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ORIGINAL RESEARCH

Study of international normalized ratio and whole blood clotting time in patients with vasculotoxic snake bite at a tertiary hospital

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ABSTRACT

Background: Snake bite is a major health problem throughout the world, more so in tropical and sub-tropical countries. One of the most important effects of snake envenomation is hematologic abnormalities including coagulopathy, most commonly a venom-induced consumption coagulopathy (VICC). Present study was aimed to study international normalized ratio and whole blood clotting time in patients with vasculotoxic snake bite at a tertiary hospital. Material and Methods: Present study was single-center, prospective, comparative study, conducted in patients of age > 18 years, either gender, with history of snake bite, features suggestive of hemotoxic envenomation - Rapid extension of local swelling from site of bite or early spontaneous systemic bleeding or early systemic symptoms of collapse (hypotension and shock) or passage of cola coloured urine OR Whole blood clotting time more than 20 minutes OR INR > 1.5. Results: In present study, out of 91 snake bite cases, 51 cases were vasculotoxic (56.04 %). Mean age of study patients was 35.23 ± 11.34 years, majority were male (60.78 %). Among 51 cases, 20-minute WBCT was positive in 23 cases (45.1 %) & negative in 28 cases (54.9 %). Based on INR, Coagulopathy (INR >1.5) was noted in 30 cases (58.82 %) & Non-coagulopathy (INR ≤1.5) was noted in 21 cases (41.18 %). Sensitivity and specificity of 20-minute WBCT (by considering INR as standard) was 60 % & 76.19 % respectively. Positive predictive value & negative predictive value of 20-minute WBCT (by considering INR as standard) was 78.2 % & 57.14 % respectively. Conclusion: Sensitivity, specificity, positive predictive value & negative predictive value of 20-minute WBCT (by considering INR as standard) was 60 %, 76.19 %, 78.2 % & 57.14 % respectively.

Keywords: international normalized ratio, whole blood clotting time, vasculotoxic, snake bite, coagulopathy

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INTRODUCTION

Snake bite is a major health problem throughout the world, more so in tropical and sub-tropical countries. Snake bite constitutes important cause of morbidity and mortality in the hills due to abundant vegetation, long rainy season, scattered population using forest paths for farming and collecting fodder for livestock makes people living in these areas particularly prone to snake bite.[1,2]

Four species popularly known to be dangerously poisonous to man are spectacled cobra (Naja naja), common krait (Bungarus caeruleus), saw-scaled viper (Echis carinatus) and Russell's viper (Daboia russelii). The most common poisonous snake among them is common krait.[3] Viperine vasculotoxic snake bite is a cause of severe morbidity and mortality in our country. The bleeding diathesis by viperine envenomation can be successfully reversed with anti-snake venom.

One of the most important effects of snake envenomation is hematologic abnormalities including coagulopathy, most commonly a venom-induced consumption coagulopathy (VICC).[4,5] Unfortunately, as most snakebites occur in remote geographical locations, conventional clotting assays are not commonly available. As a result, a number of bedside tests are used to detect clotting abnormalities—these include the 20-minute whole blood clotting test (20WBCT), 30-minute whole blood clotting test (30WBCT), capillary blood clotting time, Lee-White clotting test and Vellore manual activated clotting time (VeMac).[6,7,8] Present study was aimed to study international normalized ratio and whole blood clotting time in patients with vasculotoxic snake bite at a tertiary hospital.

MATERIAL AND METHODS

Present study was single-center, prospective, comparative study, conducted in department of general medicine, at BKL Walawalkar Rural Medical College & Hospital, Ratnagiri, India. Study duration was of 2 years (January 2021 to December 2022). Study approval was obtained from institutional ethical committee.

Inclusion criteria

- Patients of age > 18 years, either gender, with history of snake bite, features suggestive of hemotoxic envenomation - Rapid extension of local swelling from site of bite or early spontaneous systemic bleeding or early systemic symptoms of collapse (hypotension and shock) or passage of cola coloured urine OR Whole blood clotting time more than 20 minutes OR INR > 1.5,

Exclusion criteria

- Pregnant females,
- Initial negative WBCT followed by negative WBCT at 6 hours after presentation,
- Patients presenting after 72 hours of snake bite, had non envenomous/ neurotoxic snake bites,
- Patients receiving anti-coagulants or had coagulopathy due to any other reasons

Study was explained to patients close relatives in local language & written consent was taken for participation, treatment, investigations and research purpose. After the probable clinical diagnosis of snake bite, the blood sample was drawn from all the snake bite patient under aseptic precautions. Investigations include Haemoglobin (Hb), Total count, Platelet count, Bleeding time, Clotting time, Whole blood clotting test (WBCT), Prothrombin time (PT), Activated partial thromboplastin time (APTT), International normalized ratio (INR), Fibrin degradation products (FDP), Creatine kinase, Blood urea, Serum creatinine, Serum bilirubin, Serum potassium and other additional investigation (Urine, CPK-MB, ECG, Chest X ray and USG) if required done just after admission in the casualty department. The complete blood count and platelet counts were confirmed by peripheral examination of smears.

Bedside tests such as bleeding time of patient was done by Dukes method & clotting time is done by capillary method. The patients with positive result of 20 minutes WBCT and clinical picture of poisonous snake bite were started with polyvalent ASV immediately.

The patient was followed up till the discharge. The treatment and outcome data were noted in the proforma along with the results of all the investigations. The categorisation of snake bite

into non-venomous, vasculotoxic and neurotoxic bite was done after considering the clinical data and all the investigations result.

Data was collected and compiled using Microsoft Excel, analysed using SPSS 23.0 version. Frequency, percentage, means and standard deviations (SD) was calculated for the continuous variables, while ratios and proportions were calculated for the categorical variables. Difference of proportions between qualitative variables were tested using chi-square test or Fisher exact test as applicable. P value less than 0.05 was considered as statistically significant.

RESULTS

In present study, out of 91 snake bite cases, 51 cases were vasculotoxic (56.04 %), while 51 cases were neurotoxic (56.04 %) & 51 cases were nonvenomous snake bite (40.66 %).

Table 1: Distribution of snake bite cases according to clinical presentation.

Clinical diagnosis	Total cases	Percentage (%)
Non-Venomous Snake Bite	37	40.66
Venomous Snake Bite		
Vasculotoxic snake bite	51	56.04
Neurotoxic snake bite	3	3.3
Total	91	100

Mean age of study patients was 35.23 ± 11.34 years, majority were male (60.78 %).

Table 2: General characteristics

Characteristics	No. of patients/ mean ± SD	Percentage
Mean age (years)	35.23 ± 11.34	
Gender		
Male	31	60.78
Female	20	39.22

In present study, among 51 cases, 20-minute WBCT was positive in 23 cases (45.1 %) & negative in 28 cases (54.9 %). Based on INR, Coagulopathy (INR >1.5) was noted in 30 cases (58.82 %) & Non-coagulopathy (INR ≤1.5) was noted in 21 cases (41.18 %). Sensitivity and specificity of 20-minute WBCT (by considering INR as standard) was 60 % & 76.19 % respectively. Positive predictive value & negative predictive value of 20-minute WBCT (by considering INR as standard) was 78.2 % & 57.14 % respectively.

Table 3: Determination of sensitivity and specificity of 20-minute WBCT (by considering INR as standard) (n=51)

20-minute WBCT	Presence of coagulopathy based on INR		Total
	Coagulopathy (INR >1.5)	Non-coagulopathy (INR ≤1.5)	
Positive	18 (35.29 %)	5 (9.8 %)	23 (45.1 %)
Negative	12 (23.53 %)	16 (31.37 %)	28 (54.9 %)
Total	30 (58.82 %)	21 (41.18 %)	100

Sensitivity = TP/ (TP + FN).	60
Specificity = TN/ (TN + FP).	76.19
Positive Predictive Value (PPV) = TP / (TP + FP)	78.26
Negative Predictive Value (NPV) = TN / (TN + FN)	57.14

DISCUSSION

Snake bite is an important cause of morbidity and mortality among the poor, rural tropical population and management of medical emergencies like snake bite in mountainous terrains

is a challenge in itself. Due to lack of commercial diagnostic kits, the identification of snake species depends upon experience of the clinicians and symptoms of envenomation such as fang marks, local swelling, spontaneous systematic bleeding from gums, respiratory failure, cardiac arrest and/or neuromuscular paralysis, which guide the physician to predict the species of snake involved.[2,9]

Snake venoms, especially those of Viperidae contain molecules that act on the coagulation, fibrinolytic, complement and kinin system producing effects like local tissue damage, causing edema and ecchymosis, vascular endothelial damage, hemolysis, disseminated intravascular coagulation (DIC) and various systemic effects causing pulmonary, cardiac, renal and neurologic defects.[10,11] Venom alters the capillary membrane permeability, causing extravasation of electrolytes, albumin, and red blood cells through vessel walls into the envenomated site.

The 20min whole blood clotting test (WBCT20) is a simple bedside test recommended by World Health Organization (WHO) to assess hemotoxic envenomation and guide administration of polyvalent anti-snake venom (ASV). [12] The 20min whole blood clotting test (WBCT20) requires only a clean glass tube to perform and is routinely used to identify and treat patients with clinically significant venom-induced consumption coagulopathy (VICC).[13,14] The test should be carried out in a clean, dry, glass tube completely free of detergent. Deviations from this protocol such as the use of poorly rinsed glassware or any non-glass tubes can alter the outcome of the test and lead to inaccurate interpretation.[15] However, reliability and validity of this test has not been well documented in literature.

In study by Dsilva AA et al., 17 of 60 patients had evidence of hemotoxic envenomation. 4 patients had combined neurotoxicity and hemotoxicity. Sensitivity and specificity of WBCT20 were 94 and 76%; positive and negative LR were 3.9 and 0.08, respectively. WBCT20 is a highly sensitive test with excellent reliability for detecting envenomation. However, the false positive rate in this study was 24%. Asymptomatic snake bite patients with a positive WBCT20 but no corresponding clinical signs of envenomation should be tested using PT/INR before receiving ASV to prevent unnecessary waste of anti-venom.

In study by G.Kamala,[17] mean age of patients was 42.58 years and male to female ratio was 3.85:1. Local symptoms occurred in all the patients, systemic symptoms in 94%, bleeding manifestations in 82%, acute renal failure in 51.9%. Mean time to reach hospital was 15.80 ± 5.7 hours. In this study 106 paired tests (simultaneous WBCT and INR) were obtained. Ten times WBCT turned out to be prolonged with an INR < 1.5 and seventeen times WBCT turned out to be normal in spite of INR > 1.5. Monitoring of venom-induced consumption coagulopathy (VICC) using INR in addition to WBCT resulted in administering more ASV doses and a better renal outcome (oliguria duration, and lesser hemodialysis) in the subgroup of patients with SOFA> 4.

Mahendra A. Patil et al.,[18] studied 158 cases of snake bite, 98 (59.4%) cases were venomous snake bite cases. Out of the 98 venomous snake bite cases, 91 (55.4%) cases were vasculotoxic snake bite and 07 (4.2%) cases were neurotoxic snake bite. We observed a positive result of 20-minute whole blood clotting test (WBCT) in 53 (58.2%) vasculotoxic snake bite cases. The sensitivity of 20-minute WBCT was 66.2% and specificity was 97.5%. Local pain was the most common local symptom observed in 133 (84.2%) cases followed by swelling at the site of bite which comprised of 127 (80.4%) cases.

In study by Manisha V B[19], PT was raised in 85 (75.89%) cases and APTT in 77 (68.75%) cases. Out of 85 patients with raised PT, 19 (16.96%) had incoagulable plasma and rest had PT more than 16seconds. Amongst the 77 patients with raised APTT, 19 (16.96%) had incoagulable plasma and remaining had APTT higher than 32seconds but not incoagulable. Patients reaching to hospital between 1 to 6 hours and after more than 6 hours accounted for 67 and 27 respectively, out of them PT was raised in 51 (76.12%) and 24 (88.89%) patients.

This was statistically significant. Sensitivity of the20 Minute WBCT test was 50% and specificity was 89.13%.

In the absence of laboratory clotting assays, the 20WBCT remains a highly specific and fairly sensitive bedside test at detecting coagulopathy following snakebite. However, clinicians should be aware of the importance of operator training, standardized equipment and the lower sensitivity of the 20WBCT at detecting mild coagulopathy and resolution of coagulopathy following antivenom.[20]

A major difficulty is that many hospitals where snakebites are common, cannot afford to provide a new, unwashed, un-recycled bottle, tube, syringe or other vessel for each test and ordinary glass tubes/vessels may be difficult to purchase in this age of plastic. However, the commonly used recycled glass antibiotic bottles can be made suitable and reliable, provided that they are cleaned by washing with "normal 0.9% saline" for intravenous infusion, without any added detergent of other cleansing agent, followed by hot air drying.[21]

WBCT requires no sophisticated laboratory testing and resource‐limited hospitals can easily perform this at the bedside. To increase sensitivity & specificity of this test, future research is required to assess the speed and accuracy of the test in diagnosing hemotoxic envenomation and its potential role in guiding antivenom therapy. As prevention is always better than cure, public awareness, and population‐based programs have to be conducted to spread the message of snake bite prevention, first aid, and early treatment which are the main pillars of adequate snake bite management.

CONCLUSION

Sensitivity, specificity, positive predictive value & negative predictive value of 20-minute WBCT (by considering INR as standard) was 60 %, 76.19 %, 78.2 % & 57.14 % respectively. In the absence of laboratory clotting assays, the 20WBCT remains a highly specific and fairly sensitive bedside test at detecting coagulopathy following snakebite

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