EFFECTS OF HEMOTOXIC SNAKE BITE ENVENOMATION ON HAEMATOLOGICAL PARAMETERS VARIABILITY IN PREDICTING COMPLICATIONS

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Background. *Snake bite envenomation is a major public health problem in India with a high mortality rate. The major complications following a hemotoxic snake bite are disseminated intravascular coagulation (DIC), shock, acute kidney injury (AKI), acute respiratory distress syndrome (ARDS) and coagulopathy. The study explores a possible correlation of the haematological parameters studied to complications like DIC, AKI, acute renal failure (ARF), ARDS, shock and gastrointestinal (GI) bleed.*

Objective. *The aim of the study was to find out the effect of snakebite envenomation on the major haematological parameters of the body in relation to complications.*

Methods. *This cross-sectional study was conducted during a period of 18 months. 150 patients were included in the study after obtaining their informed consents. Data collection was done using a proforma. The study also compared clotting time (CT) by capillary tube method and whole blood clotting time at 20 minutes (WBCT20). SPSS software was used for statistical analysis.*

Results. *Among the people with complications, the majority (52%) of participants had AKI, 26% of them requiring dialysis, 16.7% participants had GI bleed, 11.3% participants had shock and 10% participants had DIC.*

Conclusions. *A prolonged bleeding time was found to be one of the most helpful haematological parameters in predicting shock and AKI. Clotting time by both capillary tube and WBCT20 methods were comparable in predicting complications.*

KEYWORDS: **hemotoxic snake bite; acute kidney injury; shock; clotting time; bleeding time.**

Introduction

Snakebite envenomation is a major public health problem in India with a high mortality rate [1]. The WHO estimates that there are 81000 snake envenomation in India per annum with a mortality of 11000 (13.5%) [2]. It has been reported that there are 5 million snake bites with 2.5 million envenomation and 125,000 fatalities worldwide annually [3]. India is reported to have the highest number of snake bites (81,000) and deaths (11,000) per year [3]. Snakebite is considered as one of the neglected tropical diseases by the WHO [4]. The mortality due to snakebites in India is due to various socioeconomic, cultural and environmental causes [5]. Among the 52 species of venomous snakes in India, 4 species are responsible for greatest number of snake bites which are medically significant. These are referred to as the big four, *Bungarus caeruleus* (common krait), *Daboia russelii* (Russel's viper), *Echis carinatus* (saw scaled viper), *Naja naja* (Indian cobra). But recently it has been discovered that another species, the hump-pit viper (*Hypnale hypnale*), is capable of causing lethal envenomation [6].

The venomous snakes found in India can be classified per the type and action of venom as Neurotoxic (Cobra, Krait) and Hemotoxic (Vipers). Then main complaints are pain and swelling at the site of snake bite [7–11].

The major complications following hemotoxic snake bite are disseminated intravascular coagulation (DIC), shock, acute kidney injury (AKI), acute respiratory distress syndrome (ARDS) and coagulopathy [12]. AKI is one of the serious complications developing after snake bite [13,14]. Early identification of hemotoxic envenomation and anti-snake venom (ASV) administration may help decrease morbidity and mortality [15].

The study tries to find out the common complications after hemotoxic snake bites and to explore a possible correlation of the haematological parameters to complications. The study also compares clotting time by capillary tube method and WBCT20. ASV administration is currently based on prolongation of WBCT20. Capillary tube method for estimating CT could be used in a resource poor setting, if the

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predictability of the test is comparable to that of WBCT20. In a study by Ratnayake et al [16] the diagnostic utility of WBCT20 was determined at the time of admission and it was found out that it had got sensitivity of 82% and specificity of 98% in detecting venom induced consumption coagulopathy (VICC). The aim of the study was to assess the value of haematological parameters, i.e. bleeding time (BT), clotting time (CT), prothrombin time (PT), activated partial thromboplastin time (aPTT) in predicting the complications. The primary objective was to assess the effect of snake bite on the major haematological parameters of the body in relation to complications.

Methods

This cross-sectional study was conducted over a period of 18 months after obtaining clearance from the institutional ethics committee. A total of 150 patients, who were above 18 years of age, had given written informed consent and had clinical features of hemotoxic envenomation or increase of any of the evaluated haematological parameters as bleeding time (BT), clotting time (CT), prothrombin time (PT), activated partial thromboplastin time (aPTT), were included in the study. Convenient sampling was done.

The patients who had not given written informed consent and the patients with bites other than hemotoxic snakebites were excluded from the study. Any patient who is a known case of bleeding disorder, chronic alcoholic, with acute or chronic liver disease, pregnant females and on anticoagulation therapy were excluded from the current study. After admission a complete history was taken and a thorough clinical examination was conducted. As per the protocol followed in our Institute, all patients bitten by poisonous snakes received polyvalent anti snake venom (ASV), within 15 minutes of reaching the hospital, provided they had clinical features of envenomation. The patients with no initial features of envenomation were administered with ASV as soon as they exhibited first signs of envenomation.

Initial blood samples collected from the patients admitted with hemotoxic envenomation were sent for complete hemogram, random blood sugar (RBS), renal function tests (RFT), liver function tests (LFT), serum electrolytes and important coagulation parameters including BT, CT (both WBCT20 and capillary tube methods), PT with INR, D-dimer and a PTT. All patients with features of envenomation were administered with 10 vials of ASV. The response was monitored clinically by doing WBCT20 and Clotting Time (CT) using the capillary tube method, with 2 hour intervals if prolonged initially, otherwise with 6 hour intervals.

If the features of envenomation were persistent or if the WBCT20 was prolonged after 6 hours of first dose, a repeated dose of 10 vials of ASV was given. Blood parameters like BT, CT, PT, APTT and D-dimer were investigated as per the protocol. The first sample of blood was taken on admission for evaluating BT, CT, PT with INR, and APTT. BT was subsequently estimated 2 times with a 5 minute interval, then in 2 hours, 4 hours, and 6 hours after admission. Then every 6 hours if prolonged. Once normal, it was repeated once daily. CT was estimated at time of admission. If in norm, CT was repeated with 6 hour intervals for 1 day to test for requirement of ASV. If prolonged, it was tested with 2 hour intervals till the normal rate. CT was estimated by 20-minute whole blood clotting method (WBCT20) and capillary tube method for comparison study. APTT was done on the 1st day and 7th day, but PT was done at the time of admission and daily. D-dimer was done when there was prolongation of CT on 3 consecutive occasions. ASV was given according to the standard protocol with administration of ASV every 6 hours till normal coagulation profile.

A bite was considered hemotoxic, if the culprit snake is identified as hemotoxic or by coagulopathy as suggested by haematological parameters. AKI was defined as the increase of serum creatinine ≥0.3 mg/dL within 48 hours or increase in serum creatininein ≥1.5 times from baseline. AKI staging was performed according to the "Kidney Disease: improving global outcomes" (KDIGO) clinical practice guidelines [17]. Shock was defined by a systolic blood pressure of <90 mmHg with evidence of tissue hypoperfusion (<0.5 mL/kg/h decrease in urine output, cold skin, and or requiring inotropic drugs). The data was collected, occurrence of complications and derangement in haematological parameters were studied and analysed. The data collected was recorded in a standard data collection sheet as per study proforma and later transferred to Microsoft Excel spread sheet for statistical analysis. Complications like AKI, shock were considered as primary outcome variables. CT by capillary tube and WBCT20 at different time periods, BT, PT, aPTT etc. were considered as explanatory variables.

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Descriptive analysis was carried out by frequency and proportion for categorical variables. Categorical outcomes were compared between the study groups using the Chi square test / the Fisher's Exact test (if the overall sample size was <20 or if the expected number in any one of the cells was <5, Fisher's exact test was used). P value <0.05 was considered statistically significant. IBM SPSS version 22 was used for statistical analysis [18].

Results

In the study it was observed that the snake bites were more common in males. Out of 150 subjects in our study, 24 (16.0%) cases, were bites by Russel's viper, 4 (2.7%) cases by krait, 2 (1.3%) cases by hump nosed pit viper and 120 (80.0%) were unidentified. The patients included in the study, who had any comorbidity, accounted for 36.0% of the study population (Table 1).

Among the complications, the majority (52%) of participants had AKI, 26% of them required dialysis; 16.7% participants had GI bleed; 11.3% participants had shock and 10% participants had DIC (Table 2).

Association between AKI and shock with various parameters have been shown in the Table below (Table 3). At the time of admission, 11 patients (47.8%) presenting with AKI reported prolonged CT (capillary tube). However, in 6 hours 22 (100%) participants with prolonged CT had AKI. A majority of 36 (60%) participants reported AKI with normal WBCT20 at the time of admission. The occurrence of AKI was evidenced in 30 (81%) participants with prolonged WBCT20 in 6 hours. The occurrence of AKI was found in 17 (58.6%) participants with PT >16.50 seconds. All participants with APTT >35 reported AKI (Table 3). WBCT20 and CT by capillary tube method in 6 hours were comparable in predicting AKI.

Table 1. Summary of baseline parameters in study population (n= 150)

Parameter	Summary (number, %)	Parameter	Summary (number, %)
Age		Abdominal pain	45 (30%)
18-30	37 (24.7%)	Neurological signs	28 (18.7%)
31-40	30 (20%)	Respiratory distress	25 (16.7%)
41-50	29 (19.3%)	Low back ache	20 (13.3%)
51-60	27 (18%)	Bleeding from any site	15 (10%)
61-65	27 (18%)	Respiratory failure	15 (10%)
Gender		ARDS	11 (7.3%)
Male	98 (65.3%)	Hematemesis	4 (2.7%)
Female	52 (34.7%)	**Comorbidities**	
Place of Bite		Diabetes Mellitus	25 (16.7%)
Indoor	1 (0.7%)	Hypertension	24 (16%)
Outdoor	149 (99.3%)	Ischemic Heart Disease	0 (0%)
Snake Type		Respiratory Failure	0 (0%)
Russel's Viper	24 (16%)	Bronchial Asthma	11 (7.3%)
Krait	4 (2.7%)	Chronic Obstructive Lung Disease	23 (15.3%)
Hump nosed pit viper	2 (1.3%)		
Unidentified	120 (80%)	**CT prolonged**	
Classical Bite	43(28.7%)	At the Time of admission	23 (15.3%)
Local Reaction	65 (43.3%)	2 Hours	36 (24%)
Cellulitis	27 (18%)	4 Hours	29 (19.3%)
Gangrene	8 (5.3%)	6 Hours–12 hours	49 (32.03%)
Ecchymoses/Bleeding	14 (9.3%)	Day 2	4 (2.7%)
Comorbidities	54 (36%)	**WBC T20-Prolonged**	
Pain at bite site	128 (83.3%)	At the time of admission	90 (60%)
Numbness	125 (83.3%)	2 Hours	61 (40.7%)
Sweating	98 (65.3%)	4 Hours	48 (32%)
Periorbital oedema	71 (47.3%)	6 Hours–12 hours	86 (57.3%)
Vomiting	64 (42.7%)	Day 2	15 (10%)
Facial puffiness	48 (32%)		

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Table 2. Summary of the complications observed (N=150)

Complications	Summary (number, %)
AKI	78 (52%)
Acute Renal Failure (AKI requiring dialysis)	39 (26%)
Dialysis done	39 (26%)
GI Bleed	25 (16.7%)
Shock	17 (11.3%)
DIC	15 (10%)
ARDS	11 (7.3%)
Reaction to ASV	6 (4%)
Mortality	2 (1.3%)
Intra Cerebral Bleed	0 (0%)
Hypopituitarism	0 (0%)
Guillain Barre Syndrome	0 (0%)
Peripheral Neuropathy	0 (0%)

Table 3. Association of different parameters with AKI

Parameter	AKI		P Value
	Present	Absent	
CT capillary tube at the time of admission			
Prolonged (N=23)	11(47.8%)	12 (52.2%)	0.663
Normal (N=127)	67 (52.8%)	60 (47.2%)	
CT capillary tube in 6 hours			
Prolonged (N=22)	22 (100%)	0 (0%)	*
Normal (N=120)	48 (40%)	72 (60%)	
WBCT20 at admission			
Prolonged (N=90)	42 (46.7%)	48 (53.3%)	0.109
Normal (N=60)	36 (60%)	24 (40%)	
WBCT20 at 6 hours			
Prolonged (N=37)	30 (81%)	7 (19%)	<0.001
Normal (N=105)	40 (38%)	65 (62%)	
BT			
>7 (N=12)	12 (100%)	0 (0%)	*
≤7 (N=138)	66 (47.8%)	72 (52.2%)	
PT			
>16.50 (N=29)	17 (58.6%)	12 (41.4%)	0.319
≤16.50 (N=116)	56 (48.3%)	60 (51.7%)	
APTT			
>35 (N=23)	23 (100%)	0 (0%)	*
≤35 (N=123)	51 (41.5%)	72 (58.5%)	

No statistical tests were applied due to 0 values in one of the cells.

The occurrence of shock was found in 6 (26.1%) participants with prolonged CT at the time of admission (P value of 0.039). However, 11 (50%) participants had shock with prolonged CT in 6 hours (P value <0.001). The occurrence of shock was found in 11 (12.2%) participants with normal WBCT20 at admission. 17 (42%) participants with prolonged WBC T20 in 6 hours reported shock. The occurrence of shock was found to be statistically significant with p value of <0.001 and the proportion of shock was 8 (66.7%) with BT >7 seconds. The occurrence of shock was found to be significant with a P value of <0.001 in 7 (30.4%) participants with >35 APTT (Table 4).

Table 4. Association of different parameters with shock

Parameter	Shock		P Value
	Present	Absent	
CT capillary tube at the time of admission			
Prolonged (N=23)	6 (26.1%)	17 (73.9%)	0.039
Normal (N=127)	11 (8.7%)	116 (91.3%)	
CT capillary tube at 6 Hours			
Prolonged (N=22)	11 (50%)	11 (50%)	<0.001
Normal (N=120)	6 (5%)	114 (95%)	
WBCT20 at Admission			
Prolonged (N=90)	11 (12.2%)	79 (87.8%)	0.875
Normal (N=60)	6 (10%)	54 (90%)	
WBCT20 at 6 Hours			
Prolonged (N=37)	17 (46%)	20 (54%)	*
Normal (N=105)	0 (0%)	105 (100%)	
BT			
>7 (N=12)	8 (66.7%)	4 (33.3%)	<0.001
≤7 (N=138)	9 (6.5%)	129 (93.5%)	
PT			
>16.50 (N=29)	12 (41.4%)	17 (58.6%)	*
≤16.50 (N=116)	0 (0%)	116 (100%)	
APTT			
>35 (N=23)	7 (30.4%)	16 (69.6%)	<0.001
≤35 (N=123)	6 (4.9%)	117 (95.1%)	

No statistical tests were applied due to 0 values in one of the cells.

Discussion

In this study, shock was seen in 11.3% of the total cases, AKI in 52 %, ARF (AKI requiring dialysis) in 26% and gastro intestinal bleed in 16.7%. A comparatively higher incidence of shock was reported by Harshavardhan et al. [19] in their study on hemotoxic snake bite cases (36%). But a comparable value (10.38%) to our study was reported by Kumar et al. [20].

Acute kidney injury (AKI) was established in 52% of the cases in the present study. A somewhat similar value was observed (30.71%) in a previous study [21]. Bhalla et al studied the clinical profile of snake bite in a tertiary centre and observed AKI in 47.6% of the cases [22]. Similar study on outcomes of snakebite poisoning in a tertiary centre by Meenakshi B et al. reported AKI in 44% of cases.

Proteins are an important constituent of snake venoms and they are encoded by poly-adenylated mRNA in the venomous glands (12S and 20S) [21]. Besides proteins, the other components present in snake venom include lipids, polysaccharides, nucleotides, nucleosides, free amino acids, riboflavin, serotonin and histamine. Pharmacologically active substances of the venom are enzymes and low molecular weight peptides. The main sites of action of these enzymes are cell membranes, the vascular wall and the blood coagulation cascade [20, 22]. Snake venom, mainly those of Viperidae, contain also molecules that act on the four interconnected blood systems (i) the coagulation system, (ii) fibrinolytic system, (iii) complement and (iv) the kinin system [22].

Shock is consistently the single most important factor in mortality due to Indian viper bite poisoning. The pattern of shock observed shows early transient shock, early sustained shock and late onset shock. Shock is caused by reduction in the circulating blood volume due to a venom-mediated generalized increase in endothelial permeability. Apart from this, massive limb oedema can lead to considerable compartmentalization of blood and plasma. Pulmonary intravascular coagulation, pulmonary oedema caused by increased pulmonary vascular permeability, and cardiotoxic effects of the venom may also be contributory.

The kidney is a highly vascularized organ with excretory function, so it is prone to venom toxicity. AKI, the most significant of all the renal

manifestations, has been reported to be of varying frequency in different studies [23]. Many studies have appeared in literature on snake bite-induced AKI over a decade. Phospholipase A2 is the most widespread and extensively studied of all venom enzymes. It damages mitochondria, red blood cells, leucocytes, platelets, skeletal muscle, vascular endothelium, and other membranes and leads to auto pharmacological release of histamine and anti-coagulants. Viper bites cause various systemic symptoms such as coagulopathy, haemolysis, AKI, a generalized increase in capillary permeability and rhabdomyolysis [23]. Haemoglobinuria caused by intra-vascular haemolysis and myoglobinuria resulting from rhabdomyolysis contributes to development of AKI. Haemorrhage, hypotension, disseminated intravascular coagulation, intravascular haemolysis, and rhabdomyolysis enhance renal ischemia leading to renal failure. Enzymatic activities of snake venoms account for direct nephrotoxicity and immunologic mechanism is insignificant [24].

A variety of factors contribute to shock like fright, hypovolemia (due to extravasation of fluids and blood loss), myocardial depression, haemorrhage into the adrenals and pituitary.

Conclusions

A prolonged clotting time as obtained by capillary tube method in 6 hours is helpful in predicting development of shock. However, since AKI occurred even in those patients having normal clotting time and WBCT20, these parameters may not be useful as predictors of AKI. Prolonged CT by capillary tube method and WBCT20 in 6 hours were comparable in predicting AKI. Prolongation of more than 16.5 seconds in prothrombin time was helpful in predicting the development of shock. However prolonged prothrombin time (>16.50) was not useful in predicting AKI. A prolonged APTT more than 35 seconds was helpful in predicting the onset of shock and AKI. A prolonged bleeding time was found to be one of the most helpful haematological parameters in predicting shock and AKI.

Limitations of the study

A comparatively low number of 150 cases may have strained the generalizations derived by the study. Parameters like CT by capillary tube method did not have a control test measured in patients with non-poisonous snake bite envenomation. A degree of individual variability was inevitable in the evaluation of CT both by capillary tube and WBCT20 methods as well as that of BT. The duration of envenomation prior to admission has not been taken into account in this study, possibly affecting the correlation between haematological parameters and development of complications.

Conflicts of Interest
Authors declare no conflict of interest.
Authors' Contributions
Harikrishnan M.P. – data curation; investigation; methodology; supervision; writing – original draft; writing – review & editing.

Anil Kumar C.R. – data curation; investigation; supervision; project administration; methodology; supervision; writing – original draft; writing – review & editing.

Anand M.K. – data curation; investigation; methodology; supervision; writing – original draft; writing – review & editing.

Jerry Earali – data curation; investigation; methodology; supervision; writing – original draft; writing – review & editing.

ВАРІАБЕЛЬНІСТЬ ГЕМАТОЛОГІЧНИХ ПАРАМЕТРІВ ЯК ПРЕДИКТОР РОЗВИТКУ УСКЛАДНЕНЬ ПІСЛЯ ПОТРАПЛЯННЯ В ОРГАНІЗМ ГЕМОТОКСИЧНОЇ ОТРУТИ ВНАСЛІДОК УКУСУ ЗМІЇ

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Вступ. *Одна з найбільших проблем закладів охорони здоров'я в Індії – укуси змій, які супроводжуються високою летальністю. Найбільш часті ускладнення, які розвиваються внаслідок потрапляння в організм гемотоксичної зміїної отрути, це синдром дисемінованого внутрішньосудинного згортання (ДВЗ), шок, гостре ураження нирок (ГУН), гострий респіраторний дистрес синдром (ГРДС) та кооагулопатія.*

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Мета дослідження – дослідити можливий взаємозв'язок між частотою розвитку ускладнень як ДВЗ, ГУН, гостра ниркова недостатність (ГНН), ГРДС, шок та кишково-шлункові кровотечі.

Методи. *Це перехресне дослідження проводилося впродовж 18 місяців. Було залучено 150 пацієнтів, які підписали поінформовану згоду. Збір даних проводили за допомогою спеціально розробленої форми. Також досліджували швидкість згортання крові за допомогою капіляра та 20-хвилинного тесту на згортання цільної крові (англ. 20WBCT, показники коагулограми. Для статистичної обробки отриманих даних використовували програмне забезпечення IBM SPSS Statistics.*

Результати. *Серед покусаних людей, у яких розвинулися ускладнення, у більшості (52%) розвинулося ГУН, внаслідок чого 26% серед них потребували діалізу, у 16,7% учасників дослідження були кишково-шлункові кровотечі, у 11,3% - розвинувся шок, у 10% розвинувся ДВЗ.*

Висновки. *Серед досліджуваних гематологічних параметрів для прогнозування розвитку ускладнень (гострого ураження нирок та шоку) після укусу змії найбільш інформативними був подовжений час згортання крові. Обидва методи дослідження згортання крові і за допомогою капіляра і WBCT20 були релевантні та корелювали при прогнозуванні ускладнень.*

КЛЮЧОВІ СЛОВА: **гемотоксична зміїна отрута; укус змії; гостре ураження нирок; шок; час згортання крові; час кровотечі.**

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