Acute Kidney Injury Following Eastern Russell’s Viper (Daboia siamensis) Snakebite in Myanmar

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Snakebite is a neglected tropical disease of global importance affecting at least 2.5 million people with more than 100,000 deaths annually.1,2 Morbidity and mortality are high in countries such as Myanmar, where recent hospital data reported 15,000 to 20,000 cases per year with case-fatality ratio of 10.9%.3 Experience elsewhere suggests that hospital-based data may underestimate the actual burden of snakebite by more than two-thirds.1,5

To assess outcomes of snakebite cases at Mandalay General Hospital, we established a clinical data collection system. This major hospital serves as a regional referral center for snakebite. In this region of Myanmar, Eastern Russell’s Viper (ERV; Daboia siamensis) snakebite is of the utmost importance given the high incidence of acute kidney injury (AKI) following envenoming.6,7

The primary purpose of this clinical audit, which represents one arm of an Australian Department of Foreign Affairs and Trade–funded foreign aid project to improve the outcomes of snakebite patients in Myanmar,8 is to provide accurate information to local health authorities to improve health care policies and resource allocation. In addition, we wanted to examine the clinical variables that affect the development of AKI following ERV envenoming. We report 12 months of observational data pertaining to ERV snakebites.
RESULTS

A total of 965 patients presented to Mandalay General Hospital after snakebites during the 12-month period. Data for 17 patients were incomplete, leaving 948 for analysis. Bites were attributed to ERV in 686 cases (72.4%), cobra (Naja kaouthia and Naja mandalayensis) in 17 (1.8%), “green snake” (Trimeresurus albolabris) in 61 (6.4%), krait (Bungarus spp.) in 4 (0.4%), other snakes including nonvenomous species in 35 (3.7%), and unknown snakes in 145 (15.3%). In most cases, the dead snake was brought to the hospital and identified by medical staff. In the others, the diagnostic clinical
Table 1. Clinical features of 686 cases of Russell’s Viper envenoming

| Clinical features          | Number (% of 686) | AKI group (% of 488) | No-AKI group (% of 198) |
|---------------------------|-------------------|----------------------|------------------------|
| Acute kidney injury       | 488 (71)          |                      |                        |
| Coagulopathy              | 465 (67)          | 373 (76)             | 92 (47)                |
| Thrombocytopenia          | 461 (67)          | 414 (85)             | 47 (24)                |
| Capillary leak            | 240 (35)          | 216 (44)             | 24 (12)                |
| Pulmonary edema           | 16                | 14                   | 2                      |
| Periorbital edema         | 118               | 106                  | 12                     |
| Conjunctival edema        | 91                | 82                   | 9                      |
| Generalized edema         | 15                | 14                   | 1                      |
| Shock                     | 103 (15)          | 92 (19)              | 11 (6)                 |
| Bite site infection       | 74 (11)           | 51 (11)              | 23 (12)                |
| Local necrosis            | 44 (6.4)          | 33 (7)               | 11 (6)                 |
| Gastrointestinal bleeding | 38 (5.5)          | 33 (7)               | 5 (3)                  |
| Septicemia                | 29 (4.2)          | 26 (5)               | 3 (2)                  |
| Panhypopituitism          | 19 (2.7)          | 19 (4)               | 0                      |
| Ophthalmoplegia           | 2 (0.29)          | 2 (0.4)              | 0                      |
| None                      | 59 (8.6)          |                      |                        |

In this study, AKI was defined pragmatically as a composite endpoint of either requirement for dialysis or, in the absence of requirement for dialysis, a peak serum creatinine level of >120 µmol/l in men or >100 µmol/l in women and a pattern of rising serial creatinine consistent with AKI.

Table 2. Significant explanatory variables affecting AKI as determined by multivariate logistic regression

| Explanatory variables | Group | Sig. cf. Ref.Group | Odds ratio | Lower 95% CI | Upper 95% CI |
|-----------------------|-------|--------------------|------------|--------------|--------------|
| Age group             |       |                    |            |              |              |
| (cf. 0–15 yr)         |       |                    |            |              |              |
| 50–64 yr              | P < 0.05 | 2.8                     | 1.1        | 7.2          |              |
| 65–74 yr              | P < 0.05 | 3.0                     | 1.1        | 8.3          |              |
| Gender (cf. M)        |       |                    |            |              |              |
| F                     | P < 0.01 | 1.8                     | 1.2        | 2.7          |              |
| P                     | P < 0.02 | 2.0                     | 1.3        | 3.0          |              |
| Time bite to first AV |       |                    |            |              |              |
| (cf. 0–1 h)           |       |                    |            |              |              |
| 1–2 h                 | P < 0.06 | 1.7                     | 1.0        | 3.0          |              |
| 2–3 h                 | P < 0.05 | 1.8                     | 1.0        | 3.2          |              |
| Time bite to first AV |       |                    |            |              |              |
| (cf. 0–1 h)           |       |                    |            |              |              |
| 3–4 h                 | P < 0.05 | 1.6                     | 1.1        | 11.1         |              |
| 4–5 h                 | P < 0.05 | 1.4                     | 1.5        | 11.6         |              |
| Time bite to first HCF|       |                    |            |              |              |
| (cf. 0–1 h)           |       |                    |            |              |              |
| 4–5 h                 | P < 0.05 | 1.2                     | 2.4        | 62.9         |              |
| 5–6 h                 | P < 0.05 | 1.0                     | 2.3        | 67.3         |              |
| Time bite to first HCF|       |                    |            |              |              |
| (cf. 0–1 h)           |       |                    |            |              |              |
| >10 h                 | P < 0.02 | 1.4                     | 1.4        | 16.0         |              |

AKI, acute kidney injury; AV, antivenom; cf., compared with; CI, confidence interval; F, female; HCF, health care facility; M, male; Sig.cf.Ref.Group, significance compared with reference group.

Dependent variables:

- AKI, as defined as a composite endpoint of either requirement for dialysis or, in the absence of requirement for dialysis, a peak serum creatinine level of >120 µmol/l in men or >100 µmol/l in women and a pattern of rising serial creatinine consistent with AKI.
- Categorical variables entered into the model, derived by coding continuous explanatory variables that did not exhibit a normal distribution:
  - Age group, years: 0–15 (ref.); 16–19; 20–29; 30–49; 50–64; >64.
  - Time from bite to first antivenom administration, hours: 0–1 (ref.); 1–2; 2–3; 3–4; 4–5; 5–6; 6–10; >10.

In this study, AKI was defined pragmatically as a composite endpoint of either requirement for dialysis or, in the absence of requirement for dialysis, a peak serum creatinine level of >120 µmol/l in men or >100 µmol/l in women and a pattern of rising serial creatinine consistent with AKI.

The clinical consequences of envenoming are listed in Table 1. AKI was extremely common, manifesting in 488 patients (71% of entire cohort). Of these 488, dialysis (predominantly haemodialysis) was required in 213 (31% of entire cohort), whereas the other 275 patients (40% of entire cohort) suffered a pathological rise in serum creatinine but did not need dialysis (median peak serum creatinine 245.5 µmol/l [IQR 332] in male patients, 260.5 µmol/l [IQR 322] in female patients). Female patients were 1.8 times more likely than male patients to develop AKI (P < 0.01). AKI developed more frequently in older patients, with odds ratio (OR) of 5.5 (11.4 for survivors) in those >64 years compared with those <15 years (P < 0.01).

Multivariate analysis (Table 2) showed that the time interval from bite to antivenom administration (irrespective of the initial dosage of antivenom) was the strongest predictor of subsequent AKI (OR 1.7 when antivenom was given at 1–2 hours compared...
with 0–1 hour, \( P < 0.05 \); OR 3.2 at 2–3 hours compared with 0–1 hour, \( P < 0.01 \); OR 4.2 at 3–4 hours compared with 0–1 hour, \( P < 0.01 \); OR 12.4 at 4–5 hours compared with 0–1 hour, \( P < 0.01 \). This effect was observed across the 2 AKI subgroups as defined by dialysis requirement or serum creatinine rise without need for dialysis. Early administration of antivenom was also associated with shorter duration of coagulopathy (for patients receiving antivenom at 10 hours was also associated with shorter duration of dialysis). Early administration of antivenom was also associated with shorter duration of dialysis requirement or serum creatinine rise without need for dialysis. Early administration of antivenom to patients requiring transfer to a tertiary hospital. Calculating the true risk of AKI requires accurate knowledge of snakebite incidence in the community. Our community-based survey of 2 rural townships in Mandalay indicated that the true incidence of snakebite in Myanmar may be twice as high as that derived from hospital data. Evidently, a nationwide survey of all levels of the health care system is required.

Our finding that female patients were 1.8 times more likely than male patients to develop AKI after ERV envenoming warrants further investigation. Factors such as smaller body mass relative to venom load, nutritional status, pregnancy, and anemia may contribute to this gender disparity.

The pathogenesis of AKI after ERV envenoming is incompletely known, but it is likely to be multifactorial, including microvascular fibrin deposition, direct nephrotoxicity, and hypotension. Until more effective therapies become available, antivenom will remain the mainstay of treatment. Our finding that a shorter delay before antivenom had a better outcome is in broad agreement with 2 other reports based on smaller cohorts of patients.

Over the past 4 years, Australian, UK, and Myanmar colleagues have helped Myanmar become self-sufficient in antivenom production; however, increasing the production of antivenom may not be enough to improve clinical outcomes. In response to our finding of an association between time to antivenom and AKI, the Myanmar Ministry of Health is reviewing its policies about distributing more antivenom to rural health care centers and township hospitals that are within closer reach of snakebite patients.

A limitation of this study is the lack of independent identification of snakes; the ERV cohort was based on assumed snake identity. Venom detection testing was not available, and very few dead snakes brought in by patients were kept for identification, although those that were available were predominantly ERVs. This limitation reflects the realities of clinical practice, where experienced clinicians must make pragmatic decisions about the likely culprit snake. In Mandalay Division of Myanmar, snakebite patients presenting with incoagulable blood are most likely to have ERV envenoming. The only other snakes causing this effect are green pit vipers (genus *Trimeresurus*), whose envenoming is unresponsive to ERV antivenom, and only very rarely results in AKI.

Although we had observed a beneficial effect of shorter time to antivenom, administration of 8 vials of antivenom compared with fewer than 8 vials did not correlate with decreased likelihood of AKI on either univariate or multivariate analysis. In this regard, several points are worth considering. First, this was an observational study, not a controlled clinical trial. Confounding factors, such as antivenom availability and clinical bias, may have influenced the initial antivenom dose. Antivenom rationing was common in rural health facilities; it was likely that higher antivenom dose was reserved for patients judged to have severe envenoming. Second, antivenom-specific factors such as unreliable storage cold chain and variable neutralizing potency may have limited its clinical efficacy. Efforts are under way to address these concerns and to determine the optimal initial antivenom dose through controlled clinical trials.

**DISCLOSURE**

All the authors declared no competing interests.

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SUPPLEMENTARY MATERIAL

Supplementary File (PDF)
Supplementary References.
Supplementary Methods.

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