

Original Article

Surveillance of the Clinical Use of Mamushi (*Gloydius blomhoffii*) Antivenom in Tertiary Care Centers in Japan

Toru Hifumi*, Akihiko Yamamoto¹, Kazunori Morokuma², Tomoko Ogasawara, Nobuaki Kiriu, Eiju Hasegawa, Junichi Inoue, Hiroshi Kato, Yuichi Koido, and Motohide Takahashi¹

Division of Critical Care Medicine and Trauma,

National Hospital Organization Disaster Medical Center, Tokyo 190-0014;

¹*Department of Bacteriology II, National Institute for Infectious Diseases, Tokyo 208-0011; and*

²*Human Vaccine Production Department, The Chemo-Sera-Therapeutic Research Institute (KAKETSUKEN), Kumamoto 860-8568, Japan*

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SUMMARY: We report the results of the first large-scale questionnaire surveillance on the clinical use of pit viper antivenom in tertiary care centers in Japan. The questionnaire surveillance was conducted over a period of 3 years (April 2006 to March 2009). Completed questionnaires were received from the tertiary care centers of 108 (49.3%) medical institutions. In that period, 574 cases of pit viper bites, including 2 severe cases, were reported. Antivenom was administered in 44% of the cases of pit viper bites, and of these cases, 2.4% had adverse reactions but no severe symptoms. Approximately half of the clinicians indicated that antivenom was effective. Antivenom was recognized to be safe; however, the remarkable finding was that although the severity of treated cases was unclear, some clinicians reported using cepharanthine as the first choice of treatment for pit viper bites.

INTRODUCTION

Japanese mamushi, *Gloydius blomhoffii*, a species of pit viper distributed throughout Japan excluding Ryukyu Islands, is sighted from spring to autumn. It is important that many people are bitten by this pit viper in the mountains and fields of rural Japan. The annual number of pit viper bites remains unclear because there is currently no system to report pit viper bites to the public health department in Japan. Some reports estimate the number of pit viper bites to be 1,000 with 10 deaths annually (1).

Fatalities due to pit viper bites are generally low, but severe cases involving cardiac, pulmonary, and/or renal dysfunction can be lethal (2-4). These symptoms are caused by the snake's venom, which has lethal and hemorrhagic activities (5). Passive immunization against the venom is crucial for the clinical treatment of bites. Antivenom can neutralize both the hemorrhagic and lethal activities of venom. However, since they are derived from horse serum, these exogenous serum products frequently cause shock and anaphylaxis (6). A satisfactory treatment strategy has been proposed on the basis of the progress of symptoms following pit viper bites (1). An essential and rationalized therapy for severe cases of pit viper bites is rapid intravenous administration of antivenom. Therefore, antivenom should be administered to the snakebite victim safely and quickly. The annual antivenom production in Japan is 3,000

doses, which is gradually decreasing because of the limited opportunity for use (7).

Any snakebite victim should immediately visit a hospital's emergency department, unless the snake has been positively identified as nonvenomous, because of the potential lethal effects of snake venom. We conducted this survey to elucidate the number of snakebite cases and related therapy in tertiary care centers in Japan. This is the first large-scale questionnaire surveillance on the clinical use of pit viper antivenom in tertiary care centers in Japan.

We received reports of 574 cases of pit viper bites, including 2 severe cases, from tertiary care centers of 67 medical institutions. Antivenom was administered in 44% of pit viper bite cases, and adverse reactions to the serum were reported in only 2.4% of cases, with no severe symptoms.

METHODS

We used a newly designed questionnaire to survey the clinical use of pit viper antivenom at all 219 tertiary care centers in Japan. The questionnaire was sent in October 2009. The completed questionnaires were collected within 3 months. The content of the questionnaire is provided in Table 1. The questionnaire surveillance was conducted for a period of 3 years (April 2006 to March 2009).

RESULTS

Completed questionnaires were received from the tertiary care centers of 108 (49.3%) medical institutions that reported 574 cases of pit viper bites, including 3 cases of complications. Among the centers that responded, 67 reported having treated cases of pit viper

*Corresponding author: Mailing address: Division of Critical Care Medicine and Trauma, National Hospital Organization Disaster Medical Center, 3256 Midoricho, Tachikawa, Tokyo 190-0014, Japan. Tel: +81-42-526-5511, E-mail: hitoru@tdmc.hosp.go.jp

Table 1. Questionnaire on the clinical use of pit viper antivenom

1. How many pit viper bites have you treated in the last 3 years?
2. Please select two or three grounds listed below for the diagnosis of a pit viper bite.
 - (1) identification of the pit viper, (2) appearance of the bite, (3) clinical judgment, (4) declaration of the patient, (5) local signs, (6) systemic signs, and (7) hematological parameters.
3. How many doses of antivenom were used for treating pit viper bite(s)?
4. What was the outcome of the pit viper bite(s)?
5. Did you encounter serum sickness and/or adverse reaction to antivenom in any patient? Could you tell us the outcome of the same?
6. Did you use drugs other than antivenom for treating the pit viper bite(s)? (1) Cepharanthine, (2) Others.
7. What do you think of the effectiveness of antivenom?
 - (1) Effective for both severe and mild cases
 - (2) Effective for only severe cases
 - (3) Ineffective
 - (4) Other
8. What do you think of antivenom utility?
 - (1) Essential
 - (2) Can be used only for severe cases
 - (3) Is an alternate drug
 - (4) Other

bites, and 52 (78%) of these centers reported administering antivenom in 253 cases.

Respondents were asked to rationalize their diagnosis of pit viper bites based on the following 7 criteria: (1) identification of the pit viper, (2) appearance of the bite, (3) clinical judgment, (4) declaration of the patient, (5) local signs, (6) systemic signs, and (7) hematological parameters. The responses are summarized in Fig. 1. Among the 7 criteria, criterion 4 was most commonly used for establishing a diagnosis; the other commonly used criteria included 2, 1, 5, 6, 7, and 3, in decreasing order of frequency. Criteria 4, 2, 1, and 5 accounted for 90% of diagnoses.

The distribution of cases of pit viper bites in each tertiary care center is illustrated in Fig. 2. The geometric mean number of cases in these centers was calculated to be 5.3 cases. The care centers were classified into 3 groups based on the number of cases reported: (i) no case, (ii) less than 10 cases, and (iii) more than 10 cases (Fig. 2). Among the 108 centers that responded, 41 had no cases, 50 had less than 10 cases, and 17 had over 10 cases.

Following antivenom treatment, 6 cases including 2 severe cases from K. Red Cross Hospital were reported as having adverse effects. We reconfirmed the details of the 2 severe cases, which experienced mild anaphylaxis with rapid recovery. No cases of severe adverse reaction were observed.

Other than the pit viper antivenom, cepharanthine (CEP) was administered in 52 centers, which coincided with the number of institutions where antivenom was administered. While the severity of cases in which antivenom was administered remains unclear, CEP without antivenom was administered in 17 cases. That is, CEP was the first choice for treatment of pit viper bites in these 17 cases, even though the details of these cases are still unclear.

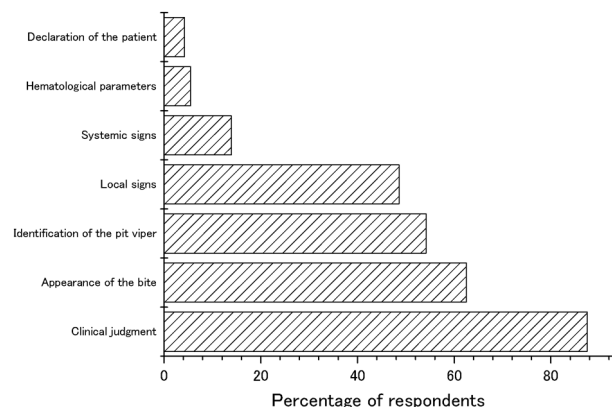


Fig. 1. Criteria for the diagnosis of pit viper bites. Respondents were asked to rationalize their diagnosis of pit viper bites based on 7 criteria. The percentage of respondents for each criterion is presented.

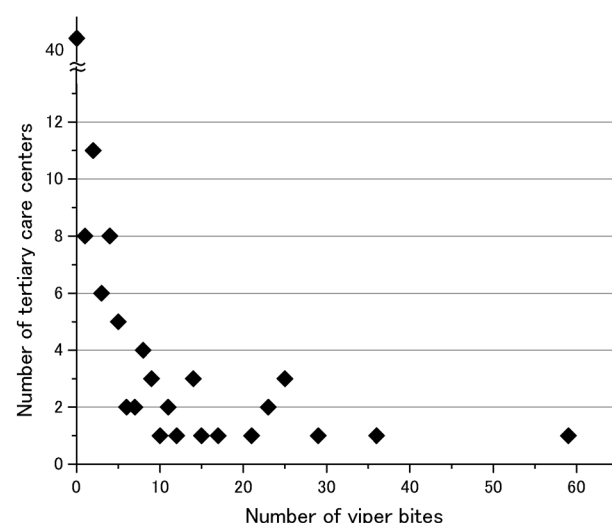


Fig. 2. Distribution of pit viper bite cases at each tertiary care center. The number of cases of pit viper bites at each tertiary care center is presented.

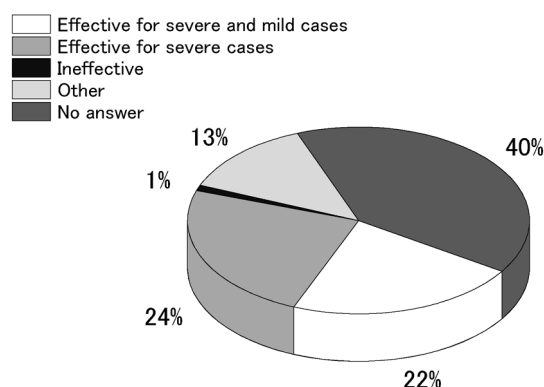


Fig. 3. Effectiveness of antivenom treatment. The responses evaluating the effectiveness of antivenom for pit viper bites were placed in the following 5 categories of answers: (i) effective for severe and mild cases, (ii) effective for severe cases, (iii) ineffective, (iv) other; and (v) no answer.

Antivenom was effective in 46% of cases of pit viper bites, but was not considered entirely effective in 13% of cases, and further study is required for evaluation of

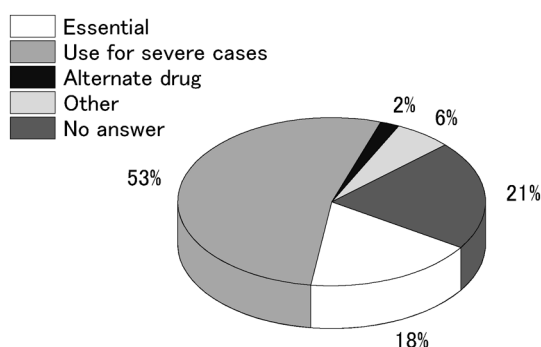


Fig. 4. Necessity of antivenom treatment. The clinicians' evaluation of the necessity of antivenom use for pit viper bites were assigned to the following 5 categories: (i) essential, (ii) use for severe cases, (iii) alternate drug, (iv) other; and (v) no answer.

its efficacy (Fig. 3).

Over 70% of the clinicians answered that they considered it necessary to use the antivenom for treating pit viper bites, whereas 6% considered the evidence inconclusive and could not evaluate its necessity because of the lack of experience in the use of antivenom during the past 10 years (Fig. 4).

DISCUSSION

Snakebites are not systematically reported in most countries. Moreover, very few countries possess a reliable epidemiological reporting system capable of providing precise data on snakebites (8). This survey is the first large-scale questionnaire surveillance on the clinical use of pit viper antivenom in tertiary care centers in Japan. It was difficult to estimate the total annual number of pit viper bite cases from our surveillance because of the lack of surveillance power as not all pit viper bite cases are transferred to tertiary care centers in Japan. However, questionnaires were received from approximately half of the tertiary care centers, and 574 pit viper bite cases during the 3 years of the study were reported. Therefore, approximately 400 cases of pit viper bites would be expected annually in all tertiary care centers in Japan.

The remarkable finding is that although the degree of severity of cases was unclear, some clinicians answered that CEP was their first choice for treatment of pit viper bites. Other centers reported adopting CEP as their first-line therapy because previous studies had suggested adverse reactions in patients receiving antivenom and because the efficacy of the antivenom had not been proven. CEP is a biscochlorine (bisbenzylisoquinoline) amphipathic alkaloid isolated from *Stephania cepharantha* Hayata. CEP or extracts from this plant are widely used, primarily in Japan, to treat a variety of acute and chronic diseases. Conditions treated with CEP include alopecia areata (9), radiotherapy-induced leucopenia (10), malaria (11), and septic shock (12). Other pharmacological activities mediated by CEP include inhibition of plasma membrane lipid peroxidation that leads to membrane stabilization (13), inhibition of histamine release (14), immunomodulation (15), anti-allergic effects (16), anti-inflammatory effects (17), anti-HIV effects (18), inhibition of platelet aggregation (19), and antitumor activity (20).

CEP has not been reported to neutralize circulating venom. Discussions on this subject took place almost 15 years ago, and it must be confirmed that CEP does not neutralize pit viper venom (21,22). No reports outside Japan recommend CEP for the treatment of pit viper bites (23). The legal ramifications for a doctor failing to administer antivenom to a pit viper bite victim also require consideration (21).

Venom sometimes causes human death, and the only antidote that can neutralize circulating venom is antivenom, which consists of concentrated immunoglobulins from the plasma of domestic animals such as the horse that has been repeatedly immunized with one or more different snake venoms. These immunoglobulins specifically target venom toxins. After intravenous injection of the venom into the snakebite patient, the antibodies bind and neutralize venom toxins, thereby preventing and, in some cases, reversing the dangerous effects of envenomization. However, antivenoms themselves can cause complications, including potentially fatal anaphylactic shock. Incorrect risk-benefit assessment can lead to the unnecessary use of antivenom in patients with mild symptoms. According to our survey, mild complications occurred in only 2.4% of cases, and hence, antivenom was considered clinically safe. This incidence rate is one-fifth of that reported in clinical trial data (3) and in a previous study (24).

Approximately half of the clinicians mentioned that antivenom was effective and useful in patients with pit viper bites. Furthermore, there is the case report of a pit viper bite victim who initially presented with mild symptoms in the emergency department, but developed multiple organ failure a few days later, because antivenom had not been administered. However, as some clinicians mentioned, there are no prospective studies evaluating the clinical effect of antivenom. This large-scale questionnaire surveillance documented the relative safety of using antivenom. Future prospective, observational, multi-center studies should take into account patient characteristics such as age, gender, clinical severity, antivenom administration, intensive care unit stay, hospital stay, outcome, and complications.

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Conflict of interest None of declare.

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