slight increases in serum enzymes after severe local muscle damage.
- ECG. To detect arrhythmia especially in envenoming involving *Naja* species bite.

It is necessary to note that the first blood drawn from the patient should be typed and cross-matched, as the effects of both venom and antivenom can interfere with later cross-matching.

Management

General Management. This involves first aid and pre-hospital care. First-aid measures include reassurance of patients and immobilization of the bitten limb with a splint or sling. If the snake is still attached, use a stick or tool to make it let go. Sea snake victims need to be moved to dry land to avoid drowning. Remove anything tight from around the bitten part of the body (e.g rings, anklets, bracelets) as these can cause harm if swelling occurs. Use a makeshift stretcher to carry the person to a place where transport is available to take them to a health facility. Paracetamol may be given for local pain. Vomiting may occur, so place the person on their side in the recovery position. Avoid the use of tourniquet (WHO, 2019).

Emergency Department Care

- In the emergency department, evaluation should begin with the assessment of the airway, breathing, circulatory status, and consciousness. Urgent resuscitation will be needed in those in shock or cardiac arrest. A large-bore intravenous catheter should be inserted. Intramuscular injections should be avoided in pit viper snakebite victims due to risk of hematoma formation as patient has potential risk of coagulopathy. Oral or intravenous route is preferred.
- Anti-tetanus toxin should be administered.
- If there is venom exposure in the eye, perform irrigation with copious amounts of normal saline (5 to 10 liters).
- For pain management opioids have some theoretical benefit over non-steroidal anti-inflammatory drugs (NSAIDs) because of the theoretical risk of bleeding associated with NAIDs use in patients who may develop coagulopathy or thrombocytopenia due to envenomation (QMoPH, 2018).
- Bleeding caused by hematoxic snake bites may be life-threatening. However. It must be stressed upon that blood products are not a substitute for antivenom. Giving blood products in these situations without concomitant administration of the appropriate antivenom will not correct coagulopathy. In cases where the antivenom is not readily available blood products should be administered if the bleeding is life-threatening until the appropriate antivenom is available (MOHM, 2019).

Specific Drug Treatment

Antivenom Therapy

Antivenom is the definitive treatment for snake envenomation and should be administered as soon as possible after a bite (Parker-Cote and Meggs, 2018). Administered early, antivenoms are not just life-saving,

but can also spare patients some of the suffering caused by necrotic substances and other toxins in snake venom, leading to faster recovery, less time in hospital and a more rapid transition back to a productive life in their communities (WHO, 2019).

Antivenoms are biologic substances comprising immunoglobulin molecules or their fragments derived typically from the plasma of animals which have been immunized with venoms (WHO, 2010). Th product is called a monospecific (monovalent) antivenom when the animal is immunized against venom of a single species, or a polyspecific (polyvalent) antivenom when a mixture of venoms from different species is used as the immunogen. In some products, polyspecificantivenom can be a mixture of several monovalent antivenoms formulated according to the need of clinical use. Antivenom works as an immunotherapy. It acts by binding to venom toxins (forming immune-complexes) rendering the toxins inactive while enhancing their elimination from the blood (Gutierrez et al., 2003).

Current pharmaceutical technologies produce three main types of antivenom: whole IgG molecules (approximately 150kDa), $F(ab")_2$ fragments (approximately 100kDa) and Fab fragments (approximately 50kDa). The Fc fragment of IgG molecule is a suspected common cause for hypersensitivity; its removal produces $F(ab")_2$ or Fab which is now the common antivenom preparation. The different forms of antivenom, however, vary in several important pharmacological properties such as the volume of distribution, elimination half-life, elimination route, and number of paratopes and the size of immune-complexes formed. These differences have important implications on the therapeutic value of an antivenom. For instance, Fab with a large volume of distribution is ideal for targeting most elapid toxins which are small and deep-tissue penetrating, however, its short elimination half-life can result in a half-life mismatch with toxins of viperid venoms that exhibit relatively long half-life (Tan et al., 2014).

Failing to maintain an adequate level of antivenom in the circulation as the antivenom is eliminated quicker than the circulating toxins gives rise to the phenomenon of recurrent envenomation (recurrence of signs and symptoms at later time after the initial effective treatment of envenomation (Ariaratnam et al., 1999). The optimization of the therapeutic outcome of antivenom relies on good understanding of the pharmacokinetic-pharmacodynamic relationships of antivenom, interpreted in the light of the toxicokinetics and mechanisms of a particular venom being neutralized (Yap et al., 2014).

The choice of antivenom is clear provided the diagnosis of envenoming species is correct or the syndrome approach is rightly applied. The dosing regimen, however, requires optimal monitoring of syndrome progression and clinical judgment from case to case. It is noteworthy that in general the potency values of antivenom used against elapid venoms are low as compared to antivenom used against viperid/crotalid venoms, presumably due to the low immunogenicity of low molecular mass proteins that form the principal toxins in elapid venoms especially the cobras (Leong et al., 2015; Tan et al., 2016; Nong et al., 2016).

This is the basis for low neutralization capacity of elapid antivenoms and the need of a higher starting dose in confirmed envenoming cases by these species (up to 10 vials initial dose). The current research trend entails the investigation of toxin-specific neutralization complemented by proteomic and antivenomic approaches for the production of highly patient and broad-spectrum antivenoms (Tan et al., 2015).

Indications for Antivenom

Antivenom treatment should be given as soon as it is indicated. Antivenom treatment can reverse systemic envenoming even if it has persisted for weeks. Clinical evidence shows that local necrosis of the bite area can be prevented if antivenom is given within few hours after the bite. Antivenom treatment is recommended if a patient with proven or suspected snakebite develops one or more of the following signs:

- Hemostatic abnormalities. Spontaneous systemic bleeding (clinical), coagulopathy(prothrombin time) or thrombocytopenia ($<100 \times 10^9$/L or 100,000/cumm) (laboratory)
- Neurotoxic signs: ptosis, external opthalmoplegia, paralysis (clinical).
- Cardiovascular abnormalities: hypotension, shock, cardiac arrhythmia (clinical), abnormal ECG.
- Renal impairment: oliguria/anuria (clinical), rising blood creatinine/urea (laboratory), dark brown urine (clinical), urine dipsticks, other evidence of intravascular hemolysis or generalized rhabdomyolysis (muscle aches and pains, hyperkalemia) (clinical, laboratory).
- Local: (a) swelling involving more than half of the bitten limb. (b) Rapid extension of swelling, swelling that has crossed a major joint, wrist, elbow, ankle or knee. (c) Development of an enlarged lymph node draining the bitten limb (MOHM, 2019).

Antivenom Dosing and Administration

- The pediatric antivenom dose is equal to adult.
- If there is no shock or serious bleeding: 4 vials in 250mL N/S IV over 1hr.
- If shock or serious bleeding is present: 8-12 vials in 250mL N/S IV over 1hr.
- Response to infusion of antivenom is marked by normalization of blood pressure. Within 15-30mins bleeding stops, though coagulation disturbances may take up to 6hr to normalize.
- A repeat dose of antivenom should be given when there is persistence of blood incoagulability even

after 6hr or continued bleeding after 1-2hr of the initial dose. Antivenom should also be repeated when there are worsening cardiovascular signs even after 1-2hr.

- Close monitoring for anaphylactoid or anaphylactic reactions require antivenom administration to occur in monitored, high-acuity area of the emergency department or intensive care unit, where the medications, equipment, and skilled personnel required to manage an airway emergency are immediately available. If there is no acute reaction to initial dosing, subsequent doses of antivenom can be administered in a less monitored setting such as a hospital ward.
- Antivenom should never be given locally at the site of the snakebite since this is ineffective and this route of administration is associated with significant risks.
- Intramuscular injections are also not preferred since antivenom is composed of large molecules (IgG or fragments) which are absorbed slowly making the bioavailability by this route poor compared to intravenous administration. Other disadvantages include pain on injection and risk of hematoma formation and sciatic nerve damage in patients with hemostatic abnormalities.
- Antivenom sensitivity testing is no longer recommended as a lack of response does not predict the large majority of early (anaphylactic) or late (serum sickness type) reactions. Such testing also delays treatment (QMoPH, 2018).

Supportive Treatment

- Analgesia. (i) For mild pain, paracetamol can be administered every 4-6hours orally as required. (ii) Aspirin or non-steroidal anti-inflammatory drugs should be avoided in patients who are at risk to developing coagulopathy. (iii) For moderate to severe pain, intravenous opioids should be administered in titrated doses.
- Antibiotics. Antibiotics should be considered in snakebite with local tissue necrosis/dermonecrosis or extensive tissue injury/damage. Selection of antibiotics should cover both aerobic and anaerobic organisms (MOHM, 2019).

Poor Availability of Antivenom in Nigeria

Research findings in Nigeria indicate that antivenom, a definitive treatment of snake envenomation confers protection of over 80% against mortality from carpet viper bites (Habib, 2012). Unfortunately, in the last few decades, a crisis in antivenom supply to sub-Saharan Africa has been observed. This has affected Nigeria to a large extent.

Some of the reasons adduced for this include: a lack of commercial incentives for the companies that used to produce anti-venoms for Africa and inefficient distribution channels within the national health systems, ignorance of true antivenom requirements due to poor epidemiological information; the high cost of some products which make them unaffordable to local health systems, and loss of confidence in antivenoms due partly to the marketing of ineffective and inappropriate products imported from overseas (Warrell, 2008; Stock et al., 2007). All these factors have adversely affected antivenom availability in Nigeria and other sub-Sahara African countries.

This prompted the Nigerian government to enter into an agreement with a UK group. This resulted in the formation of the EchiTab Study Group (Nigeria-UK) which in 1995 developed the original EchiTab (MicroPharm), an ovine Fab monospecificantivenom against Nigerian *E. ocellatus* venom (Habib, 2013).

This antivenom was clinically tested and found to be effective, but because of its association with the problem of recurrent symptoms of envenoming, work continued to develop an antivenom with a more durable effect (Meyer et al., 1997). Currently EchiTab-G (a monospecificantivenom manufactured by MicroPharm) and EchiTab-Plus-ICP (atrispecificantivenom manufactured by InstitutoClodomiroPicado, University of Costa Rica) have been developed against venoms of Nigerian snakes (Abubakar et al., 2010).

There is hope that antivenom supply in Nigeria and other African countries will improve. In addition to laboratories that have previously manufactured antivenoms for Africa, such as EgyVac (Egypt), Sanofi-Pasteur (France) and South Africa Vaccine Producers, new manufacturers have entered the market including MicroPharm (UK) and InstitutoClodomiroPicado (Costa Rica), and the InstitutoBioclon (Mexico) (Abubakar et al., 2010; Habib, 2013).

Some First-Aid Measures That Should Be Avoided

The use of tourniquet tied above the site of bite is a common practice in most rural communities and sub-urban centers. Tourniquet are constricting bands that block arterial venous, and lymphatic flow. Many victims may have used this technique as a means of reducing the spread systemically. However, this can increase local complications by increasing tissue anoxia and triggering severe systemic envenoming after their removal. This has been strongly discouraged by many researchers (Sharma et al., 2003; Aghahowa and Ogbevoen, 2019; Parker-Cote and Meggs, 2018).

The lymphatic system transports venom from the envenomation site to systemic circulation. Application of a tourniquet will sequester venom local, potentially leading to increased local tissue destruction when the venom is from those snakes that cause local tissue damage. Furthermore, tourniquets can impede venous flow and arterial blood flow, leading to limb ischemia, gangrene, and potentially amputation (Parker-Cote and Meggs, 2018).

A prospective study in Nigeria revealed that patients that used tourniquets had a larger antivenom requirement (Michael et al., 2011). One case report of death after the application of a tourniquet for 48hours occurred, the patient suffered from thrombophlebitis, local necrosis, and gas gangrene, followed by pulmonary thromboembolism (Pugh and Theakston, 1987).

Another prospective study in the Philippines of 36 hospitalized patients who developed neurotoxic symptoms after bites by *Najanajaphilippinensis* reported four patients who developed complete respiratory paralysis requiring mechanical ventilation after removal of a tourniquet. Based on this the authors recommended slowly releasing already-applied tourniquets (Watt et al., 1988).

Guidelines do not support the use of tourniquets. According to World Health Organization (WHO) recommendations arterial tourniquets are contraindicated, their effectiveness relies on occlusion of peripheral pulses causing pain, ischemia, nerve injury, and gangrenous limbs. Deleterious effects from tourniquets are seen within 20mins to 2hours of application (Warrell, 2018; WHO, 2018; Kanaan et al., 2015).

Another first-aid method that should be avoided is the use of venom extractors. Venom extractors are suction devices that are proposed to work by applying suction to the site of a snakebite. These devices are marketed by companies that target outdoorsmen. The purported design is supposed to apply negative pressure over fang marks to induce venom extraction. Venom extractors can still be purchased through major retailers online and in-stores, despite several studies proving their ineffectiveness (Alberts et al., 2004).

The use of venom extractors is associated with high risk of local tissue destruction and a false sense of security. Some researchers have reported necrosis of tissue with resultant tissue loss in two animals treated with extraction, which was not seen in untreated animals (Bush et al., 2000). Others have argued that manufacturer's claims provide a false sense of security and may delay a patient from seeking definitive and effective care (Gellert, 1992).

Current guidelines do not support the use of mechanical suction for pit viper envenomation (Watt et al., 1988; AHA, 2018). Some people have attempted the use of electric shock as a treatment of venomous snakebites, though there is no scientific rationale for it and no data to back it up. Electric shock is dangerous in experimental studies and is not recommended (Parker-Cote and Meggs, 2018).

Prevention

- Be careful about where hands and feet are placed. For example, avoid reaching into spaces, holes, or underneath objects without first being sure a snake is not hiding underneath.
- Do not lie down or sit down in areas where snakes might be located.
- Wear high-top leather boots when walking through or working in areas of dense vegetation.
- Do not attempt to capture, handle, or keep venomous snake.
- Camp only in areas away from swamps, streams, dense foliage, and other places that snakes are to inhabit.
- Slowly back away from and avoid touching any snake that is encountered (Cleveland clinic, 2019).

CONCLUSION

There is paucity of technical know among young doctors in management of snakebites as there is obvious lack in venoms supply to hospitals. Snakebites victims seek traditional care. Adults share a greater risk of occupational exposure while children share higher risk of toxicity and, or death from snakebites/envenomation.

REFERENCES

1. Aanaratnam CA, Meyer WP, Perera G, Eddleston M, Kulratne SA, Attapatu W, Sheriff R, Richards AM, Theakston RD, Warrell DA, (1999). A new monospecific ovine Fab fragment antivenom for the treatment of envenoming by the Sri Lankan Russell's viper (*DaboiaRusseliiRusselii*): a preliminary dose-finding and pharmacokinetic study. Am J Trop Med Hyg, 61: 259-265.
2. Abubakar SB, Abubakar IS, Habib AG, Nasidi A, Durfa N, Yusuf PN, (2010). Pre-clinical and preliminary dose-finding and safety studies to identify candidate antivenom for treatment of envenoming by saw-scaled or carpet vipers (*Echisocellatus*) in northern Nigeria. Toxicon, 55(4): 719-723.
3. Abubakar SB, Habib AG, Mathew J, (2010). Amputation and disability following snakebite in Nigeria. Trop Doc, 40(2): 114-116.
4. Aghahowa SE, Ogbevoen RN, (2017). Incidence of snakebite and utilization of antivenom in the University of Benin Teaching Hospital, Benin City, Nigeria. Niger J ExpClinBiosci, 5: 5-10.
5. Alberts MB, Shalit M, LoGalbo F, (2004). Suction for venomous snakebite. A study of mock venom extraction in a human model. Ann Emerg Med, 43: 181-186.
6. American Heart Association. Part 15 First Aid. Web-based integrated 2010 & 2015 American Heart Association and American Red Cross Guidelines for first aid (2018). Available online https://eccguidelinesheart.org/index.php/circulation/aha-red-cross-first-aid-guidelines/part15-first-aid.
7. Bhaumik S, Jagadesh S, Lassi Z, (2018). Quality of WHO guidelines on snakebite: the neglect continues. BMJ Glob Health, 3: e000783 doi:10.1136/bmjgh-2018-000783.

8. Bressan E, Trouska F, Vetter I, Kistner K, Kichko TI, Teixeira NB, (2016).Crotalphine desensitizes TRPA1 ion channels to alleviate inflammatory hyperalgesia. Pain, 157: 2504-2516.
9. Ferraz CR, Arrahman A, Xie C, Casewell NR, Lwis RJ, Kool J, and Cardoso FC, (2019). Multifunctional toxins in snake venoms and therapeutic implications: from pain to hemorrhage and necrosis. Front EcolEvol., https: //www.doi.org/10.3389/frevo.201900218.
10. Bush SP, Hegewald KG, Green SM, Cardwell MD, Hayes WK, (2000). Effects of a negative pressure venom extraction device (extractor) on local tissue injury after artificial rattlesnake envenomation in a porcine model. Wilderness Environ Med, 11: 180-188.
11. Cleveland clinic (2019). Snakebites. Available online: https://www.snakebites/clevelandclinic.org.
12. Cushman DW and Ondetti MA, (1999). Design of angiotensin converting enzyme inhibitors. Nat Med, 5: 1118-1113.
13. Debono J, Xie B, Violette A, Foimmy R, Jaeger M, and Fry BG, (2017). Viper venom Botox: the molecular origin and evolution of the waglerin peptides used in anti-wrinkle skin cream. J MolEvol, 84: 8-11.
14. Diochot S, Baron A, Salinas M, Douguet D, Scarzello S, Dabert-Gay AS, (2012). Black mamba venom peptides target acid-sensing ion channels to abolish pain. Nature, 490: 552-555.
15. Eske J, (2018). How to identify and treat snakebites. Available online: https://www.medicalnewstoday.com.
16. Gellert GA, (1992). A snake-venom and insect-venom extractors: an unproved therapy (letter). N Engl J Med, 327: 1322.
17. Ghosh R, Mana K, Gantait K, Sarkhel S, (2018). A retrospective study of clinic-epidemiological profile of snakebite related deaths at a tertiary care hospital in Midnapore, west Bengal, India. Toxicol Rep., 5: 1-5.
18. Gullard A, (2017). Sixty seconds on …….snakebite. BMJ 357: j3065.
19. Gutierrez JM, Leon G, Lomonte B, (2003). Pharmacokinetics of the Sri Lankan humpposed pit viper (*Hypnalehypnale*) venom following intravenous and intramuscular injections of the venom into rabbits. Toxicon, 79: 37-44.
20. Habib A, (2013). Public health aspects of snakebite care in West Africa: perspective from Nigeria. J Venomous Animals & Toxins Trop Dis., 19: 27.
21. Habib AG, (2012). Antivenom therapy following snakebite effectiveness and strategies for delivery in West Africa. Honolulu, Hawaii, USA 17th World Congress of International Society of Toxinology Animal and 4th venom week (USA).
22. Habib AG, Gebi UI, Onyemelukwe GC, (2001). Snakebite in Nigeria. Afr J Med Sci., 30: 171-8.
23. Harrison AR, (2019). Ptosis: rules of the road. Available online: https://www.healio.com.
24. JRex C, (2017). Snake venom composition and variability. Available online: https://www.owlcation.com
25. Kanan NC, Ray J, Stewart M, Russell KW, Fuller M, Bush SP, Caravati EM, Cardwell J, Norris RL, Weinstein SA, (2015). Wilderness Medical Society practice guidelines for the treatment of pit viper envenomation in the United States and Canada. Wilderness Environ Med, 26: 427-487.
26. Kularatne AM, Silva A, Maduwage K, (2014). Victims' response to snakebite and socioepidemiological factors of 1018 snakebites in a tertiary care hospital in Sri Lanka. Wilderness Environ Med, 25: 35-40.
27. Lauer MA, Houghtaling PI, Peterson JG, Granger CB, Bhatt DL, Sapp SK, (2001). Attenuation of rebound ischemia after discontinuation of heparin therapy by glycoprotein IIb/IIIa inhibition with eptifibatide in patients with acute coronary syndromes: observations from the platelet IIb/IIIa in unstable angina: receptor suppression using integrilin therapy (PURSUTT) trial. Circulation, 104: 2772-2777.
28. Mercandetti M, (2018). Chronic progressive external ophthalmoplegia (CPEO) clinical presentation. Available online: https://www.emedicine.medscape.com
29. Meyer WP, HabibAG, Onayade AA, Yakubu A, Smith DC, Nasidi A, (1997). First clinical experience with a new ovine Fab *Echisocellatus* snakebite antivenom in Nigeria: randomized comparative trial with Institute Pasteur Serum (Ipser) Africa antivenom. J Trop Med Hyg, 56(3): 292-300.
30. Michael GC, Thacher TD, Shehu MI, (2011). The effect of pre-hospital care for venomous snakebite on outcome in Nigeria. Trans R Soc Trop Med Hyg, 105: 95-101.
31. Ministry of Health, Malaysia (MOHM) (2019). Guideline: management of snakebites. Available online:https://www.moh.gov.my.
32. Ndu IK, Edelu BO, Ekwochi U, (2018). Snakebites in a Nigerian children population: a 5-year review. Sahel Med J., 21: 204-7.
33. Ochola FO, Okumu MO, Muchemi GM, Mbaria JM, Gikunju JK (2018): Epidemiology of snake bites in selected ares of Kenya: Pan African Medical Journal, 20; 29: 217.
34. Parker-Cote J, Meggs WJ, (2018). First and pre-hospital management of venomous snakebites. Trop Med Infect Dis., 3: 45. https://www.mdpi.com/journal/tropicalmed.
35. Pugh RN, Theakson RD, (1967). Fatality following use of a tourniquet after viper bite envenoming. Ann Trop Med Parasitol, 81: 77-78.
36. Pugh RN, Theakston RD, (1980). Incidence and Mortality of snakebite in savanna Nigeria. Lancet, 2(8205): 1181-1183.

37. Qatar Ministry of Public Health (MoPH) (2018). Snakebite clinical management guideline ─ first edition. Available online: https://www.moph.gov.qa
38. Sharma SK, Khamal B, Pokhrel P, Khan A, Koirala S, (2003). Snakebite ─ reappraisal of the situation in Eastern Nepal. Toxicon, 41: 285-9.
39. Stock RP, Massoughodji A, Alagon A, Chippaux JP, (2007). Bringing antivenom to sub-Saharan Africa. Nat Biotechnol, 25(2): 173-177.
40. Tan KY, Tan CH, Fing SY, Tan NH, (2016). Neutralization of the principal toxins from the venoms of Thai *NajaKaouthia* and Malaysian *Hydrophisschistosus*: insights into toxin-specific neutralization by two different antivenoms. Toxins (Basel), 8(4): 86.
41. Tan KY, Tan CH, Fung SY, Tan NH, (2015). Venomics, lethality and neutralization of *Najakaouthia* (monoclad cobra) venoms from three different geographical regions of Southeast Asia. J Proteomics, 120: 105-125.
42. Theakston RD, Warrell DA, (2000). Crisis in snake antivenom supply for Africa. Lancet, 356(9247): 2104.
43. Utikin YN, (2019). Last decade update for three-finger toxins: newly emerging structures and biological activities. World J BiolChem, 10: 17-27.
44. Vaiyapuri S, Vaiyapuri R, Ashokan R, (2013). Snakebite and its socioeconomic impact on the rural population of Tamil Nadu, India. PLoS One, 3; 8: eB0090.
45. Warrell DA, (2008). Unscrupulous marketing of snakebite antivenoms in Africa and Papua New Guinea: choosing the right product. What's in a name? Trans R Soc Trop Med Hyg, 102(5): 397-399.
46. Warrell DA, (2018). Guidelines for the management of snakebites in South-East Asia. Available online: https://www.apps.searo.who.int/PDS DOCS/B4508pdf.
47. Watt G, Padre L, Tuazon ML, Theakston RD, Laughlin LW, (1988). Tourniquet application after cobra bite. Delay in the onset of neurotoxicity and the dangers of sudden release. Am J Trop Med Hyg, 38: 618-622.
48. Wong KY, Tan CH, Tan NH, (2016). Venom and purified toxins of the spectacled cobra (*Najanaja*) from Parkistan: insights into toxicity and antivenom neutralization. Am J Trop Med Hyg, 94(6): 1392-9.
49. World Health Organization (WHO) (2010). WHO guidelines for the production, control and regulation of snake antivenom immunoglobulin. World Health Organization, Geneva.
50. World Health Organization (WHO) (2018). Guidelines for the prevention and clinical management of snakebites in Africa. Available online: https://www.who.int/ipcs.
51. World Health Organization (WHO) (2019). Prevalence of snakebite envenoming. Available online: https://www.who.ofg
52. World Health Organization (WHO) (2019). Snakebite envenoming. Available online: https://www.who.int/snakebites/resources/photo_gallery_snakes/en.
53. Yap MK, Tan NH, Sim SM, Fung SY, Tan CH, (2014). Pharmacokinetics of *Najasumatrana* (equiatorial spitting cobra) venom and its major toxins in experimentally envenomed rabbits. PLoSNegl Trop Dis, 8e2890.