

Original Research Article

PT and APTT as Early Markers in the Assessment of Hematotoxicity in Hematotoxic Snake Bite as Compared to Whole Blood Clotting Time in a Tertiary Care Hospital

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ABSTRACT

Background

This study was conducted to compare whole blood clotting time (20 minutes) with PT and APTT as early markers for hematotoxicity identification in snake bites. Early anti-snake venom administration can prevent hematotoxic consequences.

Methods

This study involved 94 patients who presented to the Department of General Medicine at the Karnataka Institute of Medical Sciences, KIMS Hospital, Hubballi, with a history of snakebites and characteristic clinical signs and symptoms. The study was conducted over a two-year period, from December 2020 to December 2022. The institutional ethics committee approved the study, and the participants provided written informed consent.

Results

Out of the 92 patients who had WBCT20 performed at admission, only 28 had positive results; the test's sensitivity in this study was 30.43%, and it missed 43% of cases with VICC. Additionally, two patients had normal coagulation profiles, and in both cases, WBCT20 was negative. These results indicate that WBCT20 has a high specificity of 100% in this study, as well as 100% PPV, 3.03% NPV, and 31.91% diagnostic accuracy. In contrast to previous research, the WBCT20 test's sensitivity, NPV, and diagnostic accuracy were low. There was also a significant likelihood that the coagulopathy in the cases would go unnoticed, which could delay ASV administration and raise the death and morbidity rates from snake bites.

Conclusion

In tertiary care hospitals managing instances of hematotoxic snake bites when PT-INR and APTT tests are feasible, prothrombin time is a very beneficial blood study in making an early diagnosis of coagulopathy compared to whole blood clotting tests.

KEYWORDS: PT, APTT, Hematotoxicity, Coagulopathy ASV, Whole Blood Clotting Time (20 mins), Sensitivity, Specificity, PPV, NPV, Diagnostic Accuracy.

INTRODUCTION

Snakebite injuries are a common environmental hazard with high rates of morbidity and mortality that are frequently disregarded. This severe medical emergency has resulted in a considerable number of hospital admissions in various parts of Asia.^[1] In 2009, the World Health Organization designated snakebite as a neglected tropical disease, recognizing its importance in addition to other infectious diseases. This is a major public health concern in tropical and subtropical regions that mostly impacts rural populations, particularly agricultural laborers in developing countries. Snake envenomation is a serious medical condition that often necessitates hospitalization and can even be fatal in certain instances. It is believed that the main causes of the high morbidity and mortality are inadequate supportive therapies, antivenom deficiency, and delayed access to appropriate medical facilities.^[2] Between 2000 and 2019, experts projected that snakebite deaths in India would average 58,000 per year, or 1.2 million (12 lakh).^[3] It is estimated that the death rate is 1.5% or such. Although the majority of patients in rural areas prefer to see traditional healers rather than hospitals, this figure is based on hospital data. In India, one can frequently come across four species: the Indian cobra (*Naja naja*), Indian krait (*Bungarus caeruleus*), Russell's viper (*Daboia russelii*), and sawscale viper (*Echis carinatus*). Coagulation assays are essential for both diagnosing and tracking VICC in snakebite patients, as well as for swiftly and accurately determining which patients should get antivenom.^[4] Testing for PT (Prothrombin Time) and the INR (International Normalized Ratio) is thought to be the most beneficial diagnostic method in VICC. The aPTT (Activated Partial Thromboplastin Time), despite being abnormal in VICC, is especially helpful in the diagnosis of anticoagulant coagulopathy since it will be high when the INR is normal.^[5] The primary therapy consists of administering antivenom, which attempts to neutralize the toxins. However, antivenom comes at a high cost, is unavailable in some parts of the world, and is associated with a significant risk of severe systemic hypersensitivity reactions. Thus, it is critical to differentiate between patients who have envenoming (and require antivenom) and those who do not (or who have been bitten by non-venomous snakes) as soon as possible and accurately.^[6] The 20-min whole blood clotting test (WBCT20) has been performed on victims of viper (and other snake) bites for many years in order to determine whether or not they have a clinically significant coagulopathy. The WBCT20 was not intended as a clotting test per se, but rather as a marker of envenoming (and the need for antivenom) in patients bitten by snakes that cause coagulopathy.^[7] Although the test is widely used and considered the standard of care for treating snake envenomation in resource-poor settings, no studies have established the conditions under which it can be performed accurately, validated it against standard tests, or demonstrated that it is accurate in the field. The WBCT20 method was first described in a publication that only said, "A few cc of blood were placed in a clean, dry glass test tube and left undisturbed for 20 min, and then tipped to detect whether the blood had clotted." The WBCT20 method is not very standardized.^[8]

AIMS AND OBJECTIVES

- PT and aPTT as early markers for detection of hematotoxicity in snake bites as compared to whole blood clotting time (20 minutes).
- Early administration of anti-snake venom to avoid hematotoxic complications.

MATERIALS & METHODS

This study involved 94 patients who presented to the Department of General Medicine at the Karnataka Institute of Medical Sciences, KIMS Hospital, Hubballi, with a history of snakebites and characteristic clinical signs and symptoms. The study was conducted over a two-year period, from December 2020 to December 2022. The institutional ethics committee approved the study, and the participants provided written informed consent.

Inclusion Criteria

1. All snake bites with suspected envenomation.
2. Definitive fang mark present in cases with a history of snake bite.
3. Adults of age >18 yrs.
4. Consented for participation.

Exclusion Criteria

1. Sepsis and DIC
2. Acute and chronic liver diseases
3. Anti-coagulation therapy such as warfarin and heparin
4. Any case of coagulation disorder
5. Pregnant women and mentally-ill
6. Any patient with prothrombotic disease
7. Patient not giving consent for the study

Statistical Methods

Data were entered into Microsoft Excel and statistical analysis was carried out using SPSS software version 17.0.

RESULTS

Bite Time to Presentation (Hours)	0 Vial		10 Vials		20 Vials		30 Vials	
	n	%	n	%	n	%	n	%
0-2 Hours	1	4.0	14	56.0	9	36.0	1	4.0
2-4 Hours	0	0.0	15	36.6	23	56.1	3	7.3
4-6 Hours	1	3.6	4	14.3	12	42.9	11	39.3
Total	2	2.1	33	35.1	44	46.8	15	16.0
Chi-square p-value = 0.001 (significant)								
Table 1: Comparison of Time of Presentation and Number of ASV Vials Required								

Of the patients who arrived during the first two hours, one (4%) did not require ASV, fourteen (56%) needed ten vials, nine (36%) needed twenty vials, and one (4%) needed thirty vials. Out of the patients who reached the 2-4 hour mark, 15 (36.6%) needed 10 vials of ASV, 23 (56.1%) needed 20, and 3 (7.3%) needed 30 vials. After four to six hours, one (3.6%) of the patients did not require ASV, four (14.3%) required ten vials, twelve (42.9%) required twenty vials, and eleven (39.5%) required thirty vials. There was a statistically significant difference in the number of ASV vials required ($p < 0.001$).

Bite Time to Presentation (Hours)	Number of ASV Vials		P-Value
	Mean	SD	
0-2 hours	14.0	6.5	<0.001
2-4 hours	17.1	6	

4-6 hours	21.8	8.2		
One-way ANOVA p-value (significant)				
Comparison of Time of Presentation and Average Number of ASV Vials Required				
Bite Time to Presentation (Hours)	Complication		No Complication	
	N	%	N	%
0-2 Hours	9	36	16	64.0
2-4 Hours	29	70.7	12	29.3
4-6 Hours	23	82.1	5	17.9
Total	61	64.9	33	35.1
Chi square p-value = 0.001 (significant)				
Comparison of Time of Presentation and Development of Complications				
Table 2				

In patients who presented within 0–2 hours of the bite, the mean (SD) number of used vials was 14 (6.5), whereas in patients who presented between 2-4 hours and 4-6 hours after the bite, the same number of vials was 17.1 (6) and 21.8 (8.2). A statistically significant variation was observed in the mean number of ASV vials required across various biting time to presentation categories ($p < 0.001$).

Of the patients who arrived within a two-hour window, nine (36%) experienced complications, whereas the remaining patients did not experience any. When comparing patients who presented 4-6 hours after biting to those who presented 0-2 hours and 2-4 hours, the percentage of patients who developed complications was higher (82.1% against 70.7% and 36%). With a p-value of 0.001, a statistically significant correlation was found between the biting time to presentation and the emergence of complications.

Bite Time to Presentation (Hours)	Hospital Stay (Days)		P-Value
	Mean	SD	
0-2 hours	3.6	1.3	<0.001
2-4 hours	4.7	1.8	
4-6 hours	6.8	3.5	
Total (n=94)	5.0	2.6	

Table 3: Comparison of Time of Presentation and Duration of Hospital Stay

Patients who presented within 0–2 hours had a mean (SD) hospital stay of 3.6 (1.3) days. Individuals who arrived between 2-4 hours and those who arrived after 4-6 hours showed similar results. With a p-value of less than 0.001, there was a significant difference in the number of hospital days between the bite time and presentation categories.

Bite Time to Presentation (Hours)	Total	WBCT Abnormal		PT/APTT Abnormal	
		n	%	n	%
0-2 Hours	25	2	8.0	24	96.0
2-4 Hours	41	8	19.5	41	100.0
4-6 Hours	28	18	64.3	27	96.4
Total	94	28	29.8	92	97.8
P-Value		<0.001		0.451	

Table 4: Comparison of WBCT with PT and APTT Based on Time of Presentation

64.3% of the patients who appeared 4-6 hours after the bite showed aberrant WBCT. Out of the patients who arrived within two hours of the bite, two (8%) and eight (19.5%) showed abnormal WBCT. A noteworthy correlation was noted between the aberrant WBCT

readings and the bite to time of presentation ($p < 0.001$). Regardless of the bite to time of presentation, almost 95% of the patient's PT/APTT results were abnormal ($p = 0.451$).

DISCUSSION

Of the 52 participants in the current study, over half (55%) were older than 35. Thirty-two (32%) and sixty-four (68%) of the 94 patients were female. mostly because they spend more time outside than females do. Ninety-six percent of the bites occurred outside, and over seventy percent occurred at night. The majority of patients, or 41 (43.6%), presented between two and four hours after being bitten by a Russell viper (27 patients, or 28%), and 67 patients were bitten by other snakes that were not identifiable. Seven (7.5%) of the hematotoxic bite's complications showed signs of bleeding when they were first seen. Fifty (53%) of the 94 individuals who had bite presentations at that time did not have any problems. The most prevalent Russell's viper complication among the population of South India was cellulitis, which was found in 20 (21%) of the bite cases. AKI was found in 13 (13.8%) cases, and cellulitis plus AKI was found in 11 (11.7%) cases. Therefore, it is now widely acknowledged that a rigorous categorization is invalid for hepatotoxic snakebite because any species can result in any form of manifestation.

25 patients, or 26% of the total, showed up two hours after the snake bite. Delays in referral, transportation, and awareness were the main causes for the 41 (43.6%) patients who presented between 2-4 hours and the 28 (29.8%) patients who arrived at the tertiary hospital between 4-6 hours.

Of the patients that showed up in 0–2 hours, 1 (4%) did not need ASV. Due to dry bite, 10 (56%) of the patients needed 10 vials of ASV, 9 (36%) needed 20 vials, and 1 (4%), 30 vials. Out of the patients who reached the 2-4 hour mark, 15 (36.6%) needed 10 vials of ASV, 23 (56.1%) needed 20, and 3 (7.3%) needed 30 vials. After 4-6 hours, 4 (14.3%) needed 10 vials, 12 (42.9%) needed 20 vials, and 11 (39.5%) needed 30 vials. Of the patients who reached this point, 1 (3.6%) didn't require ASV due to a dry bite. The average (standard deviation) amount of utilized vials was 14 (6.5) for those who presented between 0 and 2 hours after biting, 17.1 (6) for those who presented between 2 and 4 hours, and 21.8 (8.2) for those who presented between 4-6 hours after biting.

Of the patients who arrived within a two-hour window, nine (36%) experienced complications, whereas the remaining patients did not experience any. Of the patients who came in between two and four hours, 29 (or 70.7%) experienced problems. Of the patients who presented within 4-6 hours, 12 (29.3%) had no issues, 23 (82.1%) had the largest number of difficulties, and 5 (17.9%) had none at all.

Throughout their stay, the patient experienced the following complications: 53 (56%) of them got cellulitis. The majority of patients with cellulitis showed up 2-4 hours after the bite; 25 patients (26.6%) developed renal failure; most patients with renal failure showed up 4-6 hours after the bite; 17 patients (18.08%) developed both cellulitis and renal failure; and 13 patients (13.82%) developed other complications (DIC, sepsis, shock, MODS, ARDS).

Patients who presented within 0–2 hours had a mean (SD) hospital stay of 3.6 (1.3) days. The corresponding figures were 4.7 (1.8) for those who arrived after 2-4 hours and 6.8 (3.5) days for those whose presentation time was between 2-4 hours. This suggests that starting ASV early reduces the amount needed, the number of problems, and the length of the hospital stay. It is also economical in terms of treatment.

The study's mortality rate was 3 out of 91, compared to the 4.5–5 out of 100 fatalities reported nationally each year. Three of them were men, with an average age of forty. Two of them showed up six hours after the bite, and one showed up three hours later with signs of bleeding from two patients. Due to their combined renal insufficiency, all three required hemodialysis.

Two already had co-morbid conditions (essential hypertension). All three suffered from sepsis and cellulitis. Two experienced respiratory failure and ARDS, and one had DIC.

Of the 91 patients who were released from the hospital, 5 (5.3%) underwent hemodialysis, while 1 (1%) required inotrope support.

Of the 94 patients, 41 (43.6%) had prolonged WBCT along with prolonged PT and aPTT, 28 (29.8%) had prolonged PT and aPTT alone, and 2 (2%) of the patients had both WBCT20 and PT-INR, APTT was normal. Of the study population, 64 (68.1%) had PT-INR (>14, >1.4) and aPTT (>35) alone prolongation. The majority of them presented within 2-4 hours of the snake bite. When it came to differentiating participants with aberrant PT/APTT from normal, the WBCT cut off of >20 seconds showed a sensitivity of 30.4%, a specificity of 100%, a positive predictive value of 100%, and a negative predictive value of 3%.

Therefore, using prothrombin time to screen patients will aid in the early detection of coagulopathy, allowing for the earlier administration of antivenom, the prevention of further envenomation problems, and a reduction in the number of vials of ASV required to treat envenomation.

In this study, the median age is 39 years, which is the same as in the study by G. K. Isbister et al.^[9] This median age is lower than the 40 years in the study by Indira Ratnayake et al.^[10] 36 was the median age in the study by Vikram Thakur et al.^[11] It is 35 years in the study by Rekha Thapar et al.^[12] The majority of people in this age bracket work outside.

64 (68.1%) males were bitten in the current study, compared to 109 (75%) in the studies by G.K. Isbister et al. and 790 (80%) in the studies by Indira Ratnayake et al. In the research by Vikram Thakur et al., 23 (38%) and 37 (62%) of the males were bitten. In the study by Rekha Thapar et al., 63 (31.8%) girls and 135 (68.2%) males were bitten. Male patients accounted for the majority of bites, which is understandable given the rise in outdoor activity.

In every comparison study, the majority of bites occurred outdoors: 86 (91.5%) in the present study, 140 (96%) in the G.K. Isbister et al. study, 149 (82.7%) in the Halesha B.R. et al.^[13] investigation and 167 (75%) in the study by Rituparna Ghosh et al.^[14]

The majority of the cases were bitten at night since there are more people out and about at night. This is similar to studies by Rituparna Ghosh et al. and Gaurav Bhalla et al., where 162 (73%) and 109 (73%) of the patients, respectively, were bitten at night. In the current study, 64 (68.1%) of the patients were bitten at night. The majority of patients in the studies by Rekha Thapar et al. and Halesha B. R. et al. were bitten during the day, 101 (51%) and 127 (71%) of them, respectively. The bulk of cases in both studies arrived at the hospital in the evening.

The current study found that 27 (29%) of the patients were bitten by vipers; as most bites happened at night and the patients were unable to identify the snake, this is similar to studies by Halesha B. R. et al. and Gaurav Bhalla et al. that found that 58 (32%) and 42 (28%) of the patients were bitten by vipers, respectively. The study by Rituparna Ghosh et al. had the most viper bites (182; 82%), whereas the study by Rekha Thapar et al. had the fewest (41; 21%).

In the current investigation, all 94 patients (100%) showed up within 6 hours of the bite; in the study by Rekha Thapar et al., 160 individuals (80.9%) did the same. In the studies by Halesha B.R. et al. and Gaurav Bhalla et al., 70 (39%) and 64 (43%) patients presented more than six hours after bite due to delayed transportation, delayed referral, home-based care, and receiving treatment from traditional healers, respectively.

In this study, the majority of patients-87, or 92.6%-did not exhibit any bleeding symptoms at the time of presentation. This is similar to studies by Halesha B.R. et al., in which 154 patients-or 86%-did not exhibit any bleeding symptoms, and by Rekha Thapar et al., in which 159 patients-or 80%-did not exhibit any bleeding symptoms at all owing to a later presentation and fewer bites from vipers.

Compared to previous research, the Gaurav Bhalla et al. study had a higher number of

patients (66, or 44%) who had bleeding manifestations at presentation because of a delayed presentation and more viper bites.

The most common complication among snake bite patients in the current study is 53 (56%), which is similar to the findings of Halesha B.R. et al. study, where cellulitis developed in 64 patients (59%). In the current study, 25 (27%) patients developed AKI, which is comparable to the 44 (20%) individuals in the Rituparna Ghosh et al. study. The current study reveals that only 13 (14%) of the major problems (ARDS, DIC, and respiratory failure) are present. This aligns with the findings of Gaurav Bhalla et al. study, which found that 32 patients (21.3%) had similar problems to those in the current investigation. Delays in presentation time and ASV administration lead to complications.

Three patients (3.2%) in the current study perished from a snake bite, which is equivalent to the death rates of seven patients (3.8%), six patients (3%), and seven patients (4.6%) in the three previous investigations (Halesha B.R. et al., Rekha Thapar et al., and Gaurav Bhalla et al.). According to every study, the causes of death are life-threatening complications at presentation (DIC, sepsis, MODS, ARDS, respiratory failure, AKI), as well as delayed presentation.

The mean ASV requirement in the current study is 17.7 vials, which is consistent across the three experiments. The average number of ASV vials needed for the studies by Halesha B.R. et al., Rituparna Ghosh et al., and Gaurav Bhalla et al. were 18.6, 16.5, and 18.5, in that order. WBCT20 was performed at the time of admission in 140 out of the 145 Russell's viper bites with VICC in the G.K. Isbister et al. study. 56/140 individuals had a favorable result [sensitivity 40%; 95% CI: 32–49%]. Antivenom delivery was delayed as a result of a negative test [median delay for WBCT20–ve tests was 1.78 hours (IQR: 0.83–3.7) compared to a median delay of 0.82 hours (IQR: 0.58–1.48) for WBCT20 + ve tests; $p = 0.0007$]. Five patients who did not present with coagulopathy had a negative WBCT20 result. This suggests that in this context, WBCT20 showed excellent specificity for admission [100% (95% CI: 94–100%)].

In this study, coagulopathy is deemed positive when the INR is greater than 1.4. The WBCT20 minute at admission had a sensitivity of 40% (95% CI: 32–49%), and in this particular situation, the specificity of admission was 100% (95% CI: 94–100%) in the study by G.K. Isbister et al., with 100% PPV, 5.6% NPV, and 42.07% diagnostic accuracy.

WBCT20 was performed on 112 patients at admission in the Manisha V. Biradar et al.^[15] study. Of the 66 patients who had coagulopathy (INR >1.5 is considered positive for coagulopathy in this study), 33 patients had positive WBCT20 results, and 41 patients had negative WBCT20 results out of 46 patients who had no coagulopathy (INR \leq 1.5). Upon statistical analysis, the test's sensitivity was 50% and its specificity was 89.13%. With a sensitivity of 50%, the WBCT20 could accurately diagnose only 50% of disease cases, displaying the remaining 50% as negative.

Diagnostic accuracy was 66.07%, NPV was 55.41%, and PPV was 86.84% in the study of Manisha V. Biradar et al.

The study by Indira Ratnayake et al. ran both the WBCT20 and the PT on admission samples from 987 snake bites. In this group, there were 79 patients with VICC (8%). There was no coagulopathy in 13/908 of the 65/79 VICC-positive patients who tested positive for WBCT20 (sensitivity 82%; 95% confidence interval [CI]: 72-90%). 14/79 cases of VICC and 895/908 snake bites without coagulopathy had false negative results from the WBCT20 (specificity: 98%, 95% CI: 97-99%). When performed by qualified clinical personnel, the WBCT20 test had a fair degree of sensitivity for the diagnosis of VICC, although it missed roughly one-fifth of cases in which antivenom may have been required.

PPV was 83.3%, NPV was 98.46%, and diagnostic accuracy was 97.26% in the study by Indira Ratnayake et al. The great sensitivity and diagnostic accuracy of WBCT20 can be attributed to testing conducted by skilled clinical personnel using a standardized test protocol.

In G. K. Isbister et al. study, 140 Russell's viper bites with coagulopathy underwent admission using WBCT20. The results showed that 56/140 cases had positive results [sensitivity 40% (95% confidence interval (CI): 32–49%)].

The sensitivity is 50% and the specificity is 89.13% in the study of Manisha V. Biradar et al. 79 patients (8%) with VICC were included in the study by Indira Ratnayake et al. 65/79 individuals with VICC had positive results from the WBCT20 test (sensitivity 82%; 95% confidence interval [CI]: 72–90%), while 13/908 patients without coagulopathy had false positive results. With no coagulopathy, the WBCT20 was negative in 895/908 snake bites (specificity: 98%, 95% confidence interval: 97–99%), and it was mistakenly negative in 14/79 cases involving VICC.

The current study, which included 94 patients, has a 100% specificity and a 30.4% sensitivity. The present study has a high PPV, and the highest PPV, NPV diagnostic accuracy were noted in Indira Ratnayake et al. study due to the standardization of the test procedure and competent clinical staff carrying out the procedure. The diagnostic accuracy of the WBCT20 is the lowest when compared to other studies. PPV and NPV diagnostic accuracy in the present study are 100%, 3%, and 31.91%, respectively.

The present study's false negative rate of 69.6% is comparable to that of G.K. Isbister et al., study, which found a false negative rate of 60%. Manisha V. Biradar et al., study found a false negative rate of 50%, while Indira Ratnayake et al., study had the lowest false negative rate, at 18%, thanks to test administration by qualified clinical staff and standardization of procedure.

CONCLUSION

Prothrombin time is a more accurate and earlier indicator of toxicity than the WBCT (Whole Blood Clotting Test); yet, both tests are considered abnormal in patients who arrive at the hospital late. In this case, bedside-performed WBCT20 provides an early warning of poor coagulation, as opposed to PT, which is done in a lab.

- **Cost:** The evaluation increases in cost due to the need for frequent testing to detect coagulopathy earlier than with WBCT20 and the requirement for reagent use.
- **Laboratory Support:** In remote rural health centers, centrifugation and other reagents may not be available for prothrombin time measurement. Under these conditions, WBCT20 administered at the bedside is superior to prothrombin time.
- **Simplicity of WBCT20:** While bedside examination does not require a skilled lab professional, prothrombin time measurement must. The WBCT20 is a simple test that anyone with a basic understanding of laboratory techniques may administer.
- **Small Sample Size:** The number of patients studied in this study was only 94.

Hence, no major conclusions can be drawn.

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