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Coagulation Profile of Children with Snake Envenomation in Yola, Nigeria

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Authors' contributions

This work was carried out in collaboration between all authors. Authors EAE and SFA designed the study, performed the statistical analysis, wrote the protocol and wrote the first draft of the manuscript. Authors HLB and ECF managed the analyses of the study. Author AOC managed the literature searches. All authors read and approved the final manuscript.

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ABSTRACT

Background/Objective: Coagulation profile includes Prothrombin Time (PT), Activated Partial Thromboplastin Time (APTT), and Platelet count. It is a common hematological test use to determine the degree of coagulopathy cause by snake venom. Snake bite envenomation is a common rural accident**.** This study aims to evaluate coagulation profile of children with snake bite injuries in Yola, Nigeria.
Materials and Methods: 137 subjects comprising of 69 children with snake bite (21 females and 48 males with mean age of 10.46 ± 5.64 years) and 68 clinically healthy subjects (with mean age of $11.23 \pm 6.14\ years$ comprising of 29 female and 39 males) participated in this present study. Platelet count was estimated using sysmex XP 300 hematology analyzer. PT and APTT values were determined in the blood using one-stage prothrombin test method and Modified Kaolin Method respectively.
Results: The mean value of APTT test in patients was 47.0 ± 0.31 seconds while that of the control group was 39.47 ± 5.3 seconds, $P < 0.05$. The mean value of the PT test and the International

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Normalized Ratio (INR) in patients were 29.90 ± 0.12 seconds and 6.30 ± 2.92 respectively $P < 0.05$. The correlation of PT versus APTT value was significant with the correlation coefficient (r) of 0.86 at $P < 0.05$.

Conclusion: Snake bite occurred more in male children than females. Children with snake envenomation had prolonged PT and APTT time as well as thrombocytopenia. It is believed that information provided in this study will assist to improve clinical management of this group of patients in Yola, Nigeria.

Keywords: Snake envenomation; coagulation profile; children.

1. INTRODUCTION

Coagulation profile includes: INR (International Normalized Ratio), APTT (Activated Partial Thromboplastin Time), PT (Prothrombin Time), and platelets count [1]. It is a common hematological test. Platelet count estimation is an important and routinely laboratory investigation parameter for the evaluation of coagulation and bleeding disorder [2]. APTT, PT and INR are coagulation profile tests usually performed to determine if a person have enough coagulation activity for efficient blood clotting process. [3] therefore they are used to test the integrity of the hemostasis system of the human body [4]. In patients with snake bite, coagulation profile test is used to determine the degree of coagulopathy cause by snake venom as well as monitor the effectiveness of anti-snake venom.[5] Activated partial thromboplastin time (APTT) is usually used in conjunction with the prothrombin time (PT) test. APTT measures the speed of blood clotting by means of intrinsic pathway, while PT measures the speed of blood clotting by means of extrinsic pathway [6].

Snakebite envenomation is a preventable environmental health hazard usually faced by people in rural areas [7,8]. It has been reported that 1,841,000 venomous snake bites and 94,000 snake-related deaths occur annually, with incidence occurring more in rural areas of Sub-Saharan Africa [9]. An earlier study on snake bites in Savannah region of Northern Nigeria reported annual incidence of 497/100,000 and a mortality of 12.2% [10]. Snakebite causes medical problem due to snake envenomation. Snake venom can result in decrease circulating platelets [11], disseminated intravascular coagulation, edema, localized pains [12] hemolysis, tissue damage [13], vascular endothelium damage [14] and the toxins in snake venom can also interact with clotting mechanism and fibrinolytic system resulting in bleeding disorders [15], cardiotoxicity, neurotoxicity [12], blood vessel damage, unwanted coagulation [16], increased platelet consumption [17], thrombocytopenia [18], independent platelet ATP release [19] and makes fibrin polymer vulnerable to fibrinolysis and phagocytosis by removing fibrinopeptide A [20]. Some snake venoms also contain serine proteases, metalloproteinases, C-type lectins, disintegrins, and phospholipases that disturb haemostasis by activating or inhibiting coagulant factors or platelets [21]. Ultimately, the clinical manifestations of snake bite on the patient depends on the biochemical characteristics of the injected venom [22].

Children in rural areas of Yola, Nigeria are at snake risk of snake envenomation because they live in environment that provide suitable habitat for snakes as well as their tendency to walk without protective foot wears while playing in bushy areas or assisting in farm work [23]. Children are more likely to develop signs of envenomation than adult due to their relatively small body mass [24]. Medical literature report have shown an increased mortality among children with snake envenomation compared to adults [25]. Hence, snake bite in children is a particularly serious medical emergency and coagulation profile of children with snake bite in northeastern Nigeria is not yet fully study hence, this study aims to evaluate coagulation profile of children with snake bite in order to elucidate the pathophysiology of hemostatic changes in this group of patients. It is believed that information provided in this study will assist in effective clinical management of children with snake bite injuries in Yola.

2. MATERIALS AND METHODS

This study was carried out at Federal Medical Center of Yola, in Adamawa State, Northeast Nigeria. A total of 137 subjects comprising of 69 children with snake bite injuries (21 females and 48 males with mean age of 10.46 ± 5.64 years) and 68 clinically healthy subjects (with a mean age of $11.23 \pm 6.14\ years$ comprising of 29 female and 39 males) participated in this study.

Platelet count was estimated using sysmex XP 300 hematology analyzer. PT and APTT values were determined using the one-stage prothrombin test method and the Modified Kaolin Method respectively [26]. The reagent for APTT test was a commercial rabbit brain extract phospholipid containing an activator (ellagic acid) in buffered medium. The reagent for PT was commercial freeze-dried calcium thromboplastin obtain from a rabbit brain extract. The ISI (international sensitivity index) and PT value was used to calculate the International Normalized Ratio (INR). All analyses were performed according to the standard operational procedures.

2.1 Inclusion Criteria

Children less than 17 years of age with snake bite injuries who arrived the hospital within 24 hours of accident were included in this study.

2.2 Exclusion Criteria

Patients above 18 years of age and Children with snake bite who have gotten folkloric treatment before coming to the hospital were also excluded

2.3 Sample Collection

3.0 mls of blood was aseptically collected through antecubital vein of children with snakebite prior to administration of anti-snake venom within 30 minutes of arrival in the hospital. The blood was put in two separate vacutainer bottles, one containing 200 µl of 3.2% buffered sodium citrate; the other containing EDTA. The bottles were further labeled with patient number, sex and age. The EDTA blood was used for platelet count determination, while the citrate blood was used for PT and APTT values determination within one hour of collection. INR was calculated using the Prothrombin Time values and the international sensitivity index (ISI) [27,26] The ISI was given by the manufacturer of the tissue factor to be 1.5.

2.4 Sample Analyses

2.4.1 Platelet count

Using the Sysmex XP 300 machine, the procedure for platelet count determination was as follows: EDTA samples were placed in a hematology blood mixer for five minutes and the blood cells were automatically counted through a probe fitted in the Sysmex XP 300 machine. After two minutes, the results of platelet count were displayed on the color LCD screen of the machine.

2.4.2 Activated Partial Thromboplastin Time (APTT) test

Using the Modified Kaolin Method, the procedure of test was as follows:

1. All reagents were brought to required working temperature according to the manufacturer's instruction.
2. Test tubes were labeled with the sample number and pre-incubated in a water bath set at the temperature of 37°C for 15 minutes.
3. 50 µl of plasma was added to all the tubes in the water bath.
4. 50 µl of APTT reagent was further added to all the tubes in the water bath
5. The tubes containing the plasma and liquid APTT reagent were incubated in the water bath for further 3minutes.
6. 50 µl of 0.025 M liquid Calcium Chloride was added to each tube and a stop-watch was started simultaneously.
7. The time it takes for the clot to form in the tubes was recorded in seconds

2.4.3 Prothrombin time test

Using the one stage prothrombin test method, the procedure for the test was as follow:

1. 2.5 mls of distilled water was added to 2mls of freeze-dried calcium thromboplastin to obtain a rehydrated solution.
2. The rehydrated solution was allowed to stand at room temperature for 30 minutes.
3. The rehydrated solution was further incubated at 37°C for 15 minutes in a water bath.
4. 100 µl of plasma was dispensed into test tubes and incubated at 37°C for 5 minutes.
5. 200 µl of the rehydrated solution was added to the tubes containing the plasma and a stopped watch was started simultaneously.
6. The time it takes for clot to form in the tubes was recorded in seconds.

2.4.4 International normalized ratio (INR)

The INR was calculated as the PT ratio raised to the power of the ISI used ($INR = R^{ISI}$).

Table 1. Demography of the studied population

Signs of snake envenomation	Number observed	Prevalence (%)	Distance covered on arrival	
Nausea and fever	16	23.5	<50 km	07%
Vomiting	10	14.7	51 – 100km	09%
Breathlessness	02	2.9	101 - 150km	16%
Decrease urine Output	02	2.9	151 - 200 km	10%
Hematuria	01	1.5	201 - 250km	08%
Swelling and Inflammation of bite area	11	16.2	251 - 300km	06%
Fang Mark	03	4.4	301 - 350km	13%
Bleeding from bite site	12	17.6	351 - 400km	11%
Respiratory Distress	04	5.9	401 - 450km	08%
Ptosis	02	2.9	451 - 500km	09%
Drowsiness	04	5.9	>500km	03%
Bleeding from gum	01	1.6		

The Prothrombin time (PT) ratio (R) was calculated by dividing the PT values of the subject by the PT value of the control [27]. The manufacturer of the reagent provided the PT value of the Control, which is 13.5 seconds.

Table 2. Prevalence position and time of snake bite

Position of snake bite	Time of bite
Lower extremity - 47 (69.1%)	Day - 38%
Upper extremity - 19 (27.9%)	Night - 62%
Other body parts – 02 (03%)	

2.5 Statistical Analyses

Statistical analysis was performed using the SPSS computer software version 20.0. Descriptive values were given as mean and standard error of mean. Categorical variables were expressed as the number of cases and the percentage value. The Student's *t*-test was used to compare the means differences of the estimated parameters while the Pearson's correlation coefficient was used to calculate the relationship between PT and APTT values in this group of patients.

3. RESULTS

All victims showed sign of envenomation as shown in table 1. 23.5% of victims had Nausea and fever after snakebite. While 14.7% and 17.6% of victim were vomiting and bleeding from site respectively. Breathlessness and decrease urine output was observed in 2.9% of the victims. 1.5% of the subject had hematuria and evidence of fang mark on bite site was seen in 4.4% of the affected children. Four of the victim (5.9%) exhibited sign of respiratory distress while 2.9% and 5.9% of victims had ptosis and drowsiness respectively. Bleeding from the gum was seen in 1.6% of the studied group.

The distance cover by victim from point of bite to the hospital ranges from 50 to 500 km. the highest incidence was found at a distance between 101 to 150 km while the second highest incidence was seen in the distance of 301 to 400 km (Table 1). 47 (69.1%) of the victims had snakebite at the lower extremities while 19 (27.9%) had snakebite at the upper extremity and bites at other parts of the body accounted for 3% of all cases as shown in Table 2. However, 62% of the cases occurred in the night while 38% of the cases was said to happen at day time.

Table 3 shows coagulation profile of children with snakebite injuries. Children with snakebite accidents had a mean platelet value of 147 ± 0.27x 10^9/l while that of the control group was 357 ± 9.14 x 10^9/l. the prothrombin time (PT) value of the affected children was 29.90 ± 0.12 seconds and the PT of the control group was 18.13 ± 2.06. The mean APTT value of snakebite victims was 47.0 0 ± 0.31 seconds and the INR and PT ratio of the patients was 6.3 ± 2.92 and 2.2 ± 0.23 respectively at $p < 0.05$.

The mean level of PT and APTT test value was higher than the normal reference range in patients with snakebite injuries compare with that of the control group as shown in Table 3 $P < 0.05$ Table 1. The correlation of PT versus APTT and PT versus INR values were both significant at $P<0.05$ Table 4. The correlation of PT and INR with coefficient (r) of 1.0 was stronger than the correlation of PT and APTT with correlation coefficient of 0.86 at $P<0.05$. The mean difference of APTT was 12.465 sec while the

Table 3. Mean values of platelet count, APTT, PT and INR of children with snakebite

Parameters	Patient (N = 34)	Control (N = 35)	Normal range	P value
Gender (male/female)	23/11	19/16		
Age (years)	10.46 ± 5.64	11.23±6.14		0.001
Platelet Count (x 10^9/l)	147 ±0.27	357 ±9.14	150- 400	0.05
PT (seconds)	29.90±0.12	18.13 ± 2.06	16 – 23	0.05
APTT (seconds)	47.00 ± 0.31	39.47 ± 5.38	34.0–45.0	0.05
PT Ratio	2.2±0.23	1.82 ± 0.40		0.05
INR	6.3±2.92	4.17 ± 3.10	0.8-8.0	0.05

Table 4. Correlation of PT values with APTT and INR in children with snakebite

Parameters	Correlation coefficient (r)	P-Value
PT versus APTT	0.86	0.05
PT versus INR	1.0	0.05

Table 5. Comparative mean difference between APPT and PT

	Test value = 0					
	T	Df	Sig. (2-tailed)	Mean difference	95% confidence interval of the difference	
					Lower	Upper
APPT	12.465	68	.000	42.28930	23.7164	30.8622
PT	7.014	67	.000	33.26013	11.2397	13.2806

mean difference for PT was 07.014 sec (Table 5).

4. DISCUSSION

The effects of snake venom on coagulation process of children with snake bite injuries have been investigated. It is observed that victims shown differs signs of snake envenomation. Drowsiness seen in 5.9% of children with snake bite is suggestive of possibility of central sedative action cause by snake venom. Nausea and fever was the most frequent sign of snake envenomation this could implies that majority of the inoculated snake venom in this locality consist of potential systemic inflammatory enzymes [14] and toxin that can interact with protein and body cells of victims to produce inflammatory responses which also includs Ptosis, Swelling, and localized pains. Bleeding from gum and bite site is because the toxin in suspected snake venom interacts with clotting and fibrinolytic mechanism to produce abnormal bleeding in victims [15,21] and also abnormal Bleeding can be caused by combined effects of procoagulants contained in hemotoxic venom of some snake species [28]. Decrease urine output and hematuria seen in this study is a pointer to renal disorder cause by snake venom in children [12]. 2.9% of breathlessness and 5.9% of respiratory distress seen among children with snake bite is indication of snake venoms in this locality that can produce harmful effects on the respiratory system.

The epidemiology of snake bites among children in this study is similar to reports in previous medical literatures. [22,29] Snake bites tend to occur more at night than in the day as observed in this study due to low visibility and snakes tend to hide during the day to avoid human activity and usually ventures out to look for prey in the night [8]. Gender variability shows that male children had more snakebites than girls Table 3. The high preponderance of male children with snake bites may be attributed to the fact that boys are more likely to participate in occupational activities that predispose to snake bites such as farming, livestock rearing, hunting and collection of fire wood. More of the bite were at the lower extremity than in the upper extremity indicating that snakebite mostly occurred while the victims were walking or working at the locality this observation is consistent with other previous findings [30,31,8]. Most of the incidence was said to occur at a distance of 101 - 150km Table 1 which indicates that snakebites occurred most in rural areas of Yola far from the town. The distance cover by victim from point of bite to the hospital ranges from 50 to 500 km. the highest

incidence was found at a distance between 101 to 150 km while the second highest incidence was seen in the distance of 301 to 400 km (Table 1) this wide distance is due to large land mass area of Adamawa state and absence of functional community hospitals and so people in rural areas usually will need to travel for hours to see a relatively few health care facilities in the state.

Mild thrombocytopenia (mean platelet count of 147 x 10^9/l) observed in victims could be due to Envenomation of snakes that causes a decrease in circulating platelets [11]. Reduced platelet in the peripheral blood may also be due to toxin-induced damage to platelet precursors in the bone marrow or platelet aggregation and destruction initiated by the direct action of some snake venom (eg, crotalocytin) [19].

The mean Prothrombin Time and APTT test values in children with snakebite were prolonged when compare with that of the control group $p< 0.05$ as shown in Table 3. This implies that in patients with snakebite, there is abnormality in the hemostasis system. Prolonged PT and APTT is indications of presence of snakebite induce coagulopathy in victims. The extrinsic and intrinsic pathway of coagulation is impaired in children with venomous snakebite injuries as reflected by PT and APTT values [6]. The coagulopathy observed in this study is also due to blood incoagulability resulting from consumption/destruction of coagulation factors caused by snake venom anticoagulants. In addition, some snake venoms also contain several enzymes that disturb haemostasis by inhibiting coagulant factors [21].

A significant correlation between PT and APTT values with correlation coefficient of 0.86 at $P<0.05$ was observed indicating a linkage between PT and APTT and since APTT has been used as research tool for elucidating the interaction of coagulation factors [22], the result of the correlation of PT versus APTT therefore indicates inter-relationship between extrinsic and intrinsic pathway which could be hindered by snake venom in children with snakebite in Northeast Nigeria.

5. CONCLUSION

Snake bite mostly occurred in rural areas of Yola Adamawa state and male children had more snake bite than females. Snake bite injuries were seen more in the lower extremity than the upper extremity of victims and snake envenomation resulted in coagulopathy. The hemostatic changes cause by snake envenomation was reflected by prolong prothrombin time and activated Partial thromboplastin time as well as presence of thrombocytopenia in children with snake bite injuries. It is therefore recommended that, clinical efforts should also focus on improving the hemostatic processes of children with snake envenomation and it is believed that information provided in this study will assist in effective clinical management of this group of patients in Yola, Northeastern Nigeria.

CONSENT

All persons gave their informed consent through their parents/guidance prior to their inclusion in the study.

ETHICAL APPROVAL

The ethical clearance for this study was from the ethical and research committee of the federal medical center Yola, Nigeria.

FINANCIAL SPONSORSHIP

The study was sponsored by the authors, the used equipment was provided by the hospital in which this work was done.

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COMPETING INTERESTS

Authors have declared that no competing interests exist.

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