HEPARIN THERAPY IN RUSSELL'S VIPER BITE VICTIMS WITH DISSEMINATED INTRAVASCULAR COAGULATION : A CONTROLLED TRIAL

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Abstract. A controlled clinical trial of low dose heparin was carried out in confirmed cases of Russell's viper bite. Twenty patients with systemic envenoming were included in the study. They were randomized to receive low dose heparin in an initial dose of 50 units/kg body weight intravenously immediately after antivenom followed by a continuous infusion of 10 unit 3 kg/hour in isotonic saline for 24 hours, or antivenom alone. Response to treatment was assessed clinically as well as by serial measurements of coagulation factors and biochemical values.

No significant difference was observed in the outcome among two groups, the recovery rate from the clotting defect being similar in both. The mean serum creatinine values of the two groups were also not statistically different. The results indicated that there is no beneficial effect of adding heparin to the standard treatment by antivenom.

INTRODUCTION

Russell's viper venom (RVV) is a complex which contains a variety of components including procoagulants and anticoagulants. Of the two major procoagulant factors (Schiffman *et al,* 1969), one activates factor X, factor IX and Protein C (Lindquist *et al,* 1978), while the other activates factor V (Kisiel, 1979). In view of this, in patients with systemic envenoming, these potent coagulation factors activate factor X and factor V, leading to the initiation of disseminated intravascular coagulation (DIC) (Spero *et al,* 1980). In severe cases there is intense hypofibrinogenemia and very low levels of factor X and V producing non clottable blood. (Than Than *et al,* 1988; Myint Lwin *et al,* 1985). An important histopathological finding in patients who died from severe envenomation and in animal experiments was deposition of fibrin in small blood vessels, especially in the renal glomerular capillaries (Aung Khin, 1977; Myint Lwin *et al,* 1989; Than Than *et al,* 1989a).

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Heparin has been shown to be able to block the activation of Factor X by RVV *in vitro* (Gitel *et al,* 1977), it may therefore prevent or reduce the activation of the coagulation system, leading to disseminated intravascular coagulation (DIC); if given early enough it will preserve organ function by limiting fibrin deposition in vital organs. Because of this strong theoretical basis for heparin therapy in RV bite, we have been conducting studies to assess the role of heparin in management of RV bite patients to improve the therapeutic regime for these patients.

The results of our trial of heparin in patients with fully developed DIC is presented in this paper. Our objective was to prevent further deterioration of renal damage resulting from the consequences of DIC in Russell's viper bite patients with systemic poisoning.

PATIENTS AND METHODS

Patients

The study was carried out at Thayarwady Township Hospital about 130 km north of Yangon, during the rice harvesting seasons (Novem-

ber to January) of 1988-1989 and 1989-1990. Patients accepted for the study were confirmed cases of Russell's viper bite with incoagulable blood. The dead snakes were identified and/or specific venom antigen level was measured by enzyme immunoassay (EIA) in serum. A total of 20 patients were studied.

Assessment

Patients were carefully examined for both local and systemic effects of envenoming and kept under close observation. All clinical observations and laboratory tests were done as in our previous studies on patients with impending DIC. Local swelling was graded from 1 to 6 (Warrell *et al,* 1977). The 20 minutes clotting test (Warrell *et al,* 1974) was done at 6 hourly intervals. Urine output was measured carefully. Venous blood was taken at 0, 1, 6, 12, 24 and 48 hours for estimation of coagulation factors and biochemical measurement. All samples were stored at -20°C for up to one week prior to transport to Department of Medical Research in Yangon for storage at -80°C until tested.

Treatment

Patients included in the study were allotted to one of the two treatment regimes :

Regime 1. (heparin) : A bolus dose of 80 ml of lyophilized monovalent antivenom for Russell's viper (Myanmar Pharmaceutical Industry, MPI), was injected intravenously over 20 minutes, followed immediately by an intravenous injection of a low dose of heparin (initial dose of 50 units/kg body weight followed by a continuous infusion of 10 units/kg body weight/ hour in isotonic saline for 24 hours).

Regime 2. (control) : A bolus dose of 80 ml of lyophilized MPI monovalent antivenom for Russell's viper (MPI) was injected intravenously over 20 minutes followed by isotonic saline for 24 hours. Fluid balance was strictly controlled. Intravenous frusemide up to 500 mg and dopamine 2-5 μg/kg/minute were given to those who passed less than 400 ml of urine in 24 hours despite rehydration. Patients were transferred to Yangon General Hospital (YGH) for peritoneal dialysis, if indicated.

Hypotension (systolic blood pressure less than 80 mm Hg for more than 10 minutes) was corrected by giving intravenous dextran 40 (Rheomacrodex), saline and fresh whole blood until the blood pressure restored back to normal.

Laboratory investigations

Venom antigen levels was measured by an enzyme immunoassay (EIA) technique (Ho *et al,* 1986). Fibrinogen (clot weight) factor V and factor X assays, and serum creatinine were measured by standard methods.

RESULTS

The two treatment groups were well matched for age, sex and body weight. Other factors which are likely to affect the outcome such as the interval between bite and start of treatment and initial venom levels (62 ng/ml in the heparin group and 69 ng/ml in the control group) were also similar (Table 1).

Statistical analysis was performed by using students *t*-test (paired).

Clinical features at the time of admission are shown in Table 2. No significant difference was found between the two groups.

Clinical progress

Local swelling was observed in one patient among the heparin treated group and four among controls. The maximum extent of local swelling was grade V (percentage circumference of 13.04%) in patients among the heparin treated group as compared to grade IV (10%) in the two patients from the control group.

Conjunctival hemorrhage occurred in one patient and melena in two patients among those receiving heparin. Development of hypotension was observed in 1 and 3 patients among the heparin and control groups, respectively.

Oliguria was present on admission in 3 patients of the heparin group and 2 of the control group. No further development of oliguria was noted among the heparin treated group. Two patients recovered without peritoneal dialysis and one expired. Among the control group, two patients developed oliguria, out of which one had to

Table 1

Comparison of 2 treatment groups.

Ser No.	Patients characteristics on admission	Heparin (n = 10)	Control (n = 10)
1.	Average age (year) (mean ± SD)	35.7 ± 15	35.5 ± 13
2.	Average weight (kg) (mean ± SD)	47.5 ± 4	49.2 ± 3
3.	Sex ratio (male : female)	10 : 1	10 : 0
4.	Average height (cm) (mean ± SD)	162 ± 6	161 ± 3
5.	Time between bite and admission (hours)	2.4 ± 1	2.3 ± 1
6.	Time between bite and Antivenom (hours) (mean ± SD)	6 ± 4	4 ± 3
7.	Mean initiated venom Ag level (ng/ml) (mean ± SD)	62 ± 26	69 ± 27

Table 2

Comparison of clinical features on admission in heparin and control groups.

Ser No.	Clinical features on admission	Heparin (n = 10)	Control (n = 10)
1.	Local swelling (no of cases)	8 (80%)	6 (60%)
2.	Regional lymphadenitis (no of cases)	5 (50%)	7 (70%)
3.	Bleeding from site of bite (no of cases)	7 (70%)	5 (50%)
4.	Systemic bleeding		
	– gum	2 (20%)	4 (40%)
	– sputum	1 (10%)	1 (10%)
	– vomitus	1 (10%)	1 (10%)
	– conjunctival hemorrhage	–	–
	– hematemesis	–	–
	– melena	–	–
	– hematuria	1 (10%)	–
5.	Hypotension (no of cases)	1 (10%)	2 (20%)
6.	Oliguria (no of cases)	3 (30%)	2 (20%)
7.	Renal angle tenderness (no of cases)	Nil	5 (50%)
8.	Conjunctival edema	Nil	2 (20%)
9.	Urine protein	4 (40%)	4 (40%)
10.	Urine microscopic RBC	2 (20%)	5 (50%)

undergo peritoneal dialysis and two patients expired (Table 3).

All these patients with oliguria were associated with solid proteinuria and numerous RBC in urine.

Coagulation defect

Initial fibrinogen concentrations were found to be low in all patients on admission. In both groups, recovery was similar and normal values were reached in 24-48 hours.

Table 3

Comparison of complications and outcome in heparin and control groups.

Ser No.	Clinical features on admission	Heparin (n = 10)	Control (n = 10)
1.	Local swelling (no of cases)	1 (10%)	4 (40%)
2.	Regional lymphadenitis (no of cases)	1 (10%)	2 (20%)
3.	Bleeding from site of bite (no of cases)	–	–
4.	Systemic bleeding		
	– gum	–	–
	– sputum	–	–
	– vomitus	–	–
	– conjunctival hemorrhage	1 (10%)	–
	– hematemesis	–	–
	– melena	2 (20%)	–
	– hematuria	–	3 (30%)
5.	Hypotension (no of cases)	1	3 (30%)
6.	Oliguria (no of cases)	–	2 (20%)
7.	Renal angle tenderness (no of cases)	2 (20%)	1 (10%)
8.	Conjunctival edema	1 (10%)	3 (30%)
9.	Urine protein	2 (10%)	3 (30%)
10.	Microscopic hematuria cases	1 (10%)	1 (10%)
11.	Peritoneal dialysis	Nil	1 (10%)
12.	Expired cases	1 (10%)	2 (20%)

Both Factor V and Factor X levels were initially reduced in all patients. Their recovery rates were slower than that of fibrinogen (Fig 1).

Biochemical results

Serum creatinine started to rise since one hour after antivenom in both groups (Fig 2). Their levels at 48 hours were still high and although the mean value in controls was higher as compared to that in the heparin treated group, it was not statistically significant [$p > 0.5$, students t-test (paired)].

DISCUSSION

Selection of patients

Heparin therapy is essentially prophylactic and there is no evidence that it has any effect on preformed fibrin. Consequently it has to be given early to be effective enough. Hence, a study on the efficacy of heparin has been conducted in Russell's viper bite patients with impending DIC (Myint Lwin *et al,* 1989b). No beneficial response was observed. It may be due to the selection of patients with milder envenomation only. Antisera alone was sufficient for these patients.

On the other hand, those patients who arrive at the hospital within the short period after being bitten with overt DIC are the ones who are severely envenomed. These are the patients who require supportive therapy like heparin in addition to antisera. For this reason only patients with fully established DIC were included in the present study.

Dose of heparin

In Russell's viper bite syndrome, "severe envenoming" means stronger stimulation of coagulation cascade. Theoretically, patients in this category would need larger doses of heparin. Many authors have also commented that much larger quantity of heparin is required to counteract

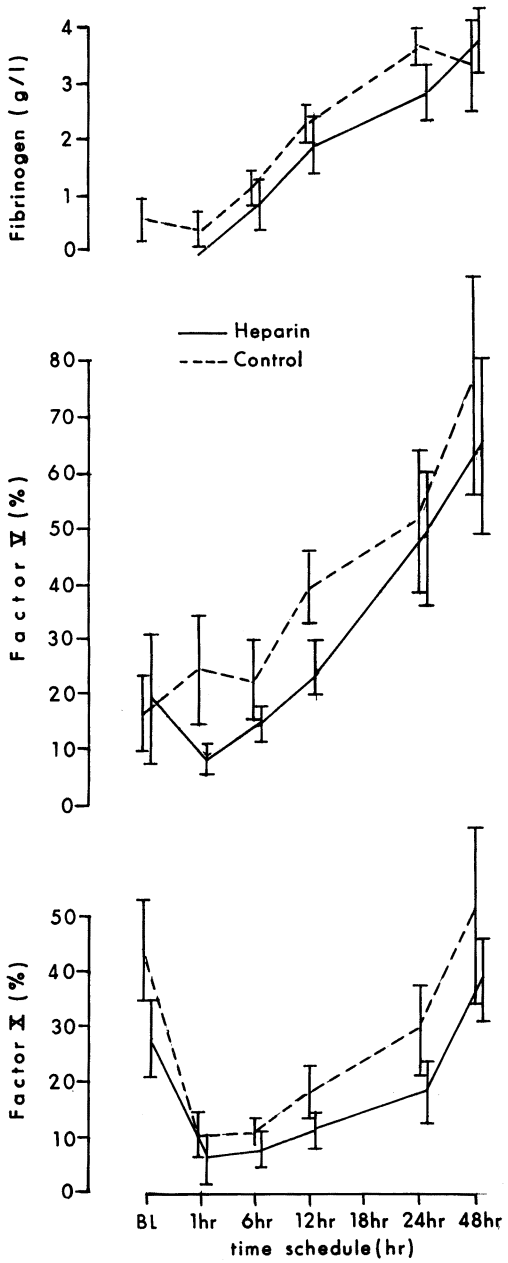

Fig 1—Levels of fibrinogen, factor V and factor X in two treatment groups.

the toxin effect of snake venom.

However, treatment of defibrinated patients with heparin is potentially hazardous. Also, other components of venom, such as hemorrhagins and

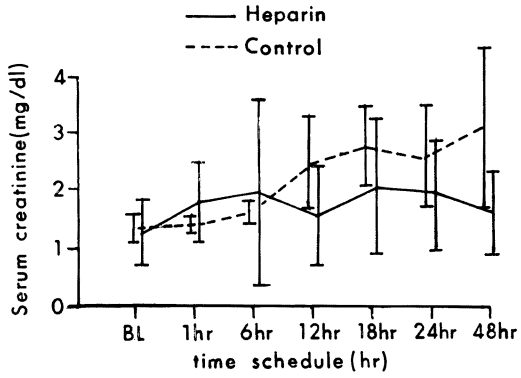

Fig 2—Comparison of serum creatinine level in two treatment groups.

increased capillary permeability factor, will further promote bleeding episodes. A relatively low dose of heparin was therefore used in this study, the total dosage over 24 hours being on average 15,000 units. The dose used in our study might be too low to have the therapeutic level.

Effectiveness of heparin

Than Than *et al* (1989b) showed in animal experiments the beneficial effects of heparin in terms of survival rate and histopathological changes in the kidneys such as notable decrease in congestion and hemorrhage in animals receive heparin and antisera. We did not have the opportunity to perform autopsies on our patients to compare the histopathological findings. Nevertheless, the clinical (Table 3) as well as the biochemical changes (Fig 2) showed a lesser degree of injury to renal in heparin treated group compared to controls.

Effects of heparin on DIC to snakebite have been studied by many workers (Weiss *et al,* 1973; Warrell *et al,* 1976). Studies by Weiss *et al* (1973) demonstrated beneficial effects of heparin on their cases bitten by Echis carinatus. However, Warrell *et al* (1976) reported that cases bitten by Echis carinatus showed no beneficial effects. Shah *et al* (1986) reported beneficial results with addition of heparin in terms of control of systemic bleeding and normalization of hematological parameters. We reported our findings on low dose heparin therapy in RV bite victims with impending DIC in 1986-88 : there was only marginal benefit in patients with very low pretreatment fibrinogen

level (Myint Lwin *et al,* 1989a, b). In our present study we again could not find any beneficial effect of adding heparin to the standard treatment with antivenom. With our present regime no hazards from heparin was noted. The later development of conjunctival hemorrhage and melena in one of the patients among the heparin treated group could be due to the toxic effects of venom in increasing capillary permeability and causing uremia. The frank hematuria that occurred in three patients in control group is due to the sequelae of renal injury.

We were not able for ethical reasons to compare heparin treatment alone with antivenom alone.

At present, antivenom is still the mainstay of treatment in RV bite victims. Further investigations are needed before heparin could be recommended.

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