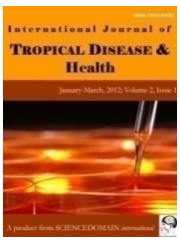

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Blister and Bulla Following Snake Bite in Nigeria: A Prospective Cohort Study

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Authors' contributions

This work was carried out in collaboration between all authors. Authors GI and AGH conceived, designed the study and wrote the protocol. Authors GI, STH, ZGH, ABT and FMD performed the statistical analysis. Author GI wrote the first draft of the manuscript. All the authors' managed the literature searches, read and approved the final manuscript.

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ABSTRACT

Introduction: Snakebites are a major health problem in several rural areas of tropical countries worldwide. Timely administration of appropriate antivenoms (AV) has been shown to significantly improve outcome. It has been hypothesized that presence of blisters may lead to poor outcome because of potential sequestration of snake venom with gradual systemic absorption. We explore the impact of blisters on outcome of snake bite envenomation.
Methods: The study was a prospective cohort, enrolling all snake bite victim reporting to hospital in Febuary-April 2013. Data on demography, type of snake, circumstances of bite, presence or absent of blisters, systemic bleeding, 20min Whole Blood Clotting Time (WBCT), amount of anti-venom needed to restore clotting, and outcomes were recorded. Analyses explored relationship between blister and poor outcome (PO) defined as deaths, gangrene, prolonged Length of Hospital Stay (LOS), amputation, altered consciousness or requiring more than 10mls or 30mls of Echitab or Echitab plus respectively to restore clotting.

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Results: A total of 128 cases were studied, 101 were males. The mean age of the victims was 25.19 years ±17.51. Carpet viper was the most common responsible snake 89/106(84.0%). Local 84/128(65.6%), systemic bleeding 33/128(25.8%) and non-clotting 20WBCT 100/128(78.1%) were common while amputations 3/128(2.3%), gangrene 5/128(3.9%), altered consciousness 2/128(1.6%) and deaths 4/128(3.1%) were fewer. Blister was present in 42/128(32.8%) which had no relationship with gender (*P*=.39). Patients with blisters compared to those without blisters had more gangrene 4/42(9.5%) vs 1/86(1.2%) (*P*=.04), non-clotting 20WBCT 40/42(95.2%) vs 60/86(69.8%) (*P*<.001) and required more amount of antivenom to restore clotting >10mls (Echitab) or 30mls (Echitab plus) in 8/32(25%) vs 3/57(5.3%) (*P*=.03). Using Wilcoxon Rank-Sum test patients with blisters had a median LOS of 6.0±2.3 days compared to those without blisters 5.0±3.5 days (*P*=.02). In a logistic regression adjusting for LOS and systemic bleeding, blister predicted PO with *P*=.043 (95%CI: 0.110- 0.963).
Conclusion: Presence of blister predicts PO (LOS, gangrene and large amount of antivenom needed to restore clotting). Deblistering of blister in snake bite patients may improve outcome. A randomised control trial is recommended to look at the effect of deblistering on outcome among patients with snake bite envenomation.

Keywords: Snake bite; blister; deblistering; anti-venom; outcome.

1. INTRODUCTION

Snakebite envenoming is a serious global public health concern, with tens of thousands of deaths annually. It is one of the most neglected environmental and occupational diseases of the modern world, mainly affecting rural communities of the tropics and sub-tropics [1]. The savannah region of West Africa, notably Benin, Burkina-Faso, Cameroon, Ghana, Nigeria and Togo bears the greatest burden of snakebite, with an estimated incidence of 500 bites and 50 deaths/100,000 population reported in rural Nigeria alone [2]. Bites by saw-scaled or carpet vipers (*Echis ocellatus*) are frequent in the savannah region of West Africa, where agricultural workers, herders and their children are at greatest risk [3-6]. The venom from this family are a complex mixture of bioactive substances and envenomation produces local pains, swelling, blisters and incoagulable blood with systemic coagulopathy [7,8]. Many snake bite victims survive with physical and psychological sequelae, like amputations, chronic ulceration, osteomyelitis, or limb deformities, largely due to venom effects or inappropriate first aid [9]. Blister fluid (BF) contain venom antigens, toxic components and other inflammatory molecules. Such components (e.g., metalloproteinases) in carpet viper venom are known to cause severe local damage [10]. Indeed carpet viper bite has been confirmed using immunologic tests on BF from the presence of venom antigen in it [11]. Timely administration of appropriate antivenoms (AV) neutralizes venom antigen in blood with subsequent improvement in clinical outcome [12-16]. It is assumed antivenom neutralises venom antigen in BF but its diffusion, bioavailability, entry and effectiveness in resolving blisters remain unknown. When effective antivenom is lacking or its administration delayed continuing envenoming from local and systemic absorption of venom progresses. We therefore explored the effect of blister or bulla on outcome following snake bite envenoming in a facility with access to effective AV in northern Nigeria.

2. METHODOLOGY

This study was conducted at the Kaltingo General Hospital (KGH), a rural hospital in savannah north eastern Nigeria, between February to April 2013. As a site of antivenom research, the facility receives patients from neighbouring communities within and outside the state. Most bites at the centre are usually due to the carpet viper. Snakes were identified by comparison with the centre's specimen collection if the dead snake was brought to hospital, by the report of the patients, witnesses or by incoagulable blood in the 20 minute Whole Blood Clotting Test (20WBCT). The 20WBCT is diagnostic of carpet viper envenoming in northern Nigeria [17].

Voluntary written informed consent was obtained from each subject. The study conformed to the ethical guidelines of the 1975 Declaration of Helsinki. Approval for the study was obtained from the management of KGH, Gombe state, Nigeria.

All patients presenting to KGH, Gombe State, Nigeria with a history of snake bite were assessed. Presence of one or more of the following features was assessed: fang marks, local pain and swelling, WBCT≥20 minutes (20WBCT) or spontaneous bleeding.

A standard questionnaire was administered in English or one of the local languages (Hausa or Fulani). Data on demography, type of snake, circumstances of bite, site of bite and first aid used prior to presentation were recorded. Vital signs were recorded and presence of fang marks, local swelling, presence of blister or bulla and spontaneous bleeding were also recorded. The extent of blister/bulla were defined as mild, moderate or severe. Swelling severity was defined as mild (less than half of the bitten limb), moderate (about half of the bitten limb) and severe (the whole bitten limb).

The 20-minutes Whole Blood Clotting test (20WBCT) was performed on all subjects by allowing 2mL of blood obtained by venepuncture to stand in a clean, dry glass tube at room temperature for 20 minutes. Venom induced coagulopathy was considered present if blood remained unclotted after 20 minutes [18,19]. 20WBCT was repeated 6-hourly for 12 hours then daily until discharge. Effective antivenom was given intravenously to subjects with evidence of systemic envenomation either as 10mL of mono-specific Echitab IgG (against carpet viper) or 30mls of tri-specific Echi Tab Plus IgG (against carpet viper, cobra and puff adder). In those with incoagulable blood, antivenom dose is repeated 6-hourly until clotting was restored as measured by the 20WBCT. These antivenoms were given free of charge to subjects through a government funded national program. They were previously proven to be effective and safe [15]. The total amount in millimeters of antivenom required to restore clotting was recorded. Vital signs were monitored every 15 minutes for the first hour after administration of antivenom, and then 4-hourly. Subjects who developed early anaphylactic or late reactions following antivenom administration were managed using epinephrine, intravenous fluids, hydrocortisone and promethazine. Intramuscular tetanus toxoid 0.5mL was given to subjects who were unimmunized or unsure of their immunization status, when their blood clotting is restored to avoid haematoma formation. The bite site was assessed daily for evidence of blister or bullae. Those with evidence of infection at the bite site were treated with a broad spectrum antibiotic (ampicillin-cloxacillin). Debridement of necrotic tissue or amputation was carried out when indicated after restoration of clotting, and open wounds were dressed using hydrogen peroxide and Edinburgh University Solution (eusol).

Poor-outcome (PO) was defined as deaths, gangrene, prolonged length of hospital stay (hospitalization for more than 7days), loss of consciousness or requiring more than >10mls (Echitab) or 30mls (Echitab plus) of antivenom to restore clotting.

The outcome measure was PO as defined. All data collected were entered and analysed using SPSS version 16. Analysis was carried out using descriptive statistics with differences and relationships determined using student t- test, Chi squared and Fisher's exact tests as appropriate, with $p<0.05$ regarded as significant. Wilcoxon Rank-Sum test was used to compare median length of hospital stay. Determinants and predictors were explored using univariate analysis and logistic regression and output reported as unadjusted (crude) odds ratio (OR) and adjusted OR, respectively.

3. RESULTS

During the study period 128 Snakebite patients were enrolled and analysed (Table 1). Out of which 101(78.9%) were males and 27(21.1%) were females. The mean age of the victims was 25.19 years±17.51. The number of snakebite cases was highest in 21-30 years age group 39/128(30.5%) followed by 11-20 years 29/128(22.7%) and 1-10 years 28/128(21.9%). Few cases were among adults' ≥60 years of age 4/128(3.1%), while the number of cases among 31-40, 41-50 and 51-60years age group were 13, 8 and 7 respectively. Most of the victims brought the dead snake to the hospital 93/128(72.7%), 13/128(10.1%) described the type of the snake while 22/128(17.2%) reported it as unknown. Out of the 106 identified snake, 89/106(84.0%), 10/106(9.4%) and 7/106 were reported as carpet viper, cobra and night adder respectively. Majority of the victims got bitten while farming 53/128(41.4%), and a sizeable number while herding 15/128(11.7%) with the lower limb being the most common site of bite 87/128(68%). Eighty seven (68%) of the victims had pain at the bite site, 126/128(98.4%) had swelling while 42/128(32.8%) had blister which had no relationship with age groups (*P*=.96). There was also no relationship between blister and gender (*P*=.39). Local bleeding and systemic bleeding were seen in 84/128(65.6%) and 33/128(25.8%) of the victims. Non-clotting 20WBCT was seen in 100/128(78.1%) of the victims. The overall median time elapsed between bite and hospital admission was 16.0hours (Range 1-237hours), while it was 16.5hours (Range 1-168) and 15.8hours (Range 1-237) in those with blisters and those without blisters respectively. Out of the 128 victims, 5/128(3.9%) developed gangrene, 3/128(2.3%) had amputation while loss of consciousness was seen in 2/128(1.6%). Death was recorded in 4/128(3.1%) of the victims, out of which 2/10(20.0%) were bitten by cobra and 2/89(2.2%) were bitten by carpet viper, with no mortality recorded among those bitten by night adder. Forty two (32.8%) patients had PO as defined. Patients with blisters compared to those without blisters had more gangrene 4/42(9.5%) vs 1/86(1.2%) (*P*=.04), non-clotting 20WBCT 40/42(95.2%) vs 60/86(69.8%) (*P*<.001) and required more amount of AV to restore clotting (>10mls {Echitab} or 30mls {Echitab plus}) in 8/32(25%) *vs* 3/57 (5.3%) (*P*=.03). Using Wilcoxon Rank-Sum test patients with blisters had a median LOS of 6.0±2.3 days compared to those without blisters 5.0±3.5 days (*P*=.02). No difference in overall mortality between the two groups (*P*=1.00). In a logistic regression adjusting for LOS and systemic bleeding, blister predicted PO with Odds Ratio=0.326 (95%CI: 0.110-0.963; *P*= .04).

4. DISCUSSION

This prospective study found presence of local blister at snakebite site is associated with poor prognosis. Envenomed patients with blisters had proportionately more gangrene,

incoagulable blood, prolonged hospital stay and required more doses of antivenoms for therapy. The patients observed were mostly males, aged 21-30 years, bitten while farming or herding and mostly on the lower limb (87%) while barefoot (Fig. 1).

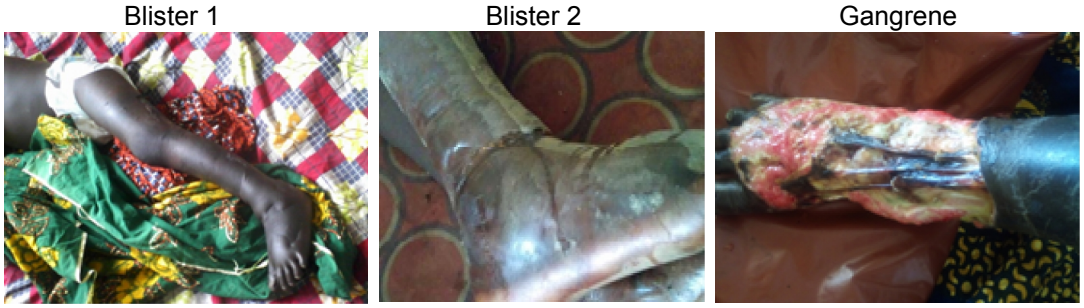

Fig. 1. Blister/bulla and gangrene following carpet viper bite

Clinical presentation following snake bite principally depends on the amount of injected venom into subcutaneous tissue or systemic circulation [15]. Although local manifestations such as swelling, local bleeding and pain are observed in majority of cases, systemic manifestations which are more serious, usually develop in smaller proportion of patients [20,21]. In this study with carpet viper bite predominance, we found that local swelling (98%), pain(68%) and local bleeding (65.6%) were the most common manifestations and these were similar to the findings in other studies [22,23]. Spontaneous systemic bleeding was relatively common seen in 25.8% of the victim, however other severe systemic manifestation such as hypotension and neurologic abnormalities were rare, similar to findings by Frangides et al. [22] and Karaye et al. [24].

Table 1. Demographic and clinical characteristic n=128

Characteristic	n=128
Mean age, years (±SD)	25.19(±17.51)
Sex	
-Male (%)	101(78.9%)
-Female (%)	27(21.1%)
Type of snake	
-Carpet viper (%)	89(84.0%)
-Cobra (%)	10(9.4%)
-Night adder (%)	7(6.6%)
Clinical features	
-Fang marks (%)	128(100%)
-Pain (%)	87(68%)
-Swelling (%)	126(98.4%)
-Local bleeding (%)	84(65.6%)
-Systemic bleeding (%)	33(25.8%)
-Blister (%)	42(32.8%)
-Hypotension (%)	2(1.6%)
-Non clotting 20 WBCT (%)	100(78.1%)
-Gangrene (%)	5(3.9%)
-Amputation (%)	3(2.3%)
-Loss of consciousness (%)	2(1.6%)
-Death (%)	4(3.1%)

Blistering of skin has been observed in human envenoming by Viperidae and Elapids, and proteomics of the blister exudate has been described which includes many proteins linked to the envenoming species of snake [25]. It is suggested that viper venoms with relatively heavier molecular weight toxins and slower distribution in to tissues and systemic circulation are more associated with local features [10]. We found presence of blister/bulla in 32.8% of the victims predominantly bitten by carpet viper (Fig. 1). Dadpour et al. [23] also reported a figure of 48%. Treatment of snakebite envenomation is mainly based on antivenom administration aimed at reversal of venom-induced effects [5,13,15]. The presence of snake venom component sequestered within blisters and bullae may negate the effect of antivenom through gradual release of venom in to the systemic circulation. In a retrospective study, Dadpour et al. [23] did not find significant association (*P*=0.13) between presence of blister/bulla and weak therapeutic response defined as increased in amount of anti-venom needed to restore clotting, even though they found a strong association with the presence of swelling (OR 12.4, *P*=0.003). However, we found that presence of blister significantly predicts poor outcome even after adjusting for the effect of severe envenoming presenting with systemic coagulopathy (Table 2).

Table 2. Relationship between presence of blister/bulla and outcome

Factors	Blister/bulla present	Blister/bulla absent	OR (95% CI)	*P* value
Gangrene	4/42	1/86	8.95(1.00-82.75)	0.04*
Amputation	2/42	1/86	4.25(0.21-253.61)	0.25*
Non-clotting 20WBCT	40/42	60/86	8.67(2.00-78.45)	<0.001*
>10mls of AV used	8/32	3/57	6.00(1.27-37.33)	0.01*
LOS	6±2.3	5±3.5		0.02#
Died	1/42	3/86	0.67(0.01-8.73)	1.00*

**Fisher's Exact; # Wilcoxon Rank-Sum test*

Our findings of local damage and blister may not be common following bites by elapid snakes with small molecular weight toxins. But viper bite envenoming is common throughout the tropics in Africa, Asia, and North and South America and our findings have huge implications for the clinical management of envenoming by these snakes. There is no randomised control trial that studied the effect of deblistering or deroofing. The effect of deblistering and deroofing in managing burns, injuries and other conditions has been controversial with reports suggesting either benefit or harm [26-30]. A study exploring the management of blister following burns showed in a non-randomised, non-blinded controlled clinical trial that Infection rate was significantly lower if blisters are left intact, compared with deblistering or de-roofing ($p<0.05$) although deblistering significantly reduced pain compared with de-roofing [31]. By contrast, in poisoning related blisters there is presence of an exogenous toxin in the BF and deroofing can reduce pain and improve outcome through toxin removal. Indeed, immediate blister excision has been used and advocated in Lion fish envenomation to prevent dermal necrosis from continuing venom release. However, deroofing may cause wound infection, complicate healing and worsen bleeding in those with incoagulable blood. Thus, deroofing should only be considered when clotting has been restored following adequate antivenom administration and when safe and aseptic techniques are obtainable.

5. CONCLUSION AND FUTURE RECOMMENDATIONS

Blister following snakebite is associated with poor prognosis. Best modalities for care are not known. In the future optimum approaches and the role of deblistering/deroofing in clinical management should be determined. An open Randomized Controlled Trial of deroofing should be considered with necessary safety measures put in place.

CONSENT

All authors' declared that voluntary written informed consent was obtained from each subject.

ETHICAL APPROVAL

All authors' declared that the study conformed to the ethical guidelines of the 1975 Declaration of Helsinki. Approval for the study was obtained from the management of KGH, Gombe state, Nigeria.

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COMPETING INTERESTS

Authors have declared that no competing interests exist.

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