

# Can Fresh Frozen Plasma Prevent Acute Kidney Injury after Hump-Nosed Viper Bite?

**Kolitha H. Sellahewa**

Department of Medicine, Melaka Manipal Medical College, Melaka, Malaysia  
Email: kolithah@gmail.com

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## ABSTRACT

Hump-nosed viper bite is the commonest venomous snakebite in Sri Lanka. Acute kidney injury (AKI) in association with coagulopathy is an important cause of mortality. Immunomodulating effects of fresh frozen plasma (FFP) could block the nephrotoxic effects of venom; and by replenishing depleted clotting factors resulting from venom induced consumption coagulopathy could offer an additional benefit in offsetting renal injury triggered by haematological disturbances. In a non-randomised observational study carried out from 2005 to 2008 in adults at the National hospital of Sri Lanka, the mean time for resolution of coagulopathy among 42 patients treated with FFP at the inception of coagulopathy was 4.7 hours compared to 18 patients treated with isotonic Saline among whom the mean time for normalisation of coagulopathy was 6.2 hours. None of these 60 patients developed acute renal failure. A separate cohort of 32 patients with coagulopathy after hump-nosed viper bite who had not received FFP during this study period developed acute renal failure and required haemodialysis. In the absence of safe and effective antivenom for hump-nosed viper in Sri Lanka, FFP may be a therapeutic option. FFP if given early to selected patients at inception of coagulopathy may prevent AKI and serve to save lives after hump-nosed viper bites.

**Keywords:** Hump-Nosed Viper Bite; Acute Kidney Injury; Fresh Frozen Plasma

## 1. Introduction

Hump-nosed viper bite is the most common venomous snakebite in Sri Lanka responsible for 22% - 77% of all snakebites [1-3]. Until recently it was considered to be a moderately venomous snake, however many deaths have been reported from time to time particularly in the recent past, so that it is now considered a highly venomous snake [4]. Even though systemic effects are rare these do occur, the commonest of which is coagulopathy [5-8]. All the reported deaths from hump-nosed viper bite had coagulopathy and acute kidney injury (AKI). The only antidote for snakebite is antivenom. In Sri Lanka poly-specific antivenom is used which is imported from India and is raised against the venoms of *Naja naja*, *Bungarus caeruleus*, *Daboia russelii*, and *Echis carinatus*, but not against hump-nosed viper (*Hypnale* spp.). The currently available antivenom is ineffective for hump nosed viper bite and is associated with a high incidence of adverse reactions including anaphylaxis and death [9-12]. In the absence of safe and effective antivenom for hump nosed viper bite a search for optional pharmacotherapeutic interventions addressing the critical clinical effects of systemic envenomation responsible for mortality was performed.

## 2. Hypothesis

Fresh frozen plasma (FFP) by immunomodulation could prevent venom mediated renal injury by acting at a site lower down the cascade of events that eventually lead to tissue injury. FFP by replenishing depleted clotting factors may also be useful in correcting the coagulopathy.

## 3. Method

An observational study was carried out at the National Hospital of Sri Lanka from March 2005 to June 2008.

### 3.1. Patients

All patients admitted to one adult medical unit with a diagnosis of having been bitten by hump-nosed vipers that developed coagulopathy were studied. Only those patients who brought the dead or live snakes that were identified as hump-nosed vipers by the attending physician were included in the study. However species identification as *H. hypnale*, *H. nepa*, or *H. zara* was not done. Coagulopathy was inferred by the detection of a positive 20 minute whole blood clotting test (20WBCT) which was performed in all patients on admission and then every 4 hours up to 24 hours. 20WBCT was performed

by adding 3 ml of blood to a clean dry glass test tube and leaving it undisturbed for 20 minutes. At The end of 20 minutes the tube was tilted, if the blood flowed the test was considered positive and if a clot was formed and blood did not flow the test was deemed negative.

### 3.2. Investigations

Detailed haematological and biochemical investigations were done in the patients with a positive 20WBCT. These constituted full blood count, prothrombin time (PT), activated partial thromboplastin time (APTT), blood urea nitrogen, serum creatinine, and serum electrolytes. Blood samples were collected for PT and international normalized ratio (PT/INR) and APTT by adding 1.8 ml of whole blood into a bottle which contained 0.2 ml of prothrombin citrate. These tests were repeated daily. All laboratory analyses were done in the hospital laboratory.

### 3.3. Interventions

The patients who developed coagulopathy received either an infusion of FFP at a dose of 15 ml/kg body weight or isotonic Saline. Saline infusion was adjusted to maintain an hourly urine output of 0.5 ml/kg body weight. The patients were not randomised, and the decision to use FFP or Saline was ad hoc at the discretion of the physician on an individualised clinical judgement of the overall clinical condition of the patient. Written informed consent was taken from all the patients prior to intervention. 20WBCTs were then repeated 4 hourly up to 24 hours after the intervention. FFP was repeated every 4 hours until the coagulopathy was normalised.

### 3.4. Monitoring and Documentation

In all the patients the clinical status, vital signs, fluid intake, and hourly urine output were monitored. The clinical features and its progression or resolution after intervention were observed and documented. Decision to discharge patients included in the study was made by the same admitting physician.

## 4. Results

### 4.1. Patients and Treatment

All patients were adolescents and adults with an age range of 14 - 69 years. The mean age was 37.3 years. 74.2% were males and 25.8% were females. During the study period 60 patients developed coagulopathy. 42 were treated with FFP and 18 with isotonic Saline.

### 4.2. Outcome

The mean times for normalization of coagulopathy in the two groups were 4.7 hours and 6.2 hours respectively. In

both these groups none developed acute renal failure (ARF) as evidenced by oliguria, elevated blood urea and a rise in the serum creatinine. Mean duration of hospital stay was also similar at 89.3 and 89.3 hours. All the 60 patients except one developed coagulopathy within 24 hours of the bite and was intervened soon after the detection of the first positive 20WBCT. One patient developed hematuria after 48 hours despite the 20WBCTs have been normal within the first 24 hours after the bite. None of the 42 patients treated with FFP developed any adverse sensitivity reactions. During this study period 32 patients who had developed ARF were transferred from the regional base hospital to this same unit for haemodialysis. All 32 patients were bitten by hump nosed vipers (*Hypnale* spp.) and were identified as such by the physician in the base hospital. Perusal of case records from the transferring base hospital revealed that all the 32 transferred patients had developed coagulopathy within the first 24 hours after the bite but none had received FFP.

Out of the 32 patients with ARF 31 recovered after haemodialysis. One patient a 38-year-old woman took a longer time to recover from ARF and required haemodialysis for 2 weeks. Her blood urea and serum creatinine normalised and had an adequate urine output but had low grade pyrexia. She died 10 days after recovering from the ARF and a post mortem examination revealed cerebral aspergillosis. She was dialysed for longer than usual and the source of infection was likely the catheter used for vascular access in the neck.

## 5. Discussion

The most consistent effects of envenomation by the hump nosed viper are local pain and swelling of the bitten limb [13]. Systemic effects are rare and unpredictable. Coagulopathy is the most common systemic effect occurring after hump-nosed viper bite. Overt bleeding of clinical significance such as haematuria, bleeding per rectum, and hematemesis are unusual and coagulopathy is usually detected by laboratory tests of the clotting status.

AKI has been reported in as many as 10% among 302 patients after bites of *H. hypnale* [10]. Association of coagulopathy with AKI has been independently reported by several workers [14-19]. It is likely that common pathophysiological mechanisms are responsible for both these important systemic complications of hump-nosed viper bite. Hump-nosed viper venom contains procoagulant, nephrotoxic, myotoxic and cytotoxic properties. AKI is caused primarily by nephrotoxicity rather than myoglobinuria or haemoglobinuria [15,19]. The procoagulant effects and venom induced consumption coagulopathy can also contribute to renal injury by the deposition of fibrin in the renal microcirculation and microvas-

cular coagulation [19]. Fibrinogen degradation products can perpetuate the bleeding tendency by its antihemostatic effects. These pathogenic mechanisms associated with the hemostatic disturbances seen could be important contributors to AKI apart for the primary venom induced nephrotoxicity. It may even be more important than the direct nephrotoxicity unlike AKI after *Daboia russelli* bites [20]. Interestingly coagulopathy was the earliest systemic manifestation among all the patients who developed ARF in this series. Arguably early correction of coagulopathy may prevent AKI in view of the observation that none of the 42 patients with coagulopathy who received FFP developed ARF; while all the 32 patients with coagulopathy who had not received FFP developed ARF. Whether this observation was a chance occurrence or was causally related to the intervention needs to be ascertained. However all the 18 patients with coagulopathy who were treated with only isotonic saline also recovered completely none of whom developed ARF even though it took a longer time for correction of coagulopathy (mean 6.2 hours) when compared with the group treated with FFP (mean 4.7).

The immunoglobulins in FFP could potentially by immunomodulation prevent nephrotoxin-induced primary renal injury. FFP is an accepted modality of intervention for consumption coagulopathy in a variety of clinical situations. In a similar way FFP by replenishing clotting factors could reverse venom induced consumption coagulopathy and arrest the cascading adverse consequences. Any added benefit in the prevention of AKI could be related to the impact of FFP on the hematopathogenic mechanisms implicated in AKI. In this study coagulopathy normalised earlier in those treated with FFP when compared with the patients who received only isotonic Saline.

## 6. Conclusions

Death due to hump-nosed viper bite though rare does occur. The primary cause for mortality is from complications associated with AKI. All patients who developed ARF developed coagulopathy within 48 hours of the bite. All who developed ARF had coagulopathy before the advent of clinical and biochemical features of ARF. It is possible that early correction of coagulopathy with FFP could prevent AKI and related adverse clinical outcomes.

The 20WBCT detects coagulopathy and can be used as a reliable and early predictor of systemic envenomation. It can easily be done at the bedside without depending on laboratories in resource poor settings where snake bite is common. Owing to the rarity and unpredictability of systemic manifestations and the recognized potential for a fatal outcome in patients with coagulopathy it is prudent that 20WBCT is monitored in all envenomed pa-

tients irrespective of the clinical status on presentation. Observation for at least 48 hours is advocated owing to the possibility of delayed or recurrent manifestation of coagulopathy. Patients who develop coagulopathy as evidenced by a positive 20WBCT should be selected for intensive monitoring and aggressive therapy aimed in the early detection, and treatment of venom induced consumption coagulopathy and thereby retards the advent of acute renal failure.

Thai Red Cross Malayan Pit Viper antivenom because of the close phylogenetic relationship between *H. hypnale* and *C. rhodostoma* may be useful in the treatment of hump nosed viper bite [10,21]. This however is not available in Sri Lanka. The only currently available antivenom in Sri Lanka is indicated for bites from *N. naja*, *B. caeruleus*, *D. russelii*, and *E. carinatus*, but not hump-nosed viper (*Hypnale* spp.). In the absence of safe and effective antivenom or any other specific therapy for hump-nosed viper bite in Sri Lanka I would advocate the use of FFP for selected patients as a safe and probably effective option to reduce morbidity and mortality from hump nosed viper bite in the Sri Lankan setting. This assertion is based on a consideration of the recognized pathogenic mechanisms implicated in hump-nosed viper venom-induced AKI and coagulopathy and application of the known pharmacological benefits of FFP for immunomodulation and consumption coagulopathy to offset these adverse consequences. Personal experience and the observation that none of the patients in this series developed ARF when FFP was used early at the inception of coagulopathy tend to support this contention. A well designed large double blind randomized controlled trial is recommended to test this hypothesis further.

Until the availability of safe and efficacious antivenom for hump-nosed viper envenomed patients, practicing clinicians have two options to reduce mortality due to hump-nosed viper envenoming in Sri Lanka.

- 1) Not offer any specific therapy and adopt a passive approach to management resigned to detect ARF early by monitoring renal function and offering dialysis once ARF is established. This intervention is expensive, not available for all, and attended with potential complications including fatalities.

- 2) Monitor 20WBCT and detect coagulopathy early. Select patients with coagulopathy for intensive monitoring of hemostatic attributes, renal function, and aggressive Intervention with FFP very early at the inception of coagulopathy. Thrombocytopenia in association with a positive 20WBCT in this clinical setting implies venom induced consumption coagulopathy and should be treated as such. Determination of APTT, PT, D-Dimers, fibrinogen degradation products and fibrinogen assays will only serve to increase the precision of the diagnosis. However in resource poor settings none of these tests are

necessary to manage the patients. On the contrary these tests can add to the cost of management and delay interventions, albeit with disastrous and often fatal consequences. The aims of intervention with FFP are to prevent nephrotoxicity and promote the early correction of coagulopathy with the intended hypothetical benefit of averting the advent of ARF and thereby reduce mortality.

## 7. Limitations

A major drawback is that this is not a randomized controlled trial and devoid of statistical evaluation of the data. Decision to treat some patients with FFP was on the investigators experience in providing individualized care in the routine case management decision making process rather than on defined criteria. The patients who developed ARF were initially managed in a regional hospital and admitted under the care of the investigating physician only after the advent of ARF which required the mixing of results from two cohorts of patients.

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