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Title: Comparison of Two Anti Snake Venom Protocols in Hemotoxic Snake Bite: A Randomized Trial

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TITLE: Comparison of Two Anti Snake Venom Protocols in Hemotoxic Snake Bite: A Randomized Trial

ABSTRACT:

The dose of Anti Snake Venom (ASV) in hemotoxic snake bite depends on the amount of venom injected and species of snake. All trials in South East Asia have studied different doses of ASV, wherein the ASV in high dose group itself was lower than the dose that is recommended in National protocol. These studies favored low dose protocol, as there was no difference in mortality and morbidity between the groups. So, this study intended to assess the efficacy of National protocol in reducing morbidity and mortality in hemotoxic snake bite in comparison to current protocol followed in institution. This was an open label randomized trial of 140 hemotoxic snakebite patients. Group A received national protocol: initial dose of 100 ml followed by 100 ml 6th hourly till 20-minute Whole Blood Clotting Time (20WBCT) was less than 20 minutes or 300 ml of ASV was given, whichever was earlier. Group B received 70 ml followed by 30 ml every 6th hourly until two consecutive 20WBCT were less than 20 minutes. There was no statistical difference in the amount of ASV required in both the groups. Mortality and acute kidney injury were higher in group A (statistically not significant), probably due to sicker patients in that group. There was no relapse of clotting time abnormality in both the groups. In a significant number of patients (12%), clotting time was persistently prolonged till death. We found that the use of National ASV dosing protocol did not decrease the mortality and morbidity.

Key words: Anti snake venom, hemotoxic, dosing protocol

INTRODUCTION:

Snake bite is an important health problem worldwide, resulting in significant morbidity and mortality, particularly in South East Asia. The incidence of snake bite in India was found to be 83000/year with mortality of 11000/year (2008). [(1)]

About 236 species of snakes are found in India of which 17 are considered medically important poisonous snakes by World Health Organization (WHO). [(2)] The snake bite can be hemotoxic, neurotoxic, myotoxic, nephrotoxic or mixed based on predominant manifestation. Among them, hemotoxic snake bites constitute an important group implicated in significant morbidity and mortality.

Anti Snake Venom (ASV) is the only available specific treatment in snake bite. They act by neutralizing the circulating venom constituents. ASV available in India is polyvalent which is effective against four common species: Russell's viper *(Daboia russelii),* Common Cobra *(Naja naja),* Common Krait *(Bungaru caeruleus)* and Saw Scaled viper *(Echis carinatus).*[(3)] The appropriate dose of ASV in hemotoxic snake bite depends on the amount of venom injected and the species of snake, but, it is practically impossible to determine both of them in an emergency setting due to lack of rapid laboratory tests. ASV must be administered as early as possible once there is an evidence of envenomation to neutralize the circulating venom and prevent further complications. Hence, empirical standard dosing recommendations are necessary for effective reduction of morbidity and mortality from the snake bite.

The appropriate protocol for ASV administration is not well established till date. The WHO, regional office for South East Asian Region (SEAR) guidelines suggest ASV dosage based on the species of snake. It suggests initial dose of 100 ml of Indian polyvalent ASV for Russel's viper bite and 50 ml for saw scaled viper bite. [(3)] But, only in few cases species of snake can be identified and thus, treatment is mainly dependent on syndromic approach. There are also

no definite guidelines on dose of ASV in case of persistent coagulopathy. The Indian national snake bite protocol consultation-meeting (2007) recommended an initial dose of 100 ml of ASV for cases with 20-minute Whole Blood Clotting Time (20WBCT) of more than 20 minutes for hemotoxic snake bite.[4] This is based on the study by Tun Pe et al in 1986 where they studied the amount of venom injected by Russell's viper snakes and found that the average amount of venom injected by an adult snake was 63± 7 mg , the maximum among the four snakes. [5] So, it is better to give the first dose which can neutralize the average amount of venom injected by an adult Russell's viper, i.e. 100 ml of Indian ASV. Total amount of 250 to 300 ml is recommended as maximum dose. This is also based on the same study where maximum venom injected was found to be 147 mg. So, this recommendation was done based on an assumption that 30 ml can neutralize the maximum venom injected. Repeat doses to be given if there is persistent coagulopathy in the form of continued bleeding at 2 hours or 20WBCT of more than 20 minutes after 6 hours. 20WBCT to be checked after 6 hours of antivenom administration since it takes about 6 hours for replenishing consumed clotting factors by liver. The repeat dose can be 50 to 100 ml and the exact dose recommendation was not done because many doctors believed as time progresses the amount of unbound ASV declines and administration of high dose like 100 ml may be unnecessary. So, a dosing range of 50 to 100 ml was recommended. It was also recommended that there is no need for maintenance doses of antivenom once coagulopathy has resolved since ASV is F(ab)2 and has a long half-life.

Though these recommendations are logical, they are not based on strong clinical evidence. Till date only four randomized trials involving 230 cases (two studies included both hemotoxic and neurotoxic cases), two prospective studies and a few observational studies have compared different doses of Polyvalent F(ab)2 anti-snake venom in hemotoxic snake bites (*Daboia russelii, Echis carinatus*) in SEAR. [6,7]

No Randomized Controlled Trial (RCT) in India has evaluated the efficacy of dose of ASV as recommended by the national committee. Few studies have been done in the past to address the issue comparing high versus low dose and have found no difference in terms of mortality and morbidity, but the dose administered in high dose group was itself lower than the recommended dose.[8,9,10,11] These studies showed to have serious methodological flaws.

This study was therefore undertaken with an objective to assess the efficacy of the National protocol in reducing morbidity and mortality in hemotoxic snake bite in comparison to the relatively lower dose protocol followed in our institution.

MATERIALS AND METHODS:

This is an open label, single center, 1:1 RCT of patients with hemotoxic snake bite treated in a tertiary care center of south India from September 2013 to July 2015. The protocol was reviewed and approved by the Institute Ethics Sub-committee on Human Research (Approval Number JIP/IEC/2014/1/24 dated: 29/01/2014).

Inclusion criteria:

All cases of hemotoxic snake bites with a positive 20WBCT at presentation

Exclusion criteria:

a Presence of neurotoxicity

b Patients who had received more than 200 ml of ASV before randomization

Since, the study was done in a tertiary care referral center; most of the cases were referred after treatment with initial dose of ASV. The estimated sample size was 192 (sample size estimation described later). In order to meet the required sample size in limited study period a maximum limit of 200 ml of ASV was defined.

Procedure:

All patients with snake bite admitted in hospital were assessed for eligibility. The 20WBCT was performed at presentation for those cases who had not received any amount of ASV prior to admission. If the patient had received any amount of ASV, 20WBCT was performed after six hours of initial ASV administration. The 20WBCT was measured using a clean glass test tube. One ml of venous blood sample was placed in a glass test tube, left untouched for 20 minutes. At the end of 20 minutes, if blood remained liquid and runs out, then the patient was considered to have positive 20WBCT. If clotting time at presentation was less than 20 minutes, test was repeated every hour up to three hours followed by second hourly.

Eligible cases were randomized after taking informed written consent from patient or caretakers. Simple randomization technique was used for the study. We used computer generated random number sequence. Allocation concealment was done by the following method. If a case was found to be eligible, the principal investigator used to call the guide through telephone and inform the case number. Based on the automated random number sequence that was generated before the beginning of study, guide used to inform to which group the patient had to be assigned.

Group-A was administered an initial dose of 100 ml of ASV in 500 ml normal saline over one hour followed by 100ml 6th hourly till 20WBCT was negative or till maximum of 300 ml of ASV was given, whichever was earlier (National protocol).

Group-B was administered with a protocol followed in institution i.e. initial ASV of 70 ml in 500 ml of saline over one hour followed by 30 ml in 100 ml of normal saline over 15-30 minutes every 6th hourly until two consecutive 20WBCT was negative, where 20WBCT was performed every 6th hourly prior to administration of ASV as depicted in figure 1 (Institutional protocol).

Patients in both groups were monitored using 20WBCT for relapse of clotting time. ASV reactions were managed accordingly. The patients, who had clotting abnormality despite ASV, were managed symptomatically with platelets, fresh frozen plasma (FFP) and cryoprecipitate accordingly. The treating physician made decision other than dose of ASV administration including vasopressor support, supportive transfusions, and antibiotics. Patients were followed until discharge or death and outcome measures were noted. Acute Kidney Injury (AKI) was defined based on Kidney Disease Improving Global Outcomes (KDIGO) criteria. [12] Progressive cellulitis was defined as cellulitis extending beyond one joint from the initial leading edge at the time of administration of the first dose of ASV.

We used polyvalent Snake Venom Antiserum I. P. manufactured by VINS bio products limited, Hyderabad, India. Multiple batches of ASV were used over a period of 2 years, based on the availability in the institution.

The primary outcome was a composite outcome including number of patients developing AKI and mortality. Secondary outcomes included individual components of primary outcome, renal replacement therapy (RRT) and duration, time required for clotting time normalization, amount of ASV required, proportion of adverse reaction to ASV, duration of hospital stay, proportion of patients developing shock, cellulitis and severity.

A subgroup analysis of treatment naïve cases was done including those who didn't receive any dose of ASV before randomization.

The incidence of AKI among the patients with hemotoxic snake bite was reported to be 64% in our hospital, where the protocol followed was same as the protocol used for control group in this study. A sample size of 192 was estimated with an expectation that National protocol for treating patients with hemotoxic snake bite would be able to reduce the AKI by 20% at 5% level of significance and 80% power.

The distribution of categorical data related to patient gender, signs and symptoms at presentation, clinical characteristics, clinical and treatment outcome were expressed as frequency and percentage. The comparison of these variables between the groups was carried out by using chi square or fisher's exact test. The data for age, duration of dialysis, the amount of ASV, duration of hospital stay, renal function parameters and routine biochemical parameters were expressed as mean with standard deviation (SD) or median with range. The comparison of the continuous variables between the groups was carried out by using independent student t test or Mann-Whitney U test and between the signs and symptoms and clinical characteristics was carried out by independent student t test or Mann-Whitney U test or one way analysis of variance or Kruskal Wallis test whichever was appropriate based on distribution of data and number of groups. The comparison of the treatment and clinical outcome in relation to signs and symptoms and clinical characteristics at the time of presentation was carried out by using chi square or Fisher's exact test. Comparison of the values of continuous variables at the time of presentation in relation to clinical and treatment outcome was carried out by using independent student t test or Mann-Whitney U test whichever was appropriate. All statistical analysis was carried out at 5% level of significance and p value <0.05 was considered as significant. Data was entered in Microsoft Excel and analyzed using IBM SPSS version 20. The trial has been registered in clinical trial registry of India, and the registration number is CTRI/2015/05/005826.

RESULTS:

A total of 263 patients who presented to medicine casualty with history of snake bite and positive 20WBCT, were assessed for eligibility. Thirty-two patients also had neurotoxic features and thus, were excluded. Fifty-six patients did not show any features of toxicity. So, 20WBCT was rechecked with the proper method and all of them were found to have negative 20WBCT, hence were excluded. Thirty-three patients had received more than 200 ml of ASV

before presentation to institution and thus, were excluded. Two patients had cardiac arrest before randomization, and thus, were excluded. Hence, 140 patients were eligible for the study. After taking written consent from patients or relatives' randomization was done. Seventy-four cases were randomized to group A, and 66 to group B. Three patients in Group A didn't receive complete dose of ASV due to the adverse reaction and 71 were treated as per protocol. In group B, there was protocol violation in two cases, and one patient didn't receive complete dose of ASV due to an adverse reaction in Group B. Hence, 63 were treated per protocol. The data is summarized in figure 2.

The mean±SD age of patients presented to the hospital was 38.8±14.2 years. Snake bite was more common among males (~74%). Majority of snake bite patients were either farmers or daily laborers. Most of the patients (~75%) were bitten at workplace in concordance with WHO considering snake bite as an occupational hazard. Most of the patients (~85% of cases) had bite in lower extremity. Among 140 cases, 82 (58.6%) cases were referred from other hospitals and approximately 50% of those cases received ASV before referral. Only 11 among 140 patients brought the snake, and of them eight were Russell's viper and three were saw scaled viper as identified at our hospital. Few patients [16 (11.4%)] had history of bite but had not witnessed the snake, but based on presence of cellulitis and coagulopathy, a syndromic diagnosis of hemotoxic snake bite was made and treated with ASV and were classified as presumed snake bite. Baseline data among the groups is summarized in table 1. There was no significant difference in the baseline parameters in both the groups. Although, patients with elevated creatinine at presentation was higher in group A, 19 of 74 (25.7%) compared to 11 of 66 (16.7%) in group B and patients with hypotension at presentation was higher in group A (9.5%) than in group B (6.1%), but these differences were not statistically significant.

Outcomes of the trial:

Overall 79 patients among 140 had AKI i.e. 56.4% and 20 out of 140 patients died in the study with the mortality rate of 14.3%. All the patients who died also had AKI. The primary outcome (AKI, death) was higher in Group A [60.8% in group A, 51.5% in group B]. However, it was not statistically significant (p = 0.268). Mortality was higher in group A (18.9% in group A, 9.1% in group B), but it was also not statistically significant (p = 0.097). This data is as summarized in table 2 and 3. Among the cases enrolled in the study, 30 cases had serum creatinine more than 1.5 mg/dl at presentation. Among the rest 110 patients 49 patients developed AKI (44.5%). The difference between AKI among these patients was also not statistically significant. (47.3% in group A, 41.8% in group B, p = 0.565).

In the trial, 45 patients required RRT as decided by the treating physician i.e. 57% of patients among those with AKI (n=79) and 32.1% of the total study population (n=140). There was no significant difference in number of patients requiring RRT between both the groups [18 (25.7%) in group A, 15 in group B (22.7%) p = 0.685]. Not all the patients who required RRT were dialyzed because few patients had significant hypotension and were not possible to be taken for RRT and few died of other complications before they could be dialyzed. A total of 24 patients received RRT i.e. 53.3% of those who required RRT (n=45) and 17.1% of total study population (n=140). There was no difference between the groups [13 (17.6%) in group A, 11 in group B (16.7%), p = 0.888].

Among these patients, three (two in group A, one in group B) patients received Slow low efficiency dialysis (SLED) in initial sessions followed by hemodialysis (HD) once blood pressure stabilized. Ten cases (3 in group A, 7 in group B) received HD alone. 11 (8 in group A, 3 in group B) patients received SLED alone.

The median duration of SLED in group A was six hours, ranging from four to 19 hours and in group B was six hours ranging from four to eight hours. This was not statistically significant

(p = 0.883). The median duration of HD in group A was 16 hours, ranging from eight to 58 hours and in group B was nine hours ranging from four to 22 hours. This was not statistically significant (p = 0.162).

The time required for clotting time normalization was defined as the time from the first dose of ASV administered after randomization to the time when 20WBCT was negative, that was measured every 6th hourly. In a significant number of patients 17 among 140 (12.1%) clotting time was persistently prolonged till death. Among the 17 patients, complete dose of ASV (i.e., 300 ml or more) was administered to 11 patients and succumbed to the disease within one to two days. Five patients died within a short period of admission so that total dose of ASV was not administered. One patient was not given full dose due to severe anaphylactic reaction to ASV. This number was higher in group A though not statistically significant. [11 (14.9%) in group A, 6 in group B (9.1%), p = 0.296]. The longest time taken was 48 hours. Since 17 cases had persistent prolongation of clotting time till death, survival analysis for time to clotting time normalization was done to statistical assessment, which showed no significant difference as shown in figure 3.

There was no relapse of clotting time abnormality in the form of prolongation of clotting time once it was less than 20 min. The amount of ASV required was lower in group B but not statistically significant. Though group B received lower dose every 6th hourly, time required for clotting time normalization was longer and, cumulative dose requirement was comparable to group A.

The median duration of hospital stay was five days with inter quartile range of 3 to 7 days. The longest duration of stay was 30 days. There was no significant difference between the groups (4.5 and 5 days in group A and group B respectively).

Hypotension was documented with the need for vasopressor support in 35% of patients (49 of 140 patients). Among them, 11 patients had evidence of capillary leak syndrome. Six patients died of the capillary leak and five patients improved. Two patients had documented evidence of adrenal insufficiency.

Though all the patients with evidence of coagulopathy i.e. with positive 20WBCT were enrolled in the trial, only 69 patients (49.3%) had clinical bleeding from at least one site. Most common was mucosal bleed from gums; one patient had intracranial bleed in the trial. The proportion of patients with clinical bleeding was higher in group B in concordance with the longer time required for clotting time normalization though it was not statistically significant.

Seventy-three patients (52.1%) had progressive cellulitis with no significant difference between the groups. Nine patients had severe local necrosis requiring debridement.

Patients with indication for blood and blood product transfusions were transfused accordingly, and there was no difference between the groups. The numbers mentioned doesn't represent those numbers which required transfusion because few patients though required transfusion, died before transfusion was done. Following number of patients mentioned in Intensive Care Unit (ICU) admission was given ICU care, and this is not only based on requirement but also on availability at given point of time. Since, exact criteria for ICU admission is not available, the number of patients requiring ICU admission is not available.

Major adverse reaction to ASV including anaphylactic shock and severe bronchospasm was seen in 5.7% of cases. All the reactions developed in initial 50 ml of ASV administration. So higher dose of ASV, may not be an issue with respect to the adverse reaction. Almost 82.1% had a minor adverse reaction in the form of chills, pruritus, and fever. Analysis of secondary outcome was also done based on per protocol and no difference was found. Data is summarized in table 2 and 3. There were few rare complications in the study. Two patients

had acute angle closure glaucoma; these patients also had capillary leak syndrome. Two patients had clinical and laboratory evidence of panhypopituitarism. Two patients had definite evidence of adrenal insufficiency. Four patients had acute respiratory distress syndrome (ARDS) and required ventilator support.

Subgroup analysis:

Subgroup analysis was done excluding those patients who received ASV before randomization. Total of 97 patients, 50 in group A and 47 in group B were analyzed. The results were similar to the main group. The data is tabulated in Table 4

DISCUSSION:

In this study use of National protocol did not reduce morbidity and mortality from hemotoxic snake bite, compared to relatively low dose protocol.

All the randomized trials in India till date have studied different dosing protocols in ASV, where the ASV administered in high dose group itself was lower than the dose that is recommended in National protocol. No trial has compared the National protocol with 100 ml of ASV as initial dose and 100 ml as repeat doses. Thomas et al administered 4 ampoules (40 ml) as initial dose in high dose group; [9] Tarring et al administered 20 ml of ASV as initial dose in high dose group. [10] Repeat doses of ASV were administered after 2 to 4 hours in these studies. Among these studies Tarring et al and Paul et al also included neurotoxic snake bites in the study.[11] Only one prospective study from the same institute by Srimannarayana et al has compared 100 ml of ASV as initial dose and 50 ml as repeat doses versus 70 ml as initial doses and 30 ml as repeat doses in the form of infusion.[8] These studies have concluded that there was no significant benefit in terms of mortality and morbidity in high dose group compared to low dose. But, amount of ASV requirement is significantly less in low dose group. Hence, they preferred low dose for hemotoxic snake bite. But, the ASV dose

in high dose group was less than recommended. In our study we studied whether the use of high recommended dose can decrease the mortality and morbidity.

In the study by Tarring et al there was no mortality and no AKI. In the study by Thomas et al. mortality was 4% and AKI was 22%. This is significantly less when compared to our study. Bite to needle time in the study by Tarring et al was less than 6 hours in around 90% of cases and mean bite to needle time in the study by Thomas et al is 4 to 6 hours. This is almost similar to our study where median bite to needle time is 6 hours. Therefore, this significant difference in mortality and AKI cannot be explained by delay in administration of ASV. The probable explanation is, this study is done in a government referral institute catering needs of rural areas around this place, where the population is more prone for snake bites and more sick cases are being referred to this center. So, based on these observations it may be considered that our study had cases with severe envenomation compared to other studies and it is impractical to use so low doses of ASV in this clinical setting.

Mortality in both the groups is significantly higher compared to other studies. Mortality rate of hemotoxic snake bite in our institution was 23% in an observational study done by Maya et al in 2012. [13] The ASV protocol used in most of the cases in this study was same as that used in group B. This is even higher than our study. This was one of the reasons to conduct this trial. Moreover, in study by Srimannarayana et al mortality was 23%, which was also conducted in the same institution. The institution is a tertiary referral government center and it is likely that more severe cases were referred resulting in higher mortality. Being a referral center, it is possible that duration for patients to reach the institution was longer and venom could have extravasated into extravascular compartment and even the higher dose of ASV might not have neutralized it. It is also known that ASV is not alone sufficient to prevent and treat all the manifestations of snake bite. [14]

Oxidative stress and inflammation are also considered as one of the pathogenesis of snake bite, which persist despite treatment with ASV. [15] Geographic variability in response to antivenoms may also be a reason for relative inefficacy of ASV in our study. [16]

In our study, time for clotting time normalization was higher in low dose group, hence though low dose was administered every 6th hourly cumulative dose requirement was not significantly different in both the group. This may favor administration of higher doses at the earliest particularly in those with active bleeding requiring early hemostasis. Though clotting time normalized earlier in high dose group, mortality and proportion of patients with renal failure was found to be higher in high dose group (statistically not significant). This may be due to higher proportion of patients with clinically severe disease, in terms of hypotension, creatinine of >1.5 mg/dl at baseline (statistically not significant). Clotting time failed to normalize in 8 patients in high dose group, even after administration of 300 ml of ASV as compared to only 3 patients in low dose group. All these patients had AKI and succumbed to bite. This may be due to envenomation by different species of snake that is not neutralized by polyvalent ASV. [17,18,19] This might be another explanation for higher mortality and morbidity in high dose group.

In our study, no patient had relapse of clotting time abnormality in both the groups even though no maintenance dose was administered in group A. This is in concordance with the results of RCT by Sean. P. Bush et al comparing Fab and F(ab)2 antivenoms. [20] This finding is discordant with the results by Srimannarayana et al. This supports the fact that there is no need for maintenance dose when F(ab)2 antivenom is used, which has a longer half-life.

Eleven patients even after receiving 300 ml or more amount of ASV had persistent elevated clotting time. This phenomenon raises two issues. One is these patients can be envenomed by other hemotoxic snakes which are not neutralized by Indian polyvalent ASV and studies to be done to identify these snakes and development of ASV. The other entity to be considered is

whether the upper limit of 300 ml of ASV is relevant in all the cases and in these it may be better to administer additional doses particularly when snake has been identified to be one among the “big four”.

The median amount of ASV required in group A was 170 ml versus 130 ml in group B. Since the difference was not statistically significant, we can’t conclude that group B had similar outcomes despite lower dose of ASV used. But it can be suggested that in those with no hemodynamic instability and active bleeding, lower dose may suffice. This is important in developing countries since it is economically beneficial and in scarcity of ASV supply, this strategy may be helpful.

This is the largest trial comparing different dosing protocols of ASV in hemotoxic snake bite in India. This is the first RCT to evaluate the ASV dosing recommendation of National Protocol of 2007. This is a pragmatic trial which evaluated the efficacy of National Protocol in routine clinical practice. There is less chance for bias in study because allocation concealment was done properly and patients from all the medicine units were included in the study.

There were few limitations in the study. This is an open label trial. We used simple randomization for the study that led to disparity in sample size. We were not able to complete the calculated sample size of 192 since the study period was limited. So, this study was under powered to detect difference in mortality and morbidity. Patients who received ASV before admission to hospital were also included because of limited availability of cases. So, subgroup analysis was done excluding those cases. The design of the study didn’t allow to compare high dose versus dose of ASV. The 20WBCT was used in the study, the sensitivity and specificity of which is questioned. But in view of non-availability of an alternative bedside test it remains the test of choice.

CONCLUSION:

Use of National ASV dosing protocol did not decrease the mortality and morbidity from hemotoxic snake bite compared to relatively low dose protocol. So, further studies with a higher sample size may be required to evaluate the efficacy of different protocols of ASV in reducing morbidity and mortality in patients with hemotoxic snake bite. There is no need of maintenance dose of ASV after clotting time normalization since there was no relapse of clotting time abnormality in both the groups. Studies may be required to identify other medically important snakes in this geographical area and development of appropriate ASV because overall mortality and AKI was higher compared to any other studies and significant number of patients had persistent clotting time abnormality despite adequate ASV administration.

Conflict of interest statement:

We have not taken any financial grant or services from the government, commercial or any private foundation. We don't have any relationships, conditions or circumstances that present a potential conflict of interest. We also declare that we don't have conflict of interest with each other.

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Fig 1: Methodology of the trial.

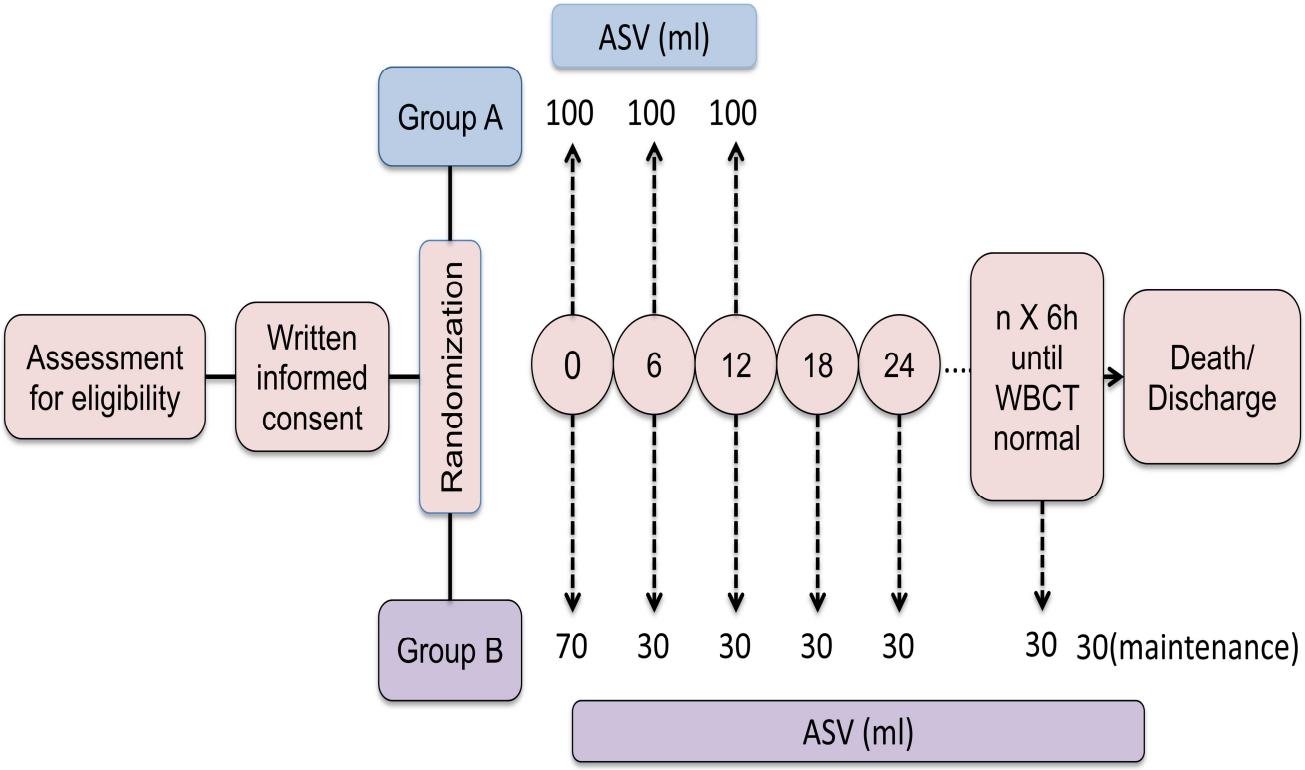


Fig 2: Flow chart of study design and enrollment of participants

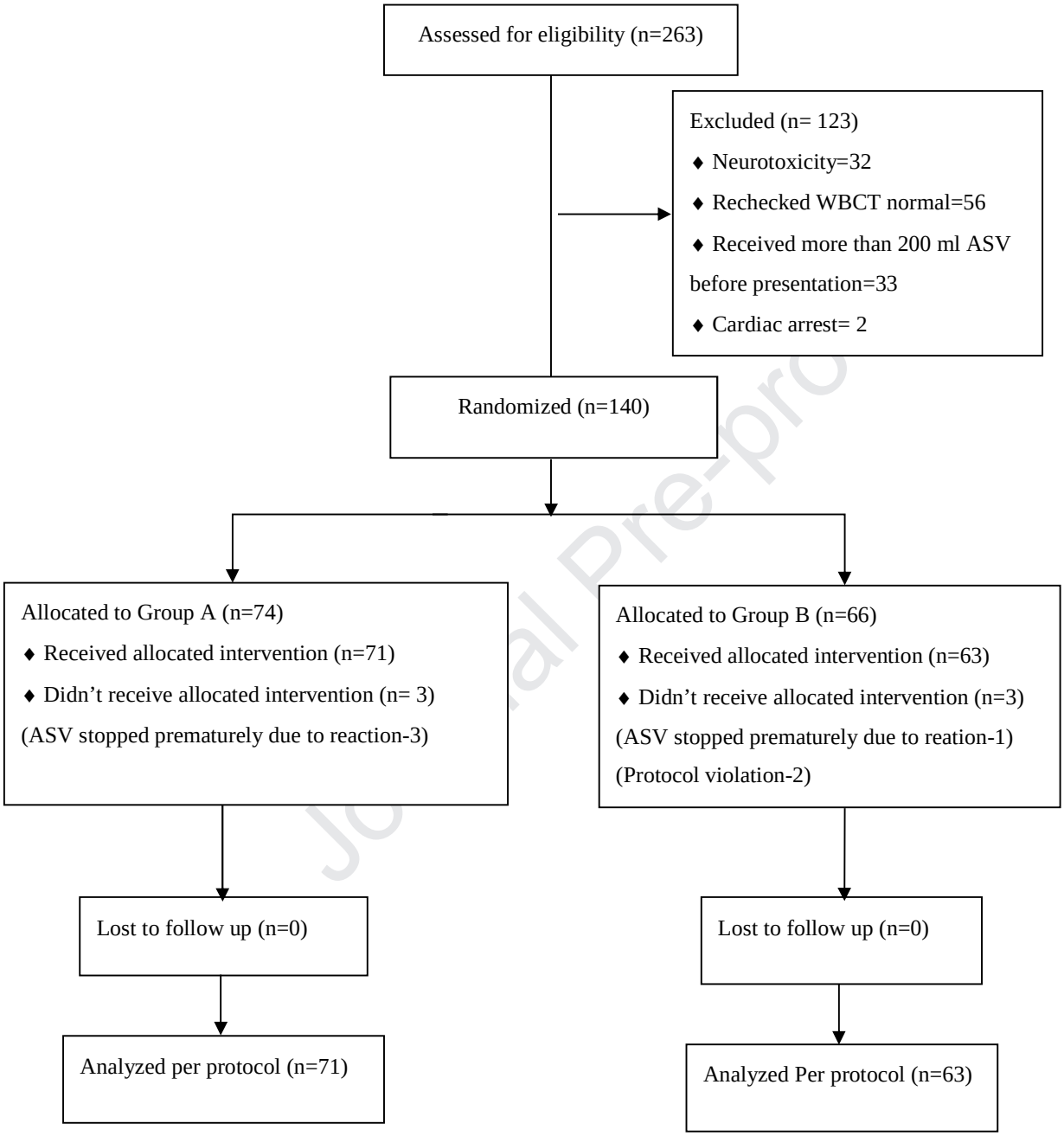
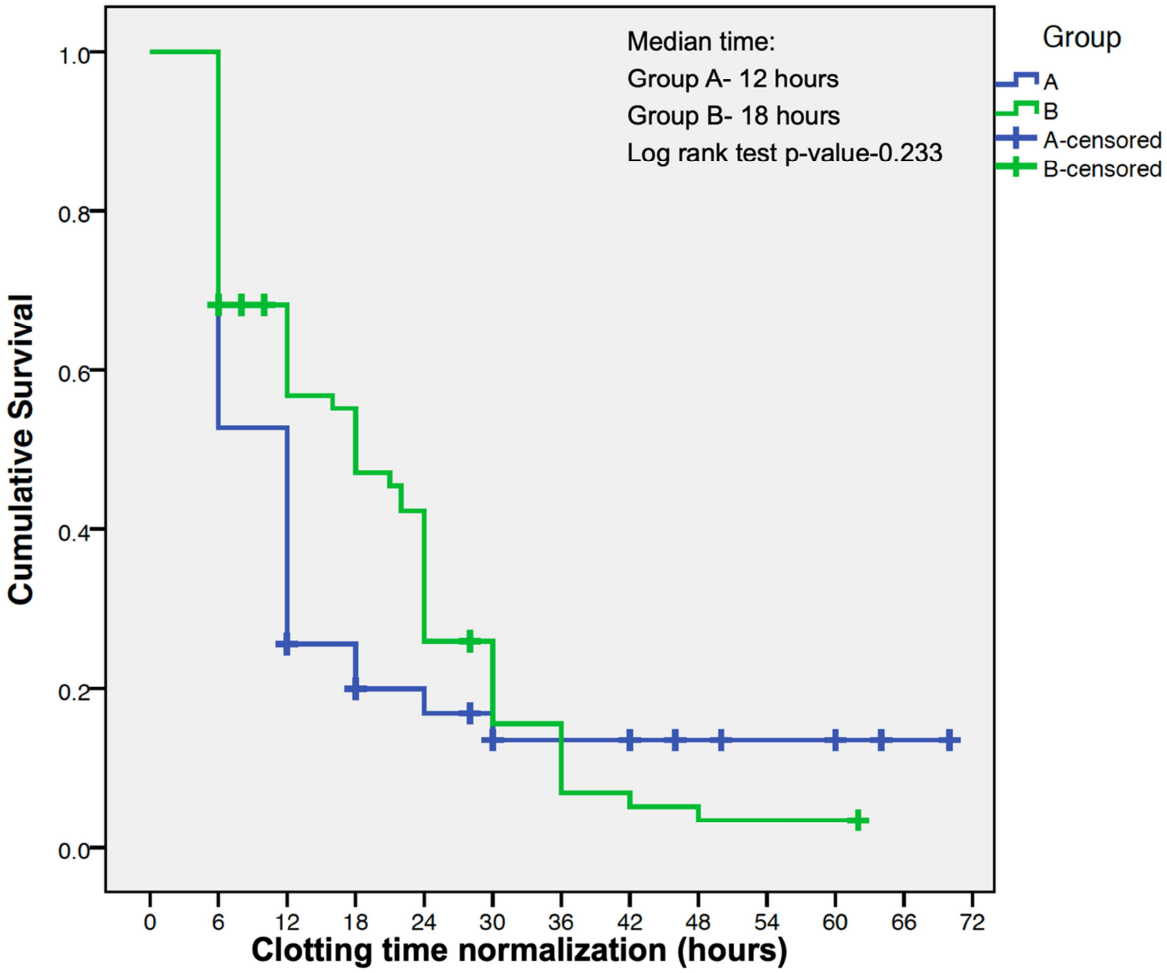


Fig 3: Survival analysis of duration for clotting time normalization.



Highlights:

1. Comparison: National Protocol versus low dose ASV for hemotoxic snake envenomation
2. No difference in mortality or AKI between groups
3. No relapse of clotting abnormality in both groups
4. Clotting time persistently prolonged till death in 12% of study population

Conflict of interest

We the author of this the article entitled "Comparison of Two Anti Snake Venom Protocols in Hemotoxic Snake Bite: A Randomized Trial" declare that we have not taken any financial grant or services from the government, commercial or any private foundation. We don't have any relationships, conditions or circumstances that present a potential conflict of interest. We also declare that we don't have conflict of interest with each others.

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