CLINICAL TRIAL OF INTRAMUSCULAR ANTI-SNAKE VENOM ADMINISTRATION AS A FIRST AID MEASURE IN THE FIELD IN THE MANAGEMENT OF RUSSELL'S VIPER BITE PATIENTS

Win-Aung[1], Tin-Tun[1], Khin-Maung-Maung[1], Aye-Kyaw[1], Hla-Pe[1], Tin-Nu-Swe[2] and Saw-Naing[3]

[1]Biochemistry Research Division and [2]Clinical Research Division, Department of Medical Research, [3]Department of Clinical Medicine, Institute of Medicine (1), Yangon, Myanmar

Abstract. Efficacy of intramuscular anti-snake venom administration immediately after bite as a first aid measure in the field followed by standard hospital management versus standard hospital management alone in the therapy of Russell's viper bite patients was studied. There was a definite reduction in the number of patients with systemic envenomation, complications following disseminated intravascular coagulation and in fatality rate of Russell's viper bite victims who had received first aid intramuscular anti-snake venom prior to hospitalization when compared with those who had not.

INTRODUCTION

Snake bite is an important national health problem in Myanmar, standing eleventh position in priority ranking of diseases based on scoring system proposed by the National Health Plan 1993-1996 of the Ministry of Health. There are 10,000 or more snake bite cases annually with a mortality rate of about 10%, taking 5th position among the leading causes of deaths in Myanmar (Myint-Lwin *et al*, 1985). More than 90% of deaths resulted from venomous snake bite in Myanmar are due to the bite of Russell's viper (*Vipera russelli*) (Aung-Khin *et al*, 1980). A safe and effective treatment for envenomation is the intravenous (iv) administration of potent monospecific anti-snake venom (ASV) for Russell's viper, a product of Myanmar Pharmaceutical Factory (MPF), in an adequate dose immediately after a bite. In spite of the availability and wide use of antivenom, the snake bite fatality rate still remains high in our country. One of the reasons for this high mortality may lie in delayed antivenom therapy, probably due to late arrival at the hospital since almost all the snake bite cases occur in paddy fields far away from health centers, where *iv* route of ASV administration is impossible. Therefore, intramuscular (*im*) injection of ASV immediately after bite at the site of incidence in the field prior to hospitalization may serve as an effective first aid measure in situations where intravenous administration is not possible. Preliminary study on *im* administration of Russell's viper antisera on experimentally envenomed mice and rats revealed that immediate administration by *im* route was able to reduce the lethality (Aye-Than and Saw J Tha, 1990; Tin-Win *et al*, 1992). However, the amount of ASV to be given was approximately 4-fold over the *iv* dosage to achieve equipotency (Win-Aung *et al*, 1996).

Therefore, this study has been extended to compare the efficacy of *im* antisera administration as a first aid measure in the field followed by standard hospital management versus standard hospital management alone in the management of Russell's viper bite victims with the aim of reducing morbidity and mortality.

EXPERIMENTAL DESIGN AND METHODS

The study was carried out in Tharyarwady Township, 130 km north of Yangon and which comprises of 50 villages with a population of around 20,000. This area of Myanmar has a high incidence of Russell's viper bites which occur mostly during the paddy harvesting season *ie* from November to January every year (Thein-Than *et al*, 1991).

About 50 basic health staff (BHS) from the villages participated in this study and served as mobile task force. Prior to the snake bite season they were trained for the techniques of *im* antisera administration. Each BHS was given a pair of antisera, disposable syringes with needles, methylated spirit swabs. They were stationed at the respective village tract near the working sites of the farming activities, and were instructed to give a total of 10 ml ASV (5 ml to each buttock) intra-

muscularly to a victim within 2 hours after a bite in the field. The present study was based solely on the field situation which required emergency medical attention and all the patients who came to BHS were explained about the nature of the experiment and their voluntary written consent was taken just before the administration of *im* ASV. Those who had received *im* ASV at the field and then been transferred immediately to the township hospital for further standard hospital management were regarded as test cases. Those who had not come to BHS, had not received *im* ASV and been directly hospitalized after a bite were regarded as control cases. Patients of both the test and the control groups were then given the same hospital management. They were kept in hospital for a minimum of 5 days. Blood and urine samples were taken at the time of admission, 6 hourly on day 1 and then daily from day 2 to day 5 or up to the day of discharge, transfer or death, for detection of disseminated intravascular coagulation (DIC) by 20-minute whole blood clotting test (Warrell *et al*, 1977), clinical proteinuria by boiling test (Varley *et al*, 1980), blood venom antigen by ELISA method (Voller *et al*, 1979) and serum creatinine by Alkaline picrate method (Bonsnes and Taussky, 1945).

The standard hospital management consisted of giving 40 ml monospecific antisera intravenously to the patient if systemic envenomation, manifested by incoagulable blood (*ie* DIC) and/or clinical proteinuria, was observed. If the systemic envenomation, as shown by the above tests, persisted even after 6 hours, another 40 ml of antisera was given to the patients. Besides, specific treatments for hypotension and oliguria were instituted to the patient if necessary. The patients with high serum creatinine and oliguria were transferred to Renal Unit, Yangon General Hospital for peritoneal dialysis (PD).

RESULTS

The total number of Russell's viper bite patients confirmed by positive circulating blood venom antigen included in this study was 116; out of which 34 had received 10 ml of *im* ASV at the field prior to hospitalization (test cases) and 82 had not (control cases). The age of the victims in the control and the test groups were found to be 30.6 (mean) ± 12.7 (SD) and 29.9 (mean) ± 11.4 (SD) years respectively. Sex distributions (male:female) among the two groups were 68:14 and 26:8. All the patients had received first aid tourniquet application in the field prior to hospitalization. The distance that a patient had to travel from the site of incidence to hospital was 5.56 ± 2.8 miles for the control group and 6.88 ± 3.8 miles for the test group. The time intervals between bite and hospital admission for the two groups were found to be 2.83 ± 2.9 and 3.19 ± 2.5 hours respectively. The lengths of the snakes brought along with the patients were measured and found to be 423 ± 254 mm (for control) and 340 ± 211 mm (for test). The comparisons between the two groups with respect to the above factors showed no significant differences probably indicating the validity of our experimental design.

Comparisons of clinical and biochemical data between control and test groups are shown in Table 1. The number of patients with DIC, clinical proteinuria, oliguric acute renal failure (ARF) and who required *iv* ASV therapy at the hospital were significantly reduced in the test group when compared with the control. None of the test patients without DIC at admission later developed DIC during the clinical course. The number of patients with systemic bleeding, hypotension, and who required peritoneal dialysis, were also apparently reduced in test cases when compared with controls although no significant differences were observed. The fatality rate and duration of hospital stay also seemed to be reduced in the test group. Blood venom antigen levels at the time of admission was found to be significantly less in test cases when compared with controls, presumably indicating that a certain amount of circulating venom introduced by snake bite had already been neutralized by the ASV given intramuscularly as a first aid resulting in lesser degree of envenomation, complications and fatality in test cases. Maximum serum creatinine levels and the number of patients with proteinuria of more than 10 g/l of urine (*ie* proteinuria 4+) were also found to be significantly lowered in the test group when compared with controls, suggesting a lesser degree of renal damage in test cases.

Patterns of proteinuria during 5 days clinical course in the control and test groups are shown in Fig 1. The mean maximum amount of protein in urine of control cases exceeded 5 g/l, (*ie* proteinuria 3+) and was persistent throughout the clinical course whereas in the test group it was found to be less than 1.5 g/l (*ie* proteinuria 2+) and disappeared within

Table 1

Clinical and biochemical features of Russell's viper bite victims who had received *im* ASV at field (test) and who had not (control).

Clinical and biochemical features	Control[a] (n = 82)	Test[a] (n = 34)	Significance
DIC (incoagulable blood)[b]	34 (41.5%)	7 (20.5%)	$p < 0.03$*
Clinical proteinuria[b]	33 (40.2%)	6 (17.3%)	$p < 0.02$*
Oliguric ARF[b]	18 (21.5%)	1 (2.9%)	$p < 0.03$*
Systemic bleeding[b]	11 (13.4%)	1 (2.9%)	NS*
Hypotension[b]	6 (7.3%)	Nil	NS**
Change from non-DIC to DIC in hospital[b]	13 (15.9%)	Nil	$p < 0.02$**
IV ASV administration received[b]	36 (43.9%)	8 (23.5%)	$p < 0.05$*
Cases requiring peritoneal dialysis[b]	12 (14.6%)	1 (2.9%)	NS*
Death[b]	7 (8.5%)	1 (2.9%)	NS*
Hospital stay (days)[c]	8.1 ± 9.6	5.74 ± 1.14	NS***
Blood venom antigen level on admission (ng/ml)[c]	46.3 ± 21.7	20 ± 13.3	$p < 0.001$***
Maximum serum creatinine (mg/dl)[c]	3.05 ± 2.81	1.42 ± 1.04	$p < 0.001$***
Proteinuria > 10 g/l[b]	18 (21.9%)	2 (3.3%)	$p < 0.05$***

[a] Data between the two groups were compared using chi-square test*, Fisher's exact test**, and unpaired student's *t* test***

[b] Number of patients

[c] Mean ± standard deviation

S means not significant at the 5% probability level

48 hours after the bite. Fig 2 shows the pattern of serum creatinine level in the two groups. After attaining maximum levels of 3.05 and 1.42 mg/dl in control and test groups respectively, the serum creatinine declined to normal within 5 days of clinical course in test cases but not in the controls, suggesting that in control cases there may be considerable renal damage which persisted throughout the 5 days clinical course as against only a mild degree of renal involvement in test cases for the first 48 hours after bite.

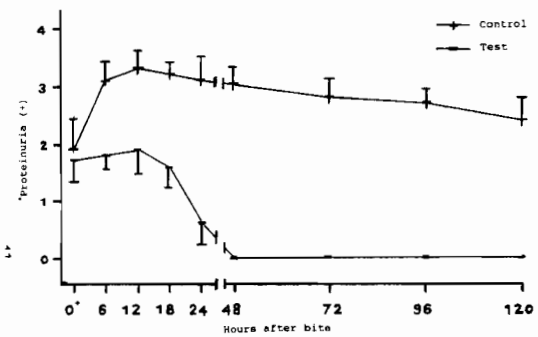

Fig 1–Patterns of proteinuria in the test and the control groups
Each value represents mean ± SEM
*Detected by the boiling test
*Represents the time of admission which generally lasted 0-5 hours

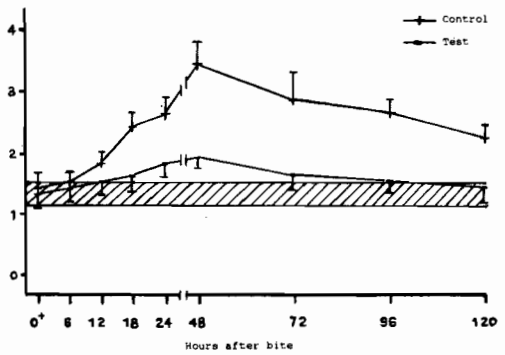

Fig 2–Patterns of serum creatinine level in the test and control groups
Each value represents mean ± SEM
*Represents the time of admission which generally lasted 0-5 hours
Shaded area represents the normal range

DISCUSSION

It is well known that *iv* administration of specific antisera in Russell's viper bite by intravenous route is an ideal treatment. However, this can only be done at the hospital. Recent studies (Myint-Lwin *et al*, 1985; Than-Than *et al*, 1988) also indicated that DIC and ARF still occurred even after antisera were given by the intravenous route in adequate dosage at the hospital. The reason may be that intravenous administration of antisera could not be done in time and irreversible organ damage might have already occurred by the time the patient was admitted to the hospital. From previous studies (Saw-Naing, 1985) the case fatality rate was found to rise with the time elapsed between bite and initiation of *iv* ASV therapy. In our study, *im* ASV first aid treatment given within 2 hours after bite prior to hospitalization could reduce the number of patients with systemic envenomation, complications following DIC and fatality rate when compared with those who had not received the first aid measure. It should be noted that there was a smaller number of patients in the test group who required further *iv* ASV therapy and peritoneal dialysis in the hospital when compared with the control group. Besides, only slight and transient damage to the kidneys might have occurred in the test cases, as judged by proteinuria and serum creatinine values (Fig 1, 2).

Hence, it may be concluded that intramuscular antisera administration immediately after bite by Russell's viper may be of value as a first aid measure in the field where the intravenous route is not possible or where transport to hospital is likely to be delayed for more than 3-4 hours, in order to prevent development of some major complications.

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