The value of coagulation parameters as prognostic indicators in snake envenomation

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Abstract

Background: Snakebite is a potentially life-threatening emergency that can be treated effectively. Snake envenomation can cause hematologic and coagulation abnormalities. In this respect, tests such as prothrombin time (PT), international normalized ratio (INR), and activated partial thromboplastin time (aPTT) are commonly used. The present study aimed to determine the value of coagulation parameters in the prognostication of snakebite patients.

Methods: This prospective descriptive observational study examined the coagulation parameters, including PT, INR, and aPTT, in consecutive cases of snake envenomation admitted to a tertiary health care hospital from October 2019 to August 2021. The correlation of coagulation parameters with each other and with prognostic indicators (ie, the number of days spent in the intensive care unit [ICU], the requirement of anti-snake venom [ASV], fresh frozen plasma [FFP], and the total number of blood products) was studied.

Results: A total of 58 patients with snakebite were studied. The majority were males (69%). The highest proportion of patients belonged to the age group of 16-40 years (60%). The correlation of coagulation parameters with each other was statistically significant. The correlation of coagulation parameters with prognostic indicators (ie, the total number of ASV vials administered, the total number of days in the ICU, the total number of FFP units administered, and the total number of blood components administered) was statistically significant.

Conclusion: Coagulation parameters (PT, INR, and aPTT) are essential laboratory investigations for treatment monitoring and can be used effectively for the prognostication of snakebite patients. In cases where the coagulation profile of snakebite patients shows abnormalities, conducting repeated coagulation studies at intervals of 12 hours can contribute to improved prognostication.

Introduction

Snakebite is a potentially life-threatening emergency that can be treated effectively (1-6). Snake envenomation is a major health problem in India (7-10). India is an agrarian country, and most of the population of India dwells in rural areas. The rural farming population most often faces the occupational hazard of snake envenomation (11-15) due to the intersection of the breeding season of prey of snakes and flooding of the natural habitat of snakes with the farming season of humans (16-21). Snake envenomation can cause hematologic abnormalities, which can present as bleeding manifestations, capillary leak syndrome, or disseminated intravascular coagulation (22-24), among which venom-induced consumption coagulopathy (VICC) is commonest (17-22). Previously, VICC was misinterpreted as disseminated intravascular coagulation. Similar to VICC, this was due to a deranged coagulation profile in DIC in the form of elevated D-dimer, prolonged prothrombin time (PT), and low fibrinogen levels. However, it should be noted that VICC differs from disseminated intravascular coagulation with respect to the absence of systemic microthrombi, absence of end-organ failure, rapid onset and resolution, difference in pathogenesis, and lower mortality compared to DIC (22). For timely detection of coagulation abnormalities and VICC, coagulation tests, such as PT, international normalized ratio (INR), and activated partial thromboplastin time (aPTT), are of utmost importance. Coagulation tests also help in monitoring patient treatment (25-30). The present study aimed to determine the value of coagulation parameters in the prognostication of snakebite patients.

Methods

All consecutive cases of snake envenomation of all age groups and genders admitted in a tertiary health care hospital from October 2019 to August 2021 were included in this prospective descriptive observational study. Patients with a history of administration of anti-snake venom (ASV) before reaching the study setting, patients with pre-existing coagulopathy (ascertained from clinical history and previous investigations), patients already on anticoagulants and antiplatelet drugs, and pregnant females with snakebite were excluded from the study. Coagulation parameters (such as PT, INR, and aPTT) were studied in all patients on admission and, if found deranged, were repeated at intervals of 12 hours till they returned to normal levels. Prothrombin time assesses coagulation factors in the extrinsic and common pathways. These coagulation factors include factors VII, X, and V, prothrombin, and fibrinogen. Samples for coagulation tests were collected in sodium citrate vacutainers. The PT-INR test was performed on a STAGO semi-automated coagulation analyzer using NeoPTimal plus reagent, which contains thromboplastin and calcium chloride. The blood samples of healthy controls were also taken and similarly processed. The values of PT were observed and classified as normal (less than 17 seconds) and abnormal (more than 17 seconds) (30). Also, INR was calculated with the help of the international sensitivity index (ISI) value of the reagent and internal control of the laboratory. The normal range for INR is less than 1.2. INR = (PT of patient/PT of control) ^{ISI}. On the basis of INR, patients were divided into 4 groups. Patients with INR more than 1.2 were divided into 3 groups as follows: 1.2- 4.0 - mildly deranged INR, 4.0-12.0 moderately deranged INR, and 12.0-20.0 severe deranged INR (17-22). Activated partial thromboplastin time (aPTT) is a measure of function of coagulation factors of intrinsic and common pathways. These pathways are controlled by coagulation factors XII and XI, high molecular weight kininogen, prekallikrein, factor IX, factor VIII, factor X, factor II, prothrombin, and fibrinogen. Thus, the activated partial thromboplastin time (aPTT) test measures overall efficiency of the intrinsic pathway and common pathway (31). aPTT was performed on a STAGO semi-automated coagulation analyzer using a reagent containing kaolin, phospholipid, and calcium chloride. In the laboratory, samples were centrifuged at 3000 rpm for 5 minutes to separate the plasma from the citrated blood sample. A volume of 0.1 mL of platelet-poor citrated plasma was collected, placed in a micro cuvette, kept in a well with a magnetic steel ball, and incubated for 1 minute. Then, the micro cuvette was placed in the coagulation well, and 0.2 mL of reagent was added to it. The coagulation analyzer detects the time of clot formation in seconds. The normal range for aPTT is 25-30 seconds. aPTT values were categorized into normal (less than or equal to 30 seconds) and abnormal (more than 30 seconds) groups (17-22). All the patients were followed up during their hospital stay, and the data of the total number of ASV vials administered and fresh frozen plasma (FFP) units administered, as well as the total duration of hospitalization and the number of days spent in the intensive care unit (ICU), were recorded.

All procedures performed in the current study were approved by the Institutional Review Board of MIMER Medical College, Talegaon Dabhade, India (code: MUHS/Medical/MUHS-020660/2019) in accordance with the 1964 Helsinki Declaration and its later amendments.
Informed consent was obtained from all participants included in the study.
Coagulation parameters on admission were correlated with each other using the Pearson correlation in SPSS version 26 (SPSS Inc, Chicago, IL, USA). *P* values less than 0.05 were considered statistically significant. The prognostic parameters

used were the total number of ASV vials administered, the total number of days of hospital stay, the total number of days in ICU, the total number of FFP units administered, and the total number of blood components administered. Coagulation parameters (ie, PT, INR, and aPTT) were correlated with each of the prognostic parameters using the Pearson correlation in SPSS version 26. *P* values less than 0.05 were considered statistically significant. The international normalized ratio on admission and after 12 hours was correlated with the total number of days in the ICU using repeated measures analysis of variance (ANOVA) using SPSS software version 26. *P* values less than 0.05 were considered statistically significant.

Results

A total of 58 patients who met the inclusion criteria were included in the study between November 2019 and August 2021. Among these 58 patients, the majority, specifically 40 individuals (69%), were male. The highest proportion of patients (approximately 60%) belonged to the age group of 16-40 years. The age range of the participants varied from 6 to 72 years old. PT-INR was performed in all 58 patients on admission. If deranged, it was repeated after 12 hours. It was found that the number of times PT-INR was repeated was directly proportional to the severity of envenomation of that patient (Figure 1).
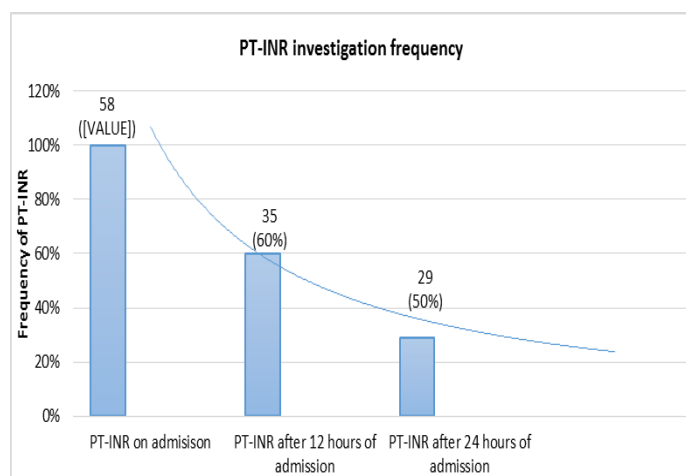

Figure 1. The frequency of the prothrombin time and international normalized ratio conducted on admission, 12 hours after admission, and 24 hours after admission
Abbreviations: PT, prothrombin time; INR, international normalized ratio

Prothrombin time on admission was graded into normal (≤17 seconds) and deranged (>17 seconds). Of the 58 patients, PT on admission was deranged (>17 seconds) in 81% of patients.

The international normalized ratio on admission was graded into normal (0-1.2), mildly (1.21-4.0), moderately (4.1-12.0), and severely deranged (12.1-20.0). Of the 58 patients, 26 (45%) had mildly deranged INR on admission, 3 (5%) had moderately deranged INR on admission, and 13 (22%) had severely deranged INR on admission.

PT-INR was repeated when clinically indicated or when the previous value was deranged. PT-INR after 12 hours of admission was performed on a total of 35 patients. It was graded into normal (0-1.2) and mildly deranged (1.21-4.0) values. Of the 58 patients, PT-INR was repeated in 35 patients. Of the 35 (77%) patients with repeated PT-INR, 27 showed mildly deranged INR, and 8 (23%) showed INR restoring to normal after administration of a repeat dose of ASV. PT-INR was repeated as indicated after 24 hours of admission in 17 (29.31%) patients. They were categorized into normal and mildly deranged groups.

Eleven (65%) patients had mildly deranged INR, and 6 (35%) patients had restoration of INR back to normal after administration of repeat doses of ASV and blood products.

aPTT was performed in all 58 patients on admission. They were categorized into normal (< 30 seconds) and deranged (>30 seconds) groups. Of the 58 patients, 48 (83%) had deranged aPTT, and 11 (17%) had normal aPTT.

A statistically significant correlation was observed between PT and aPTT values on admission (P = 0.008). The values of INR and aPTT were correlated with each other on admission, which was statistically significant (P = 0.008).

A statistically significant correlation was found between the total number of ASV vials administered and PT, INR, and aPTT values on admission (P = 0.004; Table 1).

A significant correlation was found between the INR levels and the total number of days spent in the ICU on admission and after 12 hours of admission (P = 0.042; Table 2).

Table 1. The correlation of the total number of anti-snake venom vials administered with prothrombin time, activated partial thromboplastin time, and international normalized ratio on admission

		PT on admission	Total number of ASV vials administered	aPTT	Total number of ASV vials administered	INR on admission	Total number of ASV vials administered
PT, aPTT, INR on admission	Pearson correlation	1	0.368	1	0.375	0.371	1
	Sig.(2-tailed)		0.004*		0.004*	0.004*	
	N	58	58	58	58	58	58
Total number of ASV administered	Pearson correlation	0.368	1	0.375	1	1	0.371
	Sig.(2-tailed)	0.004*		0.004*			0.004*
	N	58	58	58	58	58	58

The P value is statistically significant
Abbreviations: PT, prothrombin time; aPTT, activated partial thromboplastin

The correlation between other coagulation parameters was not statistically significant. A significant correlation was found between the total number of FFP units administered and PT and INR on admission (P < 0.05; Table 3). The correlation between the total number of FFP units administered and aPTT was not statistically significant (P = 0.832). The correlation between the total number of blood components administered and PT was statistically significant on admission (P = 0.001). The correlation between the total number of blood components administered and INR was statistically significant on admission (P ≤ 0.001). The correlation between the total number of blood components administered and aPTT was not statistically significant (P = 0.785).

Table 2. The correlation of the total number of days in the intensive care unit with the international normalized ratio on admission

		Total number of days in the ICU	INR on admission
Total number of days in the ICU	Pearson correlation	1	0.394
	Sig. (2-tailed)		0.042*
	N	27	27
INR on admission	Pearson correlation	0.394	1
	Sig. (2-tailed)	0.042*	
	N	27	58

*The P value is statistically significant.
Abbreviations: INR, international normalized ratio; ICU, intensive care unit.

Table 3. The correlation between the total number of fresh frozen plasma units administered and prothrombin time and international normalized ratio on admission

		PT on admission	FFP issued	INR on admission	FFP issued
PT, INR on admission	Pearson correlation	1	0.518	1	0.539
	Sig. (2-tailed)		< 0.05*		< 0.05*
	N	58	58	58	58
FFP issued	Pearson correlation	0.518	1	0.539	1
	Sig. (2-tailed)	< 0.05*		< 0.05*	
	N	58	58	58	58

*The P value is statistically significant.
Abbreviations: PT, prothrombin time; INR, international normalized ratio; FFP, fresh frozen plasma.

Discussion

In our study, the majority of the patients were male (69%), which is consistent with the study by Agrawal et al (64%) and Hariprasad et al (75%) (17, 32). However, Karthikeyan et al showed a female predominance (51%) (30).

In our study, 81% of patients showed prolongation of PT on admission. Agrawal et al showed prolongation of PT-INR in 26% of cases, while Harshvardhana et al showed prolongation of PT (>15 seconds) in 56% of patients (32, 33). Karthikeyan et al showed prolongation of PT (PT > 17 seconds) in 75.6% of patients (30).

Ireland et al showed deranged INR (>1.2) in 86% of cases on admission (34). Prolongation of PT significantly correlated with the total number of ASV vials administered. Patients with deranged PT on admission required a greater number of ASV vials to achieve normal coagulation. Ramamurthy et al also showed the increased requirement of ASV with the prolongation of PT (33). Prothrombin time >17 seconds was also associated with the increased requirement of FFP in the current study. Similarly, Harshvardhana et al showed that 136 FFP units were required for patients with PT of more than 15 seconds (33).

In the current study, PT-INR was performed on admission. Of the 58 patients, 26 (45%) had mildly deranged INR (1.2- 4.0), 3 (5%) had moderately deranged INR, and 13 (22%) had severely deranged INR on admission. Agrawal et al showed prolongation of INR in 26% of cases, while Hariprasad et al showed prolongation of INR (>1.2) in 85% of patients (17, 32). Ireland et al showed deranged INR (>1.2) in 86% of cases on admission (34).

In our study, it was observed that the administration of ASV resulted in the restoration of INR to normal levels in some cases. However, in a significant proportion of patients (specifically, 77% of those whose INR was reassessed), the INR remained prolonged even after 12 hours of admission. Prolongation of INR beyond 12 hours was seen in 3.7% of cases in the study by Agrawal et al (32). Ireland et al showed deranged INR beyond 12 hours in 14% of cases (34). Of the 17 patients, 11 (65%) required a repeat INR measurement 24 hours after admission, showing that the INR values were mildly deranged. However, in the existing literature, the prolongation of INR has only been studied for up to 12 hours. The international normalized ratio on admission and 12 hours after admission demonstrated a significant correlation with the total number of days spent in the ICU. Mean INR on admission and 12 hours after admission was 8.5 and 1.5, respectively, for 4 days in the ICU, whereas it was 1.4 and 1.3 for 1 day in the ICU. This result was significant as morbidity can be predicted significantly by following up INR 12 hours after admission. In our study, a significant correlation was found between the derangement of INR on admission and the total number of days spent in the ICU. Patients with severely deranged INR had a significantly longer duration of stay in the ICU compared with those with mildly deranged INR values. These results are consistent with the results of Hariprasad et al (17). In our study, a significant correlation was found between the derangement of INR on admission and the total number of ASV vials administered. This correlation was also significant in the studies by Ramamurthy et al and Harshvardhan et al (29, 35). Prolonged INR is thus an indication of a repeat dose of ASV and FFP.

In the current study, the total number of FFP units administered significantly correlated with INR on admission. Similarly, Harshvardhana et al found that 136 FFP units were required for 25 days of hospitalization days in patients with PT of more than 15 seconds. (33) In the study by Hariprasad et al, 112 patients with INR more than 1.5 also required FFP (17).

In our study, aPTT was prolonged in 83% of patients. Similar results were seen in the study by Patil et al (73.6%) and Agrawal et al (26.4%) (32, 35). In the current study, aPTT significantly correlated with the total number of ASV vials administered. Ramamurthy et al also showed that the prolongation of aPTT was associated with an increased requirement of ASV (29). In our study, prolonged aPTT was associated with increased days of hospitalization in the ICU. These results are consistent with the results of Harshvardhana et al (33).

Implications of the study

This study offers practical guidelines for the use of coagulation tests in the management of snakebite patients. It provides insights into the optimal timing and frequency of conducting coagulation tests in these patients, as well as predicting the need for ASV and blood products such as FFP.

Limitations of the study

In the present study, the proportion of mild to moderate cases was more than severe cases.

Conclusion

Coagulation parameters (ie, PT, INR, and aPTT) can be reliably used for predicting the requirement for ASV, FFP, other blood products, and duration of ICU stay. Thus, coagulation profile estimation can be used in predicting snakebite patients' prognosis. To enhance the prognostic value of coagulation tests, it is recommended to repeat these tests at 12-hour intervals in patients with deranged coagulation profiles.

Ethical statement

All procedures performed in the current study were approved by Institutional review board (IRB) of MIMER Medical College, Talegaon (D) (approval number- MUHS/Medical/MUHS-020660/2019) in accordance with the1964 Helsinki declaration and its later amendments.
Informed consent was obtained from all individual participants included in the study.

Conflicts of interest

The authors declare that they have no potential conflict of interest to disclose.

Author contributions

1. GSM contributed significantly in conceptualization, methodology, project administration, managing resources, supervising the project, validation visualization, writing original draft and writing review.
2. SPS has contributed significantly in data curation, formal analysis, conducting investigations, using software for statistical analysis and writing original draft.

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