Prognostic indicators in patients with snakebite: analysis of two-year data from a township hospital in central Myanmar

Myo-Khin\textsuperscript{a}, Theingi-Nyunt\textsuperscript{b}, Nyan-Tun-Oo\textsuperscript{c}, Ye-Hla\textsuperscript{d}

Background: Rural people seek medical treatment for snakebite at peripheral health care facilities. Hence, identification of the characteristics, which can be used at peripheral levels of health care as reliable predictors of mortality, are required.

Methods: Hospital records of 101 patients (70 males and 31 females) with age ranging from 3 to 80 years, admitted to Nahtogyi township hospital in central Myanmar during January 2005 to December 2006 were reviewed retrospectively. Binary logistic regression was used for estimating odds ratio (OR) and 95% Confidence Interval (CI) for various prognostic indicators of mortality.

Results: Almost all snakebites were on extremities; more in legs (62%) than hands (37%). Most (52.5%) bites occurred in the morning (4 am to noon). Mean (SD) time for bite-to-hospital and bite-to-injection of anti-snake venom (ASV) was 134.6 (78.6) and 167 (187.8) minutes respectively. Eleven cases (10.9%) had died. Case fatality ratio (CFR) was significantly higher in 39 patients with un-clotted blood as compared to 62 patients with clotted blood (25.6% vs 1.6%, p <0.0005). Significantly higher CFR was observed in 49 patients who received ASV in >2 hours after the bite compared to 52 cases who received ASV within two hours (9.9% vs 0.9%, p <0.0001). Odds ratio of fatality were higher among those who had urine output of <400 ml in the first 24 hours (OR 26.4; 95% CI 2.4 to 288.3), un-clotted blood (OR 4.6; 95% CI 0.3 to 66.7), bite-to-injection time of >2 hours (OR 4; 95% CI 0.1 to 219.8) bite-to-hospital time of >2 hours (OR 3.1; 95%CI 0.1 to 136.3) and bites in the morning (OR 2; 95% CI 0.3 to 16.0).

Conclusions: Clinical parameters could be used by healthcare providers to identify snakebite patients for referral, who may have fatal outcome.

Key Words: Snakebite, urine output, anti-snake venom, prognosis, predictors, Myanmar.

Introduction

Snakebite, an important cause of death in agriculture workers of developing countries, is a priority health problem for rural populations. Recent studies show that most of the snakebites occur in South Asia, South-East Asia and Sub-Saharan Africa.\textsuperscript{2} About 5 million cases occur annually throughout the world leading to 125 000 deaths.\textsuperscript{2}
In Myanmar, snakebite cases occur in almost all the regions especially in Mandalay, Bago, Sagaing, Ayeyarwady and Yangon Divisions. It has been reported that 10,000 cases of snakebite occur annually with more than 1,000 deaths. Seventy percent of the bites are caused by Russell’s vipers (Daboia russelli siamensis). Therefore, mortality from snakebite is quite high (10%) in Myanmar. A prospective study on 500 snakebite victims revealed that the mortality could be as high as 50% in cases with severe envenomation.

Most of the snakebite patients are from rural populations living in villages and working on agricultural land. Once bitten by snakes, they seek medical treatment at rural health centres or township health care facilities. However, apart from simple clotting test and urinary examination, many of the facilities have limited laboratory and clinical capabilities required for care of critically ill patients with multi-organ dysfunction as a complication of snakebite. Thus, it is important that the health care providers should be able to identify patients with snakebites at high risk of fatal complications so as to be able to refer them to a hospital with more facilities.

The availability of complete clinical records of all snakebite patients at a township hospital prompted us to study prognostic indicators keeping in view relative interdependence or interaction of various factors that could determine morbidity and mortality. The specific aim of the study was to identify simple healthcare-related clinical characteristics, for use at peripheral levels of health care, that can serve as reliable predictors of mortality.

**Methods**

This retrospective study was carried out using hospital records. The hospital records of all snakebite cases admitted to Nahtoogyi township hospital, Mandalay Division, during the period of January 2005 to December 2006, were reviewed. The clinical outcome was listed as survived or died. Those classified as absconded, discharged on request, left against advice, referred to the tertiary centre were followed up in 2008 to classify them as alive or dead.

Descriptive characteristics of the patients and the snakebite event such as gender, age, time of bite, site of bite, bite-to-hospital time were recorded. Clinical data such as bite-to-injection time of antisnake venom (ASV), urine output on first day, clotting time, unclotted to clotted time interval, initial and total anti-venom doses administered were also noted. Signs and symptoms such as hypotension, tachycardia, swelling, vomiting, epigastric pain, and renal angle pain were also documented. Majority of hospitals in Myanmar used Mono-specific Liquid Equine Russell’s Viper Anti-Venom in liquid form (Myanmar Pharmaceutical Factory, Yangon, Myanmar).

**Statistical analysis**

MINTAB Statistical Software, Release 14 for Windows, Minitab Inc. USA was used for data entry and analysis. Following univariate analyses, comparison of the descriptive features and clinical data between survivors and non-survivors were done using ‘t’ test and chi-square test as appropriate. Bite-to-hospital interval and bite-to-injection of ASV interval, urine output in first 24 hours, clotting status, were further categorized as binary variables. Binary logistic regression models were constructed and the most significant model with the highest number of concordant and discordant pairs was selected and odds ratios (OR) and 95% Confidence Interval (CI) were calculated.

**Results**

One-hundred-and-one snakebite cases were admitted to the hospital during the two-year
study period. The age of the victims ranged from 3 to 80 years with a mean (SD) of 32.3 (15.5) years. Males predominated with a ratio of 2.2: 1. The number of snakebite cases was highest in 21-30 years age group (34, 33.7%), followed by 13-20 years (19, 18.8%), 31-40 years (16, 15.8%), > 50 years (14, 13.9%), and 41-50 years age group (13, 12.9%). Lowest numbers of cases were in children under 12 years of age (5, 5%).

Snakebite occurred throughout the year but high peaks were observed in October and January. Very low occurrences were observed in February to April. More than half (52.5%) of the bites occurred in the morning (4 am to noon), followed by afternoon (noon to 6 pm) (28.7%) and evening hours (6 pm to midnight) (18.8%). Most of the patients who died (72.7%) were bitten in the morning. Almost all bites were on extremities; legs were the more common site (62%) as compared to the hands (37%).

The time to reach the hospital ranged from 20 minutes to 7.5 hours with a mean (SD) of 134.6 (78.6) minutes (median 120 minutes). Among them, 79 (78.2%), 47 (46.5%) and 19 patients (18.8%) failed to reach the hospital within one, two, and three hours of snakebite. About a third (32%) of the cases had swelling at bite site, 31% complained of epigastric pain with or without vomiting and 5% had renal angle pain. Only a few (6%) presented with hypotension (blood pressure less than 90/60 mmHg) and or tachycardia (heart rate more than 100/minute). Although, mean (SD) urine output during the first 24 hours was 794.4 (576.6) ml (median 600 ml), 28 cases (28%) passed less than 400 ml of urine in the first 24 hours. Thirty-nine cases (38.6%) had ‘non-clotted’ coagulation status. A significantly higher mortality was observed in cases with ‘non-clotted’ coagulation status as compared to those with ‘clotted’ blood status (25.6% vs 1.6%, p <0.0001).

The mean (SD) bite-to-injection time of the initial dose of ASV was 167 (187.8) minutes (range 20 to 1560 minutes; median 120 minutes). ASV was administered to 22, 30 and 26 cases within one, two, and three hours respectively and 23 cases failed to receive ASV within three hours. The initial amount of ASV received was 20 ml in 51 cases (51%), 40 ml in 35 (35%), 10 ml in 14 (14%) and 50 ml in one case (1%). On an average (SD), 25.6 (11.3) ml of ASV was given initially; median dose being 20 ml. Seven cases received ASV at the village-based primary health care centre before they were referred to the hospital.

During the course of the treatment up to 120 ml of ASV was given at the hospital. On average (SD), 43.9 (39.0) ml of ASV was used per snakebite case (median 40 ml). A significantly larger amount of ASV (almost three times) was used in ‘non-clotted’ cases as compared to ‘clotted’ cases (Table 1). Also, a significantly larger amount of ASV per case

<table>
<thead>
<tr>
<th>Coagulation status (number)</th>
<th>Total amount of ASV used (ml) per case</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean</td>
<td>Standard Deviation</td>
</tr>
<tr>
<td>Non-clotted (39)</td>
<td>70.8</td>
<td>27.8</td>
</tr>
<tr>
<td>Clotted (62)</td>
<td>26.9</td>
<td>18.3</td>
</tr>
<tr>
<td>All cases (101)</td>
<td>43.9</td>
<td>39.0</td>
</tr>
</tbody>
</table>
was used in those who died as compared to those who survived (7.5% vs 4.0%, p <0.002). Among 39 cases with 'non-clotted' blood status, 32 cases reverted to 'clotted' stage following ASV therapy. The median clotting time on hospital admission was 540 minutes (range 60 to 1110 minutes).

Eighty-six patients recovered and were discharged from the hospital. The average (SD) duration of stay in hospital was 6.9 (3.2) days with a range of 1 to 21 days and a median of 7 days. Some of the patients (6) had to be referred for further management. Among them, three patients died and three survived. One patient, who had absconded from the hospital, was later confirmed to be alive and well. One patient who left against advice was later confirmed as died. Thus a total of 11 cases had died and 90 cases survived. Although a higher case fatality ratio (CFR) was observed in males (11.4%) than females (9.7%), the difference was not statistically significant. Higher CFR was also observed in children under 5 years of age (20%) as compared to older children and adults (Table 2).

Binary logistic regression models were constructed and the final model revealed that the odds of fatality were higher in urine output less than 400 ml in first 24 hours (OR 26.4; 95% CI 2.4 to 288.3), ‘un-clotted’ blood status (OR 4.6; 95% CI 0.3 to 66.7), bite-to-injection time of >2 hours (OR 4; 95% CI 0.1 to 219.8), bite-to-hospital time of >2 hours (OR 3.1; 95% CI 0.1 to 136.3), and bite in the morning time (OR 2; 95% CI 0.3 to 16.0).

## Discussion

In Myanmar, viper snake bites are estimated to be 7000 to 8000 per year with over 500 deaths. Although there is no doubt that the disease course may be fulminant and lethal, recognition of predictor signs with prompt necessary action could reduce the mortality.

The regression model we constructed in this study for the first time indicates that oliguria, ‘un-coagulable blood status’ on admission to the hospital, delayed bite-to-injection time, delayed bite-to-hospital interval, and morning bites have association with increased mortality for snakebite in Myanmar though only oliguria was found to be statistically significantly associated with mortality. The importance of these factors as major determinants of mortality in viper bite has been studied from various aspects using different types and levels of scientific evidence. Our model also reveals the importance of these predictors by providing the degree of statistical significance of each factor. Other factors such as the length of snake, characteristic of snakes which are

<table>
<thead>
<tr>
<th>Age group (years)</th>
<th>Number of cases</th>
<th>Died</th>
<th>Case Fatality Ratio (%)</th>
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</thead>
<tbody>
<tr>
<td>&lt;12</td>
<td>5</td>
<td>1</td>
<td>20.0</td>
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<tr>
<td>13-20</td>
<td>19</td>
<td>3</td>
<td>15.8</td>
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<tr>
<td>21-30</td>
<td>34</td>
<td>3</td>
<td>8.8</td>
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<tr>
<td>31-40</td>
<td>16</td>
<td>2</td>
<td>12.5</td>
</tr>
<tr>
<td>41-50</td>
<td>13</td>
<td>1</td>
<td>7.7</td>
</tr>
<tr>
<td>&gt;51</td>
<td>14</td>
<td>1</td>
<td>7.1</td>
</tr>
<tr>
<td>All</td>
<td>101</td>
<td>11</td>
<td>10.9</td>
</tr>
</tbody>
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Table 2: Case fatality ratio from snakebite by age group in a township hospital of Central Myanmar
Prognostic indicators in patients with snakebite

Myo-Khin et al.

beyond control have been studied previously by others.7

Haemostatic disturbances are known to be the pathological mechanism causing fulminant disease in viper bite, and bleeding tendency is well recognized as an indicator of greater risk of death.6,8,9 The present study also indicates blood incoagulopathy as a predictor of mortality.

The importance of bite-to-injection time is also well known as a significant factor influencing mortality. A study from Nepal showed that the delay in receiving treatment was significantly longer for victims with a fatal outcome.10 The optimum time for administration of ASV has been previously suggested as "as soon as possible" or within 4 hours. Bite-to-injection time of less than 4 hours is associated with rapid recovery of renal function.11 Although we were not able to determine the renal function of our patients, we found that bite-to-injection time of more than two hours could increase the mortality by four times than those who receive ASV within two hours. Our findings indicate that a delay of even two hours in neutralizing the action of venom would be enough to do pathological damage and increase the mortality.

Viper bites is one of the most common causes of acute renal failure in hospital practice in Myanmar.12 It has been demonstrated by in-vitro and in-vivo studies that viper venom has direct nephrotoxic effect in addition to causing renal impairment through disturbed blood coagulation mechanism.13,14,15 Oliguria as evidence of renal function impairment has been pointed out but opinion differs as to when it should become a deciding factor in clinical management.16 We found that urine output of less than 400 ml in the first 24 hours is a strong predictor (26 times higher risk) of mortality.

A recent paper shows the value of low dose dopamine-high dose furosemide regimen in the management of acute renal failure and suggests that this regimen may abort onset of acute renal failure if given early and should therefore be considered when a warning red flag such as oliguria or albuminuria signals impending renal failure.17 Albuminuria which is easy to perform has also been shown to be a sign of renal impairment but it may sometimes be a late sign.14,15 Detection of urinary N-acetyl-beta-D-glucosaminidase (NAG) may be an early indicator of renal damage in viper envenomation but it is not practical to do this test in township or most other hospitals.18

Numerous studies and guidelines have discussed the quantity of ASV to be given in viper bite. It is generally agreed that this should neutralize the average quantity of venom injected by the viper at one bite. Based on studies of the average quantity of venom injected by Russell’s viper (given as 63mg) and the neutralization capacity of ASV produced by Myanmar Pharmaceutical Factory (MPF) (given as 2 mg per ml) it has been recommended that the standard dose of ASV should be 40 ml for patients with systematic envenomation but with no complications.19 This ASV dose regimen was used at our study hospital during the study period, and served as a basis for our analysis.

Regarding the seasonal pattern of snakebite, the present study is one of many other studies that have shown the importance of season in snakebite problem in Myanmar. However, the morbidity pattern of the present study differs from previous findings where highest incidence of snakebite was found during the harvesting season from October to December.20 This might be due to the difference in study area; the present study focused on data from central Myanmar where
paddy as well as other crops are planted as compared to the data from lower Myanmar which has mainly paddy plantations. In the study township, in addition to rice, green peas and sesame were cultivated during the months of May, June and July. The paddy harvesting season is during September and October. In addition to the peaks in snakebite morbidity during the sowing and harvesting seasons, a third peak was observed during the months of December and January when sunflower and groundnuts were cultivated. The only period of the year where cultivation work is not done is between the months of February and April. This period coincided with a decreased snakebite morbidity observed in the present study.

Male predomination in this study was similar to the findings of previous studies. This risk is associated with greater number of outdoor activities of males than their female counterparts. Although the CFR of 10.9% is higher than our previous findings from central Myanmar; it is in agreement with other previous reports from Myanmar.

It has been documented that longer snakes cause more severe envenoming and more extensive swelling than the snakes with shorter length. In the present study, the length of the snake was not documented. Hence, length of the snake as a predictor of fatality should be investigated in future studies.

Regarding hypotension, a significant rise of blood cortisol in patients with unclotted blood has been reported. In a large study carried out in India, hypotension was identified as a large (22 times) predictor of mortality. However, relatively few cases had presented with hypotension in the present study, therefore, its significance could not be assessed.

The present study has some limitations. It was focused mainly on the predictors of mortality based on retrospective analysis of a small number of medical records from a township hospital. It will be interesting to carry out a larger clinical auditing study prospectively to identify imperfections in the management of snakebite at the peripheral level where manpower and laboratory facilities are inadequate.

In conclusion, snakebites are still a common medical emergency encountered in township hospitals, especially in rural areas. Timely treatment is the mainstay for reduction of mortality. Recognition of predictor signs is essential for clinical management and early referral which could lead to a significant decrease in mortality. Our study has established the validity of some of the predictors being used in Myanmar which will help in deciding clinical management options including ASV dose and onward referral to tertiary centers.

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References


