Title	<Case Report>Therapeutic Experience of Venomous Snakebites by the Japanese viper (Agkistrodon halys Blomhoffii) with Low Dose of Antivenin : Report of 43 Consecutive Cases
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Therapeutic Experience of Venomous Snakebites by the Japanese viper (Agkistrodon halys Blomhoffii) with Low Dose of Antivenin: Report of 43 Consecutive Cases

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Abstract

Forty-three consecutive patients of venomous snakebite by the Japanese viper (Agkistrodon halys Blomhoffii, "Mamushi" in Japanese) were treated with an uniformly scheduled therapy from 1990 and 1994. The therapy was mainly composed of minimal dose of antivenin, methylprednisolon and cepharanthin. There were two clinical courses, i.e., the minimal envenomation course (Group A, n=14) and the severe one (Group B, n=29). Our treatment was so satisfactory that all patients of both groups fully recovered activities of daily living with neither organic disorders nor sequelae of the bitten extremities.

The high appearance ratio of atypical lymphocytes ($P<0.05$) and the increased ratio of lymphocyte count to White blood cell count ($P<0.02$) could be indicators that predict which clinical courses the patients take.

Introduction

The Japanese viper (Agkistrodon halys Blomhoffii, "Mamushi" in Japanese) is one of the representative venomous snakes in Japan. It prevails from the western area around Caspian Sea to the Far East, and to Taiwan in south area[1]. The venom is composed of several enzymatic components such as phospholipases and proteinases, which constitute the venom in other snakes as well[2,3]. They cause local tissue necrosis at the bitten site, alter blood vessel permeability and destroy red blood cells. Furthermore, as a result of hemorrhagic, degenerative and coagulation-necrotic changes in the parenchymal organs, the venom brings about hypovolemic shock, renal failure, cardiomuscular disorders, and disseminated intravascular coagulopathy (DTC)[4]. These systemic abnormalities sometimes result in death. Several deaths are reported among two or three thousand annual victims in Japan[5].

In the present paper, we report satisfactory outcomes of our uniformly scheduled treatment, which depended in its main effect on early usage of low dose antivenin, for Japanese viper bite of 43

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consecutive patients. We also present statistical data, which show what kinds of laboratory findings or maneuvers on admission could predict the severity of the clinical course.

Materials and Methods

1. Patients

From 1990 to 1994, 47 patients were consecutively admitted to our hospital for Japanese viper bite. Four patients among them were eliminated from the present study, since, due to positive skin tests to antivenin, they were not given the treatment mentioned below. Forty-three patients were, therefore, investigated in this study.

2. Manner of treatment

The 43 patients were managed under an uniformly scheduled treatment. Namely, intravenous fluid administration, which was continued until the envenomation subsided, was started at first, and then small scarification at the fang marks was performed. One gram of methylprednisolone sodium succinate and 10 mg of cepharanthin were subsequently given intravenously, the latter being daily used in 10 mg until edema and erythema disappeared. A broad-spectrum antimicrobial agent (Cefazolin sodium) was daily given prophylactically. Three thousand units (a half vial) of freeze-dried Japanese viper antivenin (Takeda Co. Lot. No. 876331, Japan) dissolved in 500 ml of lactate ringer was administered after confirmation of negative skin test. Thirty minutes was spent in completing it. After no allergic reactions to the antivenin were ascertained, more 3000 units of antivenin (another half vial) diluted in 0.9% sodium chloride (10 ml) was intravenously injected slowly. The bitten extremity was immobilized and elevated to the level of the heart.

3. Grading of envenomation severity and patients' classification

Envenomation grading was determined by the modified method of *McCollough* and *Gennaro* (Table 1)[6]. The patients in grade 0, 1 and 2 were assigned to Group A as a minimal envenomation group whereas those in grade 3 and 4 were assigned to Group B as a severe envenomation group.

4. Reviewed subjects

1) Clinical items

The following items were reviewed: age, sex, bitten site, interval between the bite and the arrival at the hospital, history of personal treatment maneuvers immediately after the bite, severity of envenomation, clinical manifestations of envenomations, hospitalized period and final clinical outcome.

2) Laboratory data

White blood cell (WBC) count, blood picture, platelet count, lactate dehydrogenase (LDH), creatine kinase (CK), blood urea nitrogen (BUN) and creatinine (Cr) were analized.

Table 1 Envenomation grading (6)

Grade	Severity	Description
0	None	Swelling and erythema around the fang marks of <2.5 cm
1	Minimal	Swelling and erythema around the fang marks of 2.5 to 15 cm
2	Moderate	Swelling and erythema around the fang marks of 15 to 40 cm
3	Severe	Swelling and erythema around the fang marks of >40 cm
4	Very severe	Severe systemic signs including coma and shock

3) Statistical methods

Differences between quantitative variables were determined by the Student's t test or by the two sample Wilcoxon test. All statistical analyses were performed as two-tailed tests, and results are expressed as the mean±SD. Categorial variables were compared using the chi-square test. Differences were considered to be significant for $p<0.05$.

Results

Patients ranged in age from 6 to 87 years, with an average 54.5 years. Twenty-three patients were males and 20 females. The bites occurred on the upper extremity in 24 patients (56%), while on the lower extremity in 19 patients (44%). Before arrival at the hospital, personal maneuvers had been done in 33 cases; tying the limb proximal to the bitten site (29 patients), suck by mouth (13 patients) and scarification by hand (2 patients).

Immediate hypersensitivity reactions to antivenin occurred in 4 patients (9.3%). All the 4 patients presented urticaria. Two of them showed urticaria alone. Among the remaining two, one was accompanied by chest discomfort, and another suffered from shock, which could be successfully treated with epinephrine, dopamine and aminophylline. Delayed hypersensitivity reactions (serum sickness) were not observed in all the 43 patients during the hospitalized periods.

Necrosis and infection in the bitten extremities were not observed in all cases. Therefore, fasciotomy was not necessary in any of them. No motor and sensory disturbances of the bitten extremities developed in all cases and all patients recovered activities of daily living (ADL) completely.

The values of renal function tests (BUN and Cr) remained normal during the hospitalized interval in all cases (Table 4). Platelet counts did not changed in all cases (the value on admission: the lowest value in hospital stay=$21.9\pm6.5\times10^4$: $19.2\pm5.4\times10^4$ Counts/mm^3). Abnormalities in laboratory tests (CK, LDH and WBC) wholly returned normal by the patients' discharges (data not shown).

The envenomation grading of patients was as follows: seven patients belonged to grade 0, four to grade 1, three to grade 2, twenty-nine to grade 3 and none to grade 4. The comparison between

Table 2 The comparisons of clinical background between Group A and B

	Group A: Minimal envenomation (n=14)	Group B: Severe envenomation (n=29)	Statistical Significance
Mean age	55.2±18.1 (6–87)	54.1±20.8 (6–73)	n.s.
Man : Woman	8 : 6	15 : 14	n.s.
hospitalization (days)	5.5±3.5	11.3± 5.3	$p<0.003$
Intervals between bite and arrival (minutes)	38.7±30.0	39.5±27.2	n.s.
Number of people with personal maneuvers	14	19	$p<0.05$
Number of side effects with antivenin	0	4	n.s.
Number of people with systemic symptoms of envenomation	2	11	$p<0.05$

n.s.: no significant

Group A (minimal envenomation group, n=14) and Group B (severe envenomation group, n=29) is listed in Table 2. There was no significant difference between these groups in the patients' age, sex and interval from bite to arrival at the hospital. The rate of the patients who had performed personal maneuvers mentioned-above was significant higher in Group A (100%) than in Group B (70.4%) ($p<0.02$, chi-square test). As systemic envenomation, mild nausea was seen in one of 14 patients (7.2%) in Group A, whereas eleven out of 29 patients (37.9%) in Group B exhibited such symptoms and signs as chest discomfort in 4, vomiting in 2, sore throat in 2, diplopia in 2, fever in 1, headache in 1, abdominal pain in 1 and arrhythmia in 1 ($p<0.02$, chi-square test).

Table 3 shows the laboratory data on admission in both groups. WBC count, LDH, CK, BUN and Cr never showed a significant difference between Group A and B. However, the ratio of lymphocyte count to WBC count was significantly higher in Group B (44.4±12.0%) than in Group A (30.3±16.3%) ($p<0.03$, two sample Wilcoxon test). Atypical lymphocytes appeared more frequently in Group B (67%) than in Group A (20%) ($p<0.02$, chi-square test). The ratio of atypical lymphocyte to WBC count was also higher in Group B ($p<0.02$, two sample Wilcoxon test). The peak values of LDH and CK correlated well with the envenomation grading, whereas WBC, BUN and Cr did not have any significant relationships with the grading (Table 4).

Discussion

The Japanese viper venom can be life-threatening. Acute renal failure due to shock or systemic coagulopathy was reported to be the leading cause of death[7].

Antivenin, uniformly used in our series, is the mainstay of treatment of serious snake envenomation[8, 9]. Antivenin therapy is intended to neutralize and eliminate the toxic potential of venom. Antivenin can minimize morbidity and mortality when administered early in the treatment of snakebite poisonings[8]. *White* et al. experienced the patients of viper bites who showed immediate recoveries from coagulation disorders after intravenous administrations of antivenins[10]. The

Table 3 The comparisons of laboratory tests on admission between Group A and B

	Group A: Minimal envenomation (n=14)	Group B: Severe envenomation (n=29)	Statistical Significance
WBC (number/mm 3)	7092±1673	7286±2606	n.s.
The ratio of lymphocyte to WBC (%)	30.3±16.3	44.4±12.0	$p<0.03$
The ratio of atypical lymphocytes to WBC (%)	0.2±0.4	2.1±3.1	$p<0.02$
Number of people with atypical lymphocytes	2 (n=10)	14 (n=21)	$p<0.02$
Creatine Kinase (CK) (IU/L)	129±46	213±145	n.s.
Lactate Dehydrogenase (LDH) (IU/L)	398±86	476±177	n.s.
Blood Urea Nitrogen (BUN) (mg/dl)	16.8± 5.4	17.4± 4.8	n.s.
Creatinine (Cr) (mg/dl)	0.7±0.3	0.7±0.2	n.s.

n.s.: no significant

Table 4 The comparisons of peak values of laboratory tests during hospitalization between Group A and B

	Group A: Minimal envenomation (n=18)	Group B: Severe envenomation (n=29)	Statistical Significance
WBC (number/mm 3)	12608±4021	12069±2906	n.s.
Creatine Kinase (CK) (IU/L)	221±186	906±970	$p<0.005$
Lactate Dehydrogenase (LDH) (IU/L)	425±46	605±222	$p<0.002$
Blood Urea Nitrogen (BUN) (mg/dl)	18.8± 4.5	19.2± 4.0	n.s.
Creatine (Cr) (mg/dl)	0.7±0.2	0.8±0.2	n.s.

n.s.: no significant

effectiveness of Japanese viper antivenin was ascertained in the experimental study using guinea pigs[4]. Among 7 guinea pigs injected with Japanese viper venom, 4 died without entivenin and all the other three lived with antivenin.

Several authors consider, however, that in snakebite the antivenin is unnecessary for the patients with mild envenomation[10–12]. Their thought is based on the ground that antivenin is potentially hazardous due to allergic reactions. For copperhead snakebites (Agkistrodon species), *White* et al recommended withholding antivenin therapy since their symptoms were generally milder than those of rattlesnake bites[10]. *Burch* et al reported on an antivenin-free therapy given to 42 patients with copperhead snakebites[12]. They regarded the results to be satisfactory, since they experienced no cases of death or extremity amputations. Thirty-two per cent of the patients, however, showed the abnormalities in platelet counts, 14% suffered from coaglopathy during the treatment, and 16% developed tissue necrosis or infection at the betten site. With antivenin-used therapy, we experienced neither deaths nor sequelae of the extremities. In addition, we met with no abnormalities of platelet counts. No local lesions such as tissue necrosis or infection took place. The above comparison between antivenin-free and antivenin-used therapies revealed that the latter was superior to the former.

The incidence of allergic reactions in our series was much less than that in other reports. It was reported that 23% of the patients developed immediate allergic reactions to Crotalidae antivenin[13]. Fifty percent of these reactions could be life threatening. Another paper presented that 75% of the patients, who received antivenin, experienced serum sickness[14]. Three causes are probably surmised for the small allergic incidence in our cases. First, we used a specific antiserum to the Japanese viper venom, while Crotalidae antivenin was polyvalent. Second, the patients in our series received small doses (one vial, 6,000 unit) of antivenin, while the patients in other reports tended to receive further more vials of antivenin. *Wingert* et al stated that serum sickness always occurred when greater than seven vials of antivenin were administered[15]. Third, we used methylprednisolone with antivenin. Steroids are said to relieve the systemic toxic effects of envenomation[16] and to prevent allergic reactions to antivenin[8].

Our analysis showed that WBC count, LDH, CK, BUN and Cr on admission could not predict the severity and clinical course in the Japanese viper bite. On the other hand, the increased ratio of lymphocytes to WBC and the high percentage of atypical lymphocytes could be the promising indicators for severity of the clinical course. These hematological data are consistent with *Kosuge's* his-

tological demonstration that, in mice, the Japanese viper venom induced damage to the lymphocytic organs such as the thymus, spleen and lymph nodes[4].

The treatment strategy of poisonous snakebites remains controversial. Since this is not a prospective study, the result in this review never indicates that the antivenin needs to be used. We are rather impressed that it is not necessary for such a mild envenomation as seen in Group A. However, Japanese viper venom is potentially hazardous to human life. For a severer envenomation seen in Group B, we recommend the antivenin therapy. At least, our therapeutic experience with low dose of antivenin for the Japanese viper shows the satisfactory outcomes with few complications.

Cepharanthin, which constituted our scheduled treatment, is one of the biscoclaurin-typed alkaloids extracted from the root of Stephania cepharantha[17]. It is said that cepharanthin is effective for the Japanese viper bite by stabilizing the cell membrane and inhibiting phospholipase A2 activity known as a hemolytic poison[18]. In Japan, it is routinely used for the Japanese viper venom, chiefly because there are almost no side effects by this drug. However, its genuine clinical efficacy has not been demonstrated yet and a randomized study is needed to confirm this.

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和文抄録

マムシ (Agkistrodon halys Blomhoffii) 咬傷における少量抗毒素血清投与の経験—43症例の検討

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1990年から1994年までの5年間に当院で治療したマムシ咬傷43例について検討した．当院では原則として抗毒素血清，ステロイド，セファランチンの投与を行っているが，死亡例はなく，咬傷部の機能障害を示した症例もなかった．4例（9.3%）に即効型過敏反応が認められた．1例は anaphylaxy shock を呈したが治療により即時改善をみた．遅延型血清病は入院期間中観察されなかった．McCollough らの分類により軽症例 (n=14) と重症例 (n=29) に分け予後因子を検討した．治療開始前の WBC, CPK, LDH, BUN, Cr はいずれも重症化指標とはなりえなかったが，白血球中のリンパ球比率 ($P<0.02$), 異型リンパ球出現率 ($P<0.05$) が高い程，重症化することが示唆された．死亡報告が散見されるマムシ咬傷に対し受傷早期の抗毒素血清投与は有用であり，即効型過敏反応に即座に対応すれば比較的安全に投与できるものと考えられた．しかし，軽症例に対しての抗毒素血清投与には疑問が残り，今後は重症化が危惧される症例を的確に選択する必要があると思われた．