PROGNOSTIC FACTORS OF GREEN PIT VIPER BITES

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Abstract. Clinical features of green pit viper bites vary from asymptomatic to fatal bleeding. Antivenin promptly reverses the coagulopathy but has considerable adverse side effects. In this study, potential clinical predictors of severe outcomes (wound necrosis, wound infection, and systemic bleeding) and antivenin allergy were determined in 271 moderate to severe cases of green pit viper bites by multivariate analysis. The incidences of systemic bleeding, wound necrosis, secondary infection, and antivenin allergy were 17.3%, 6.6%, 5.5%, and 20.8% respectively. The predictors of systemic bleeding were the combination of thrombocytopenia and prolonged venous clotting time and bite sites away from digits. A bite on the fingers or toes was a risk factor for skin necrosis (P = 0.03). Systemic absorption of the venom from digits may be poor, resulting in severe local but mild systemic effects. The presence of blisters often led to necrosis and secondary infections (P = 0.0037 and P = 0.0006, respectively). Although negative skin test results do not exclude the possibility of antivenin allergy, positive results indicate a high risk (P = 0.016) requiring special precautions.

Venomous snake bite is a common health problem in Thailand. In Bangkok and nearby areas, green pit vipers (Trimeresurus albolabris and T. macrops) comprise more than 90% of biting species. Their venom has a thrombinlike effect and platelet-aggregating activity causing hypofibrinogenemia and thrombocytopenia. The clinical features manifest as local and systemic symptoms. Local effects are vasculopathy resulting in edema, ecchymosis around the wound, blisters, and necrosis. The systemic effect is mainly mucosal bleeding.

In an analysis of clinical features and natural courses of 281 Thai patients bitten by a green pit viper, 2–3% of the patients had necrosis of fingers that necessitated surgery and 10% of the cases had coagulopathy. Only one percent of all cases manifested systemic bleeding, mostly as gum and gastrointestinal hemorrhage. However, few cases of fatal hemorrhage have been reported. Although antivenin can promptly reverse systemic effects (Manasandana S, unpublished data), 20% of patients had antivenin hypersensitivity and 2% had severe reactions. Because 90% of green pit viper bites do not cause coagulopathy, antivenin should not be administered indiscriminately. Patients should be monitored for coagulopathy and given antivenin only in severe cases. The purpose of the present study is to determine clinical variables at presentation that reliably predict the major events complicating the management of these patients, namely skin necrosis, wound infection, systemic bleeding, and antivenin hypersensitivity. The results will be used for developing a guideline for the management of green pit viper bite patients to avoid severe morbidity, prolonged observation, and unnecessary antivenin administration.

MATERIALS AND METHODS

The medical records of 278 definitively diagnosed patients with green pit viper bites who were admitted to Chulalongkorn Hospital from 1987 to 1995 were reviewed. The diagnoses were verified either by doctor’s identification of snakes brought with the patients or the patient’s identification of green snakes with red tails. (This is a specific and easily recognizable identifying characteristic of the species biting in Bangkok.) Symptoms were classified as severe when systemic bleeding was observed. Either prolonged venom clotting time (VCT) > 15 min or thrombocytopenia (platelet count < 150,000/mm³) were classified as moderate. The absence of these findings was classified as mild. Mild cases were monitored on an outpatient basis for clinical signs, VCT, and platelet count for 72 hr because almost all severe effects manifest within this period. Moderate and severe cases were admitted to the hospital. The indications for antivenin therapy are 1) presence of systemic bleeding, or 2) markedly prolonged VCT (> 30 min). Skin tests were done by the nursing staff before antivenin administration in all cases. Antivenin was diluted 1:100 with normal saline and 0.02 ml was injected intradermally along with saline controls. Wheals larger than 5 mm at 15 min were interpreted as positive. Most cases with a positive skin test result did not receive antivenin.

Severity of edema was defined by highest levels of swelling: 0 = no edema, 1 = local swelling, 2 = up to one joint, 3 = across one joint, 4 = up to two joints, 5 = across two joints, 6 = up to three joints or to the body. The VCT determinations were performed by attending doctors according to the method of Lee and White. Platelet counts were done with automated cell counters. Conventional antivenin (before July 1991) and purified antivenin (after July 1991), the products of the Queen Saowapha Memorial Institute (Bangkok, Thailand), were given at doses of 60 ml and 30 ml, respectively. Determination of the VCT was repeated every 6 hr and similar doses of antivenin were readministered until the VCT became normal.

Independent variables used for prediction of systemic bleeding were age, sex, bite sites (1 = digital versus non-digital, 2 = upper versus lower extremities), no antivenin requirement at 24 hr (no bleeding and a VCT < 30 min), severity of edema, presence of ecchymosis, presence of blisters, presence of necrosis, platelet count, presence of thrombocytopenia, VCT (min), presence of a prolonged VCT, and presence of both thrombocytopenia and prolonged VCT. Factors predictive for skin necrosis and secondary infection were the same as for bleeding with the addition of the presence of systemic bleeding. Proposed risk factors for the reactions to antivenin were age, sex, skin test results prior to antivenin administration, and purity of antivenin.
**TABLE 1**

Significant prognostic factors for severe systemic and local effects by multivariate analysis (n = 271)*

<table>
<thead>
<tr>
<th>Predictors of systemic bleeding (%)</th>
<th>Incidence</th>
<th>Odds ratio</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prolonged VCT and thrombocytopenia</td>
<td>56.5</td>
<td>4.19</td>
<td>0.0005</td>
</tr>
<tr>
<td>Bite sites: fingers or toes</td>
<td>41.0</td>
<td>0.36</td>
<td>0.0070</td>
</tr>
<tr>
<td>No antivenin indication at 24 hr</td>
<td>41.4</td>
<td>0.37</td>
<td>0.0092</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Predictors of necrosis (6.6%)</th>
<th>Incidence</th>
<th>Odds ratio</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Presence of blisters</td>
<td>24.7</td>
<td>2.39</td>
<td>0.0037</td>
</tr>
<tr>
<td>Bite sites: fingers or toes</td>
<td>41.0</td>
<td>4.54</td>
<td>0.0309</td>
</tr>
<tr>
<td>Prolonged VCT</td>
<td>84.5</td>
<td>0.11</td>
<td>0.0002</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Predictors of secondary infection (5.5%)</th>
<th>Incidence</th>
<th>Odds ratio</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Presence of blisters</td>
<td>24.7</td>
<td>2.64</td>
<td>0.0006</td>
</tr>
</tbody>
</table>

*VCT = venous clotting time.

Forward stepwise logistic regression was used for analysis of the independent factors predicting the outcomes of interest with the SPSS 6.1.3 program for Windows (SPSS, Inc., Chicago, IL). A P value < 0.05 was considered significant. The risks were reported as odd ratios.

**RESULTS**

There were 271 cases. Seven cases were excluded because they did not show some of the variables stated above. Sixty-four patients (23.6%) brought the snakes to be identified by doctors. A total of 82.5% were bitten in Bangkok and 14.2% were bitten in the adjacent provinces. Green pit vipers contribute the great majority (94%) of bites in these areas. The mean ± SD age of the patients was 32.79 ± 15.76 years. Fifty-nine percent of the patients were males. All bite sites were on the extremities, except for one case of a bite on the forehead. Upper limbs were bitten in 42% of the cases. Twenty-nine percent were bitten on fingers and 12% on the toes. Fang marks could not be identified in 8.7% of the cases and only one fang mark could be seen in 11.8%. The median degree of edema, as defined by the distance between the bite site and the highest level of edema, was up to two joints apart, ranging from local edema to edema extending up to the trunk. Fifty-two percent of the cases came to the hospital within the first 24hr after the bites. The mean ± SD time of onset of systemic symptoms was 29.7 ± 27.5 hr and 58.6% of them were within 24 hr. Systemic bleeding was found in 17.3% of the cases. The bleeding sites were the gums, gastrointestinal tract, and urinary tract in 50%, 30%, and 19.6% of the cases, respectively. Forty-one percent of the bleeding patients had multiple sites of hemorrhage. No deaths were reported during the nine-year study period. Laboratory investigations found VCT prolongation and/or thrombocytopenia in all cases according to the indications for admission. Incidences were 84.5% and 72.0%, respectively. The mean ± SD platelet count was 102,132.8 ± 88,146.4mm³. The incidences of severe outcomes and their predictors are listed in Table 1.

Univariate analysis showed that the significant predictors of systemic bleeding were bite sites other than the fingers or toes, a requirement for antivenin within 24 hr, platelet counts, and the presence of both prolonged VCT and thrombocytopenia (P = 0.01, 0.006, 0.027, and 0.005, respectively). Severe local effects could not predict systemic bleeding. Bleeding was inversely correlated with the degree of edema, but this effect was not statistically significant (P = 0.052). The presence of VCT prolongation alone had only a marginal P value (0.057). Even markedly prolonged VCT (> 30 min) or extreme thrombocytopenia (< 20,000/mm³) alone was not significantly correlated with hemorrhage, partly because antivenin is usually promptly administered in these patients. Platelet count alone was not a significant predictor in multivariate analysis (Table 1). The significant predictors for necrosis by univariate analysis were the presence of blisters, bite on fingers or toes, bites on upper extremities, no antivenin requirement for 24 hr, and the absence of VCT prolongation (P = 0.002, 0.0017, 0.03, 0.048, and 0.0002, respectively). Bites on upper extremities alone were not significant in multivariate analysis. Because a large proportion of upper extremity bites was on the fingers, the incidence of necrosis seemed to be high. The presence of blisters, necrosis, and the absence of VCT prolongation were significantly correlated with secondary infection by univariate analysis (P = 0.001, 0.0055, and 0.018, respectively). Antivenin was indicated in 192 cases (70.8%). Skin test results were positive in 9.9% (19 cases) of these patients. Two were desensitized and had no reactions to antivenin. Antivenin was given to four cases without desensitization by the judgment of their attending doctors. Although all four received antihistamine and steroid prophylaxis, three had allergic reactions. Of 178 patients who received antivenin, 20.8% exhibited hypersensitivity. The most common reaction was urticarial rash. Anaphylactic shock and bronchospasm were observed in four (2.25%) and six (3.37%) cases, respectively. One hundred two patients received antivenin in purified form (57.3%). The risk of hypersensitivity to purified antivenin was 10.78%, including two cases of anaphylactic shock. The statistically significant risk factors for reactions to antivenin were the positive skin test results and the using of nonpurified antivenin. Their odd ratios were 2.99 (P = 0.016) and 2.33 (P = 0.0001), respectively.

**DISCUSSION**

Green pit viper bite is a model of combined coagulopathy. In addition to hypofibrinogenemia and thrombocytopenia, hyperfibrinolysis (defined by elevated levels of plasminogen activator antigen and activity) has been observed.22 Thrombocytopenia and high plasminogen activator activity in saliva may explain frequent mucosal bleeding, especially at oral sites. Cases with severe coagulopathy (VCT > 30 min) usually received antivenin. However, we have shown that patients with a combination of a prolonged VCT and thrombocytopenia had about four times higher risk of bleeding than patients with either abnormality alone, even if coagulopathy was not very severe. The severity of either VCT prolongation or thrombocytopenia alone had no predictive role. This suggests that the combination of two types of moderate coagulopathy can cause serious results similar to a single, severe defect. The toxicity of green pit viper venom
is relatively mild compared with other hematotoxic snake venoms, such as Russell’s viper and Malayan pit viper, which are found in Thailand. No deaths due to the bite of the green pit viper have been reported in our hospital since the development of the specific antivenin.

After a bite, the venom is rapidly absorbed but the toxic effects may be delayed for days because it takes some time to reduce fibrinogen and platelets to a clinically significant level. If a large amount of venom is absorbed, coagulopathy will develop quickly. Therefore, if severe symptoms are not found within 24 hr after the bite, this indicates a good prognosis because of the small amount of venom absorbed. Local and systemic effects of green pit viper venom seem to be inversely correlated. Cases with a prolonged VCT tended to have a lower incidence of necrosis. The absorption of venom may play a role. Poor systemic absorption will result in a mild systemic effect but cause severe local complications because of more local venom deposition. Alternatively, cases with severe systemic effects tended to present within the first day and receive antivenin. This may partially prevent the progression of local effects because severe local symptoms take a few days to develop irrespective of systemic toxicity. Moreover, patients who were bitten on the fingers or toes had about 4.5 times more necrosis but about three times less systemic bleeding. The limited space for edema and limited blood supply of these areas may result in ischemic necrosis. The factors causing differences in venom absorption from various bite sites are unknown. We measured serum venom levels by ELISA in 52 cases of green pit viper bites and found that venom levels were not different between cases bitten on the fingers or toes (n = 23) and the other sites (n = 29). Blisters that may spontaneously rupture and be a portal of entry for bacteria constitute a significant risk for skin necrosis and secondary infection (Table 1). Therefore, patients who have blisters should be managed with great care. Local dressing and antibiotic prophylaxis are justified for ruptured blisters. These risk factors should be taken into consideration in outpatient management. For instance, patients who were bitten on the fingers more than 24 hr previously were unlikely to have clinical bleeding but should be monitored for local complications.

All antivenin used in Thailand is now purified and has less incidence of allergic reactions. Purified antivenin still poses a risk of hypersensitivity and even anaphylaxis. Skin testing before antivenin administration is a controversial procedure. One study found no correlation between skin test results and systemic reactions,13 but the sample size was small, especially for cases with both positive skin test results and antivenin administration. We agree that a negative result does not preclude severe reactions. However, a positive result indicates higher risk of reactions. A large prospective study is required for confirmation because the incidence of severe reactions is very low. Patients with coagulopathy and positive skin test results without systemic bleeding are very difficult to manage because although the antivenin is clinically indicated, the risk of allergic reactions to antivenin is high. The skin test procedure should be reviewed and properly repeated. A judgment can be made in individual cases according to their risks of bleeding. For example, cases presented within the first 24 hr or with both a prolonged VCT and thrombocytopenia are in the high risk group; thus, antivenin desensitization is suggested.

This study includes only patients with coagulopathy. Although the cases account for only 10% of the total patients, many unresolved problems in clinical management exist in this group of patients. The risk of life-threatening bleeding must be balanced against the risk of hypersensitivity to antivenin. Because incidences are quite low, a large number of patients are needed to estimate the risk accurately. Although the present study was a retrospective analysis, all chosen factors for analysis could be verified objectively before or at the occurrence of severe outcomes.

In conclusion, the independent risk factors for systemic bleeding in moderate-to-severe cases of green pit viper bites are both a prolonged VCT and thrombocytopenia and non-digital bite sites. After 24 hr, patients are less likely to develop bleeding. The predictors for skin necrosis in these cases are digital bite sites and presence of blisters. Cases with a prolonged VCT have lower risk for necrosis. Blistering is a predictor for secondary infection. Finally, because positive results indicate higher risk for allergic reactions, desensitization or omission of antivenin should be considered in these cases.

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