Original Research Article

Study of coagulation disorder following haemotoxic snake envenomation in a tertiary care centre

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ABSTRACT

Background: Coagulopathy is the most common manifestation in cases of haemotoxic snake bites. The most common coagulopathy associated with snake envenoming worldwide is venom-induced consumption coagulopathy (VICC). The existence of overlapping clinical syndromes of VICC and thrombotic microangiopathy (TMA) in snake envenoming is the likely reason for the mistaken idea that snake bite causes disseminated intravascular coagulation (DIC). This study aims to look into the exact type coagulopathy in haemotoxic snake envenomation.
Methods: Prospective observational study was conducted from January 2017 to January 2018 at a tertiary care centre in Odisha.
Results: Out of 54, 23 (42.6%) cases were having DIC and 31 (57.4%) cases were not confirmed to be having DIC. In DIC group there was significantly delayed hospitalization (46.3±28.5 hours) when compared to group B (13.5±11.1 hours, p<0.05). Mean anti-snake venom (ASV) requirement in DIC group was significantly higher (28.3±14) than in those DIC is not confirmed (11.13±3.1, p<0.05). 21.7% cases in DIC group had kdigo stage III AKI compared to 3.3%cases of group B. 13% cases of DIC group required hemodialysis when compared to 3.2% cases of group B.
Conclusions: Early hospitalisation (preferably <12 hours and not >24 hours), early ASV administration are important to prevent full blown DIC and more serious complications. Most of the non DIC cases appears to be DIC in evolution but not confirmed to diagnosis by DIC scoring system as they reached hospital early before the development of frank DIC. TMA has not been found in this study. However further studies are needed to ascertain the exact cause of coagulopathy in non DIC group.

Keywords: Snakebite, DIC, TMA, AKI, ASV

INTRODUCTION

India is inhabited by more than 60 species of venomous snakes. Some of the most common found in India are spectacled cobra (*Najanaja*), common krait (*Bungaruscaeruleus*), saw scaled viper (*Echiscarinatus*) and Russell's viper (*Daboiarusselii*).[1,18,25] India is estimated to have the highest snake bite mortality in the world. In a recently published study 0.47% of total deaths were assigned to snakebites amounting to 40,900 to 50,000 annual deaths.[19,20] It occur mostly in rural areas, and more commonly among males than females and peaking at ages of 15-29. Besides Andhra Pradesh, Madhya Pradesh, Odisha is having highest Snake bite death rates (5.6/1,00,000) population.[21-24] It is estimated that in Odisha 2200 cases die every year are due to snake bites. Haematoxic snakebites are common in Odisha. Coagulopathy is the most common manifestation in cases of haemotoxic snakebites like Russell's viper, saw scaled viper and pit vipers and its abnormality can be detected by blood coagulation tests.[9,12,14,16,17] The most common causes of deaths due to haemotoxic snake bite are bleeding

due to coagulopathy and coagulopathy can also contribute to acute kidney injury (AKI).

The most common coagulopathy associated with snake envenoming worldwide is venom-induced consumption coagulopathy (VICC), which results from activation of the coagulation pathway by snake toxins including thrombin-like enzymes, prothrombin activators, and factor X activators.[3-5]

VICC has been often linked to disseminated intravascular coagulation (DIC) because of the elevated D-dimer, prolonged prothrombin time and low fibrinogen.[2,3] However, VICC is not characterised by the other important features of DIC, such as evidence of systemic microthrombi and end organ failure.[32-34] In addition the time course of VICC differs from DIC with rapid onset of coagulopathy within hours of snakebite and the resolution over 24 to 48 hours. VICC can either resolve spontaneously, which has been reported in Australian snake envenoming and also from Orissa or after antivenom therapy over 24 to 48 hours.[2-4,9] DIC is mediated by activated tissue factor/factor VIIa pathway, which is not balanced by physiological anticoagulant system due to impairment in the major anticoagulant pathways.[6,7,27,28,35,36] In contrast, the initiation of coagulation activation in VICC is usually due to the action of snake procoagulant toxin at one point in the coagulation pathway and not via tissue factor/factor VIIa pathway.[29-31]

In a proportion of patients with VICC, a clinical syndrome consistent with thrombotic microangiopathy (TMA) has been reported and is characterised by acute renal failure, thrombocytopenia, and microangiopathic haemolytic anemia.[3,8,11] Coagulopathy occurs early and resolves over 48 hours (consistent with VICC) while the abnormalities consistent with TMA (platelets, hemoglobin, and renal function) remain over long period suggesting a distinct but related process. The existence of overlapping clinical syndromes of VICC and TMA in snake envenoming is the likely reason for the mistaken idea that snake bite causes DIC. But previous studies from Orissa were also found DIC was the predominant coagulation abnormality in haemotoxic snake bite.[2] But newer diagnostic criteria for diagnosing DIC was not used.

Diagnosis of DIC has changed with time and newer diagnostic criteria using scoring system has been approved International society on thrombosis and hemostasis (ISTH) which were not used in previous studies from India.[10,15,16,49] Presence of TMA has not been evaluated in Indian haemotoxic snake bite which is uncommon in Odisha but seen in Srilanka.

Therefore there is need to look into the type of venom induce coagulopathy following haemotoxic snake bite in Odisha, keeping in view due to the possibility of DIC or TMA in haemotoxic snake envenomation the present study has been undertaken from Odisha with the following aims and objectives.

Objectives

Objectives of the research were to study the type of coagulation disorder in haemotoxic snakebite envenomation and to study effect of ASV on coagulation disorder.

METHODS

Study design

This study was a facility-based observational study.

Study population

Fifty four patients admitted with history of haemotoxic snake bite with abnormal 20 min whole blood clotting test and compatible physical findings were taken for the study. This prospective observational study done from January 2017 to January 2018 in the department of medicine, SCB Medical College, Cuttack, India.

Inclusion criteria

Patients with history of snake bite with signs and symptoms compatible with envenomation like local swelling, bleeding manifestations, 20 min whole blood clotting test abnormal and age >15 years were included.

Exclusion criteria

Patients with pre-exiting coagulopathy, on anti-coagulants and anti-platelet drugs, with pre renal disease and chronic liver disease. Patients with risk factors like diabetes, hypertension, connective tissue diseases, chronic infection, malignancy and patients who doesn't give consent for participation were excluded.

Methodology

All the issues including ethical issues pertaining to the study was evaluated by the institutional review board and clearance for the same was obtained for the study.

Informed consent taken in all cases. All the clinical features are recorded in a proforma attached within. Diagnosis of DIC is done using ISTH Scoring system.[10,49]

The study population was divided into two groups based on DIC scoring system group A (DIC group) and group B (DIC not confirmed) for descriptive analysis.[49]

Investigations include 20 min whole blood clotting time, complete blood count (CBC), peripheral smear (schistocytes), liver function tests, urea, creatinine, urine microscopy, stool routine and for occult blood.[12,13] Global coagulation tests like platelet count, fibrinogen degradation product (FDP), fibrinogen, prothrombin time and activated partial thromboplastin time (aPTT).

Statistical analysis

Quantitative variables were compared using unpaired t-tests between two groups. Qualitative variables are compared using Chi-square test. Pearson correlation was used to determine the association between two variables, p value <0.05 was considered statistically significant. The data was entered in Microsoft excel spreadsheet and analysis was done using statistical package for social sciences (SPSS) version 25.

RESULTS

Out of total 54 cases 23 (42.6%) cases were confirmed to be having DIC (DIC score ≥5) and 31 (57.4%) cases were not confirmed to be having DIC (DIC score <5) majority of these cases had a score of 3 (31.48%) followed by score of 1 (18.5%) (Table 1).

Table 1: Distribution of cases according to DIC score (N=54).

DIC score	Number (%)	Total
<5		
1	10 (18.5)	
2	3 (5.6)	
3	17 (31.48)	31 (57.4%)
4	1 (1.8)	
≥5		
5	15 (27.8)	
6	6 (14.8)	23 (42.6)
7 and 8	0	

Bleeding diathesis, oliguria, shock and hepatic dysfunction were found statistically significant higher in DIC group (group A) when compared to group B except fang mark which is more commonly found in group B (Table 2).

The commonest type of bleeding was bleed at site of bite (18.5%) followed by gum bleed (12.9%) and hematuria (9.3%) (Table 3).

Patients with DIC score≥5 the delay in ASV administration was significantly higher (46.3±28.5 hours) in comparison to patients with DIC score<5 (13.5±11.1 hours). 61.3% cases in group B have arrived to hospital in <12 hours whereas 73.9% cases in DIC group arrived after >24 hours (Table 4).

In cases with score <5 none of them progressed to frank DIC after receiving ASV for 48 hours. Majority of these cases remained stable and even in few cases complete recovery is seen. In cases who already presented with DIC at the time of hospitalization (score 5 and 6), majority of these cases remained as DIC even after 48 hours of receiving ASV even though few cases showed recovery which was not complete and 2 cases progressed to higher scores (Table 5).

10 vials of ASV found sufficient in most (87.1%) of the cases where DIC not evolved. Those presented with DIC required 21-30 vials in 56.5% cases and even 31-40 vials in 21.7% cases. Mean ASV requirement in DIC group is significantly higher than in those DIC is not confirmed (Table 6).

Table 2: Comparison of clinical manifestations between group A (confirmed DIC) and group B (DIC not confirmed DIC score <5).

Parameter	Group A DIC (n=23) (%)	Group B coagulopathy (n=31) (DIC not confirmed) (%)	P value
Age	43.48±16.1	37.4±18.62	0.214
Anemia (Hb<10 g%)	5 (21.7)	4 (12.9)	0.388
Local cellulitis	23 (100)	31 (100)	
Bleeding manifestation	21 (91)	5 (16.1)	0.0
Fang mark	9 (39)	22 (71)	0.019
Oliguria	14 (60.9)	2 (6.5)	0.00015
Shock	12 (52.2)	0	0.00001
Hepatic dysfunction	14 (60.9)	1 (3.2)	0.00003
Gangrene	2 (8.7)	0	0.176
Hematuria	2 (8.9)	1 (3.2)	0.568

Table 3: Comparison of bleeding manifestations between group A (confirmed DIC, score ≥5) and group B coagulopathy (DIC not confirmed DIC score <5).

Type of bleeding	Group A (n=23) % (confirmed DIC, score ≥5)	Group B (n=31) coagulopathy (DIC not confirmed, score<5) %	Total %
Bleed at site of bite	7 (30.4)	3 (9.6)	10 (18.5)
Gum bleed	6 (26.1)	1 (3.2)	7 (12.9)

Type of bleeding	Group A (n=23) % (confirmed DIC, score ≥5)	Group B (n=31) coagulopathy (DIC not confirmed, score<5) %	Total %
Echymosis/hematoma/purpura	1 (4.3)	0 (0)	1 (1.9)
Hematuria	4 (17.4)	1 (3.2)	5 (9.3)
Hemoptysis	3 (13)	0 (0)	3 (5.6)
ICH	0 (0)	0 (0)	0 (0)
No bleeding	2 (8.7)	26 (83.9)	28 (51.9)
Total	23	31	54 (100)

Table 4: Distribution according to duration between time of bite and hospitalization (in hours).

Duration between time of bite and hospitalization (in hours)	Score1	Score 2	Score 3	Score 4	Score ≥5	Total %
≤12	5 (50)	2 (66.7)	12 (70.6)	0 (0)	0	19 (35.2)
>12-24	4 (40)	1 (33.3)	3 (17.6)	0 (0)	6 (26.1)	14 (25.9)
>24	1 (10)	0 (0)	2 (11.8)	1 (100)	17 (73.9)	21 (38.9)
Total	10	3	17	1	23	54 (100)

Table 5: Evolution of DIC score in snake bite cases with time after administration of ASV.

DIC score	Day 1 (No %)	Day 3 (No %)			
		Stable (%)	Decreased (%)	Increased but <5 (%)	Increased ≥5 (%)
1	10	6 (60)	2 (20)	2 (20)	0
2	3	1 (33.3)	1 (33.3)	1 (33.3)	0
3	17	10 (58.8)	1 (5.9)	6 (35.3)	0
4	1	1 (100)	0	0	0
5	15	12 (80)	1 (6.7)	0	2 (13.3)
6	8	5 (62.5)	3 (37.5)	0	0
Total	54	35 (64.8)	8 (14.8)	9 (16.6)	2 (3.7)

Table 6: Comparison of ASV requirement between group A and group B.

ASV range (vials)	Group A DIC (n=23) %	Group B (n=31) (DIC not confirmed score<5) %
1-10	0	27 (87.1)
11-20	5 (21.7)	4 (12.9)
21-30	13 (56.5)	0
31-40	5 (21.7)	0
Mean±SD	28.3±6.14	11.13±3.1 (p value <0.0001)

The study included a total 54 cases with haemotoxic snake bite. Out of total 54 cases (Table 1) 23 (42.6%) cases were confirmed to be having DIC (DIC score ≥5) and 31 (57.4%) cases were not confirmed to be having DIC (DIC score<5) majority of these cases had a score of 3 (31.48%) followed by score of 1 (18.5%). Majority of were in age group of 20-39 years (57.7%). Males (81.5%) were more prone to the bites with a male to female ratio of 4.4:1. Most common site of bite was in the lower extremity (85.1%). Maximum number of bites occurred between 12 noon to midnight (69.4%), most of the bites were encountered in cultivation field (61.1%). Local swelling was the commonest manifestation in both groups while bleeding including local and systemic (gum bleed 26.1%, hematuria 17.4%), oliguria (60.9%), shock (52.2%), hepatic dysfunction (60.9%) were significantly higher (p<0.05) in DIC group compared to group B (Table 2). The commonest type of bleeding was bleed at site of bite (18.5%) followed by gum bleed (12.9%) and hematuria (9.3%) (Table 3). Patients with DIC score ≥5 the delay in ASV administration was significantly higher (46.3±28.5 hours) in comparison to patients with DIC score <5 (13.5±11.1 hours).

61.3% cases in group B have arrived to hospital in <12 hours whereas 73.9% cases in DIC group arrived after >24 hours (Table 4). Significantly (p<0.05) higher incidence of thrombocytopenia 86.9%, prolonged [prothrombin time (PT) 100%, aPTT 73.9%, international normalized ratio (INR) 82.6%] values, elevated FDP 100%, low fibrinogen levels 95.6%, stage III acute kidney injury (AKI) 21.7% and raised [bilirubin 69.6%, serum glutamic oxaloacetic transaminase (SGOT), serum glutamic pyruvic transaminase (SGPT) 82.6%, lactate dehydrogenase (LDH) 73.9%] were present at the time of admission in DIC group than group B. In DIC group there was significantly delayed hospitalization (46.3±28.5 hours)

when compared to group B (13.5±11.1 hours, p<0.05). 61.3% cases in group B had arrived to hospital in <12 hours whereas 73.9% cases in DIC group arrived after >24 hours (Table 5). In cases with score <5 none of them progressed to frank DIC after receiving ASV for 48 hours. Majority of these cases remained stable and even in few cases complete recovery is seen. In cases who already presented with DIC at the time of hospitalization (score 5 and 6),majority of these cases remained as DIC even after 48hrs of receiving ASV even though few cases showed recovery which was not complete and 2 cases progressed to higher scores.

Mean ASV requirement in DIC group was significantly higher (28.3±14) than in those DIC is not confirmed (11.13±3.1, p<0.05) (Table 6). Out of 31 cases in group B commonest abnormalities seen were low fibrinogen in 74.2% cases followed by elevated FDP 61.3%, low TPC 54.8%, INR 19.4%, pronged PT 16.1% and aPTT in 13% cases. Blood film for schistocytes were absent. 21.7% cases in DIC group had kdigo stage III AKI compared to 3.3% cases of group B. 13% cases of DIC group required hemodialysis when compared to 3.2% cases of group B.

DISCUSSION

The maximum number of patients were in the age group 20-39 years they constituted 57.4% patients, which is comparable to that of Sawai et al 71%.[37] The incidence of snake bite was more common in males (81.5%) compared to females (18.5%) with a male to female ratio of 4.4:1 which may be because predominantly males were involved in outdoor activities. Most common site of snake bite was lower extremity (85.1%). Overall maximum bites occurred between 12 pm to 12 am, in our study the commonest manifestation was local swelling (100%) followed by fang mark (57.4%), bleeding (48%), oliguria (29.6%), icterus (27.7%), shock (22.2%) and gangrene (3.7%). Similar observations were made by Harshavardhana et al and Shubhamagarwal et al. For the convenience of description and analysis the study population was divided into two groups based on DIC scoring system, group A (DIC group)-23 patients with DIC score ≥5 (5-8), group B (DIC not confirmed) - 31 patients with DIC score <5 (1-4).[36] In cases with score <5 none of them progressed to frank DIC after receiving ASV. Majority of these cases remained stable and even in few cases complete recovery is seen. In cases who already presented with DIC at the time of hospitalization (score 5 and 6). Majority of these cases remained as DIC even after 48 hours of receiving ASV. Even though few cases showed recovery which is not complete and 2 cases progressed to higher scores. Thrombocytopenia and low mean TPC were significant in group A (p<0.001) and (p=0.007) respectively. Significantly prolonged (p<0.05) PT (87%), aPTT (73.9%), INR (82.6%), elevated FDP (100%), low fibrinogen levels (87%) on the day of admission seen in group A when compared to group B. Similar observations were seen in study by Harshavardhan et al and Shubhamagarwal et al.[38,39] They also concluded that first line of coagulation markers (PT, APTT, fibrinogen) should be evaluated early to identify the coagulopathy. There was significantly high incidence of stage III AKI in DIC group (p=0.03) compared to stage I and II AKI (p=0.7). Mean creatinine levels significantly higher in DIC group (2.3±1.3) than group B (1.5±1.04) p=0.016. Contributing factors are DIC, direct nephrotoxicity, shock, intravascular haemolysis (Chugh et al).[40] Even though 3 cases in our study had normal coagulation profile with only 1 case consistent with thrombocytopenia and normal clotting was seen raising the possibility of TMA but blood film for schistocytes were absent in all 3 cases. It was found that the coagulation parameters (PT, aPTT, thrombocytopenia, elevated FDP and low fibrinogen) DIC group remained abnormal upto day 7 even after receiving ASV. Similar observation were made by Choi in which they founded that the period of extended PT averaged 6.17±4.3 days and it continued to 7.61±4.08 days after poisonous snake bite.[41] The period of consistency of thrombocytopenia was about 6-7 days. ADAMTS13 levels could not be evaluated in suspected TMA cases but direct coombs test was negative.

CONCLUSION

Coagulopathy was the most common haematological complication in haemotoxic snakebite. Though the root cause of coagulopathy was said to be Disseminated intravascular coagulation, in our study only 42.6% cases were confirmed to be having DIC whereas in remaining non DIC cases as anti-venom was administered early (<12 hours) the coagulopathy immediately appeared to be stopped, the DIC process to evolve fully was interrupted resulting in not progressing to have full features of DIC. So these case were appeared to be DIC in evolution. TMA was not found in this study. We therefore emphasise the importance of early hospitalisation (preferably <12 hours and not >24 hours), early ASV administration to prevent full blown DIC and more serious complications and also for early recovery. Further studies are needed to ascertain the exact cause of coagulopathy in non DIC group. DIC scoring system can be used to recognise patients at risk of developing serious complications.

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