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A Prospective Observational Study on Early Use of Fresh Frozen Plasma for Coagulopathy in Patients with Haematotoxic Snake Bite Envenomation

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Abstract: *Snake bite can lead to hematotoxicity which can lead to fatal hemorrhages which is termed as Venom Induced Consumptive Coagulopathy (VICC). The administration of exogenous coagulation factors in the form of fresh frozen plasma (FFP), can restore normal coagulation before endogenous factors are produced. Aim of the current study is to study on early use of fresh frozen plasma (FFP) in patients with Venom Induced Consumptive Coagulopathy (VICC).*

At admission all snakebite victims with WBCT >20 min recieved ten vials of ASV according to World Health Organization (WHO) criteria. Then, after 6 hours, patients with Whole Blood Clotting Time(WBCT) >20 min were divided into control and test groups. Control group received only ten ASV vials whereas test group received both ten ASV vials and four units of FFP. Results depicted that there was higher percentage (83.30%) of clotting incidences in test group as compared to control group (66.70%). In conclusion, earlier reversal of coagulation defect was observed where FFP was used along with second dose of ASV.

Keywords: *Snake envenomation, FFP, ASV, Coagulopathy, Clotting factors*

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I. Introduction

Snakebite envenoming is a neglected tropical disease that kills >100,000 people and harms >400,000 people every year. Snake venoms are complex mixtures of proteins that exert a wide range of toxic actions. The high variability in snake venom composition is responsible for the various clinical manifestations in envenomings, ranging from local tissue damage to potentially life-threatening systemic effects. Intravenous administration of antivenom is the only specific treatment to counteract envenoming. Analgesics, ventilator support, blood products, fluid therapy, haemodialysis and antibiotic therapy are also used. Novel therapeutic alternatives based on recombinant antibody technologies and new toxin inhibitors are being explored.[16]

The venom of snakes of the genus *Pseudonaja* contains prothrombin activators which initiate unchecked procoagulation in human blood. This process is recognised clinically as disseminated intravascular coagulation (DIC), it exhausts the supply of circulating coagulation factors and exposes the envenomated victim to the risk of spontaneous haemorrhage. In addition, uncontrolled coagulation may obstruct small calibre blood vessels which could cause ischaemia in vital tissue, including the myocardium.[1] Snakebite, a neglected global public health problem.[2,3] Snakebites and their related mortality are most common in India, but have a varied distribution across the country.

The treatment of Venom-induced consumption coagulopathy (VICC) is the administration of anti-snake venom which is assumed to bind to the numerous components of snake venom including its prothrombin activators. However, antivenom as such does not restore plasma coagulation factor levels instead it merely allows newly produced hepatic coagulation factors to accumulate in the blood without getting attacked by prothrombin activators. However, but the dose has to be repeated several times, at 6-hour intervals, to restore the blood coagulability permanently. Lack of availability, cost and risk of allergic reactions are some of the important considerations related to the use of anti-snake venom (ASV).[4,5]

The administration of exogenous coagulation factors in the form of fresh frozen plasma (FFP), can restore normal coagulation in the intervening time of many hours before endogenous factors are produced. However, there are disputes exist on FFP that may provide a substrate which actually worsens coagulopathy.[6]

With this viewpoints, we designed the current study with the main aim to evaluate early use of FFP in patients with haematotoxic snake bite for its role in restoration of clotting function and coagulopathy.

II. Material And Methods

Study design

This tertiary care observational study was conducted at Department of Emergency Medicine, J. J. M Medical College, Davangere, Karnataka from June 2021 to November 2021. The study was approved by the institutional ethics committee of J. J. M Medical College. The study aim was explained for patients and informed written consent was obtained from all the participants.

Study subjects

A total of 40 patients admitted to emergency department of Department of Emergency Medicine, J. J. M Medical College, Davangere with history of snakebite and who is having persistent VICC inspite of administering 10 vials of ASV, and fulfilling the following inclusion and exclusion criteria were enrolled.

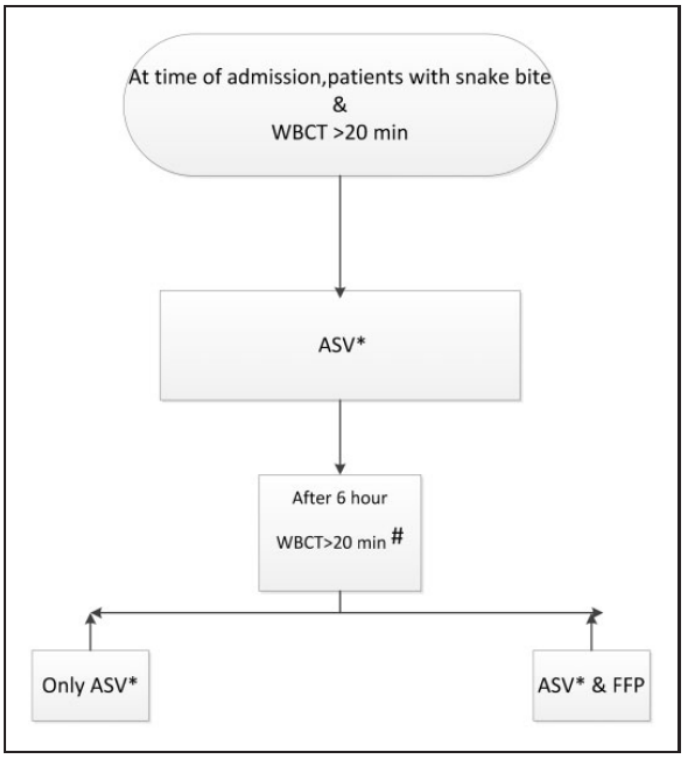
Inclusion criteria

- Patients who are above 18 years of age.
- Snakebite victims with a whole blood clotting time (WBCT) >20 min after 6 hours of administration of first dose of ASV

Exclusion criteria

- Patients with deranged RFT and fluid overload state
- Patients with bleeding diathesis and underlying Liver Disease
- Patients who got discharged against medical advice
- Patients with neurotoxicity and who are on ventilator
- Patients less than 18 years of age
- Patients with prior history of allergy to blood products

Patients' demographic data were recorded in proforma datasheet. At admission all snakebite victims with WBCT >20 min received ten vials of ASV according to World Health Organization (WHO) criteria. Then, after 6 hrs., patients with WBCT >20 min were divided into two groups viz. control and test groups at the discretion of the treating physician. Control group received only ten ASV vials and Test group received both ten ASV vials and four units of FFP. The diagrammatic representation of treatment procedure was depicted as below.



Statistical analysis

The collected data was analysed using statistical package for social sciences (SPSS) IBM, version 20. The data are presented as frequency, mean and standard deviation as appropriate. Differences in the findings between the two groups were examined by using chi-square tests for comparison of categorical variables. $p<0.005$ was considered statistically significant**.**

III. Result

Majority of the study subjects i.e., 27.80% each were in the group of 21-30 & 41-50 years of age in control group. Whereas in test group majorly (33.30%) of study subjects belonged to age group of 31-40 years. The mean age of study subjects in control & case group was found to be 40.89 ± 11.83 & 43.89 ± 13.42 respectively. Slightly male predominance (55.60%) was observed as compared to females (44.40%) in control group. Whereas, in test group equal distribution of male and females was observed (Table 1).

Table 1: Distribution of study subjects based on demographics

Variables	Control Group		Test Group	
	N	%	N	%
	Age			
10 – 20 years	0	0.00	0	0.00
21 – 30 years	5	27.80	3	16.70
31 – 40 years	4	22.20	6	33.30
41 – 50 years	5	27.80	5	27.80
51 – 60 years	3	16.70	0	0.00
61 – 70 years	1	5.60	3	16.70
71-80 years	0	0.00	1	5.60
Mean ± S.D	40.89 ± 11.83		43.89 ± 13.42	
Minimum	21		21	
Maximum	62		72	
	Gender			
	N	**%**	**N**	**%**
Male	10	55.60	9	50.00
Female	8	44.40	9	50.00

There was higher percentage (83.30%) of WBCT >20 clotting incidences in test group as compared to control group (66.70%). The finding depicted that early administration of FFP along with second ASV dose would promote the clotting factors (Table 2).

Table 2: Comparision of incidences of WBCT >20 on clotting function

Variables	Control Group		Test Group	
	Clotted	Not Clotted	Clotted	Not Clotted
	N (%)	N (%)	N (%)	N (%)
WBCT > 20 at Admission	0	18 (100)	0	18 (100)
WBCT > 20 After 6 hrs of ASV	0	18 (100)	0	18 (100)
WBCT > 20 After 6 hours of ASV 2nd Dose	12 (66.70)	6 (33.30)	15 (83.30)	3 (16.70)
Chi-square (χ^2) = 1.800				
P = 0.180				

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IV. Discussion

The coagulation defect seen in VICC is due to consumption of fibrinogen, factor V, factor VIII and prothrombin. Coagulopathy may be reversed by ASV administration, but for complete neutralization of venom, a large quantity of ASV is required. Though ASV neutralizes venom, resynthesis of coagulation factors take 24–48 h which again places the patient at high risk of bleeding.[7] This provides the official basis for the use of FFP. The current advice of the Association of Physicians of India, based on the WHO guidelines, recommends an initial administration of ten vials of ASV for in patients with WBCT>20 followed by repeat doses every 6 h based on the WBCT result.[8] Hence we designed the present prospective observational study at tertiary care hospital with the main goal to study on early use of fresh frozen plasma (FFP) for coagulopathy in patients with haematotoxic snake bite envenomation.

Our study findings delineated that There was higher percentage (83.30%) of WBCT >20 clotting incidences in test group as compared to control group (66.70%). The finding depicted that early administration of FFP along with second ASV dose would promote the clotting factors. These findings are in concurrence with various other research studies reported in the literature. FFP alone has been administered to snakebite victims with coagulopathy with desirable outcomes.[7,9,10] A study done in Australia showed administration of FFP hastens recovery but is less effective when administered in <4h.[7] Two small observational studies suggest that the administration of FFP after a course of ASV reduces the number of vials of ASV required for treatment of snakebite.[11,12]

Furthermore, studies reported by Lallo *et al.*, and Johnston *et al.*, demonstrated the benefit of antivenom is measured in hours, particularly within the first 6 h post-bite.[13,14] Isbister *et al.*, reported that FFP in snakebite showing a highly significant improvement in coagulopathy.[15]

In summary, we clearly showed a more rapid reversal of coagulation defect where FFP was used. FFP is easily available throughout the world, even in many resource-poor countries such as India, at a price lower than ASV. Therefore, if supplies of ASV are conserved and faster recovery is achieved, its use should be considered and suitable protocols introduced

V. Conclusion

In conclusion, it was demonstrated based on the findings of our study that early use of FFP along with second dose of ASV in patients with haematotoxic snake bite would promote the clotting of blood. Early reversal of coagulation defect was observed where FFP was used.

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