



A retrospective study of antivenom-associated adverse reaction and anaphylaxis at Ngwelezana Hospital, South Africa

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ABSTRACT

Background: Snakebite victims are commonly seen in KwaZulu-Natal Hospitals, with only a minority of patients requiring antivenom. This study reviewed antivenom-associated adverse events at our institution, after administration of the South African Vaccine Producers (SAVP) polyvalent antivenom.

Methods: A retrospective review, over 52 months (January 2016–April 2020), of patients who received antivenom. Demographics, clinical details and clinical course following antivenom administration were analysed.

Results: Emergency department doctors treated 758 snakebites; 156 patients were admitted of which 51 (33%) received antivenom. Indications for antivenom included: neurotoxicity (24%), haemotoxicity (18%) and significant cytotoxicity (58%). Antivenom-associated adverse events occurred in 61% of patients; with 47% developing anaphylaxis requiring adrenaline infusion. There was a higher incidence of anaphylaxis in children (57%) than in adults (40%), $p = 0.55$. There was no association between antivenom dose and anaphylaxis. No benefit was noted with adrenaline premedication ($p = 0.64$), nor with the addition of antihistamine or steroid pre-medicants to adrenaline ($p = 0.61$). Multivariable logistic regression identified age as a predictor for anaphylaxis, but not dose or duration of antivenom and not any particular form of premedication. Intubation was required in 29% of patients developing anaphylaxis. There were no deaths and all patients made full recovery. **Conclusion:** Almost half of the patients at Ngwelezana hospital in Kwazulu-Natal receiving the SAVP polyvalent antivenom developed anaphylaxis requiring adrenaline infusion, with children at higher risk. The administration of this antivenom must only be given for valid indications, in a high-care environment by medical personnel ready to manage anaphylactic shock. The addition of antihistamine and corticosteroids to adrenaline for pre-medication has no added benefit.

1. Introduction

Snakebite is common during the summer months in Kwazulu-Natal (Coetzer and Tilbury, 1982). Many patients present to hospitals with snakebite and a small proportion of patients will require antivenom (Wood et al., 2009), as part of the syndromic management originally outlined by Blaylock. (Blaylock, 2005). The three main syndromes for which antivenom is reserved include rapidly progressive swelling (polyvalent antivenom), neurotoxicity (polyvalent antivenom), and coagulopathy (Boomslang monovalent antivenom). Although most patients present with a predominant clinical feature, some patients with significant envenomation may exhibit a combination of the above. For example, a patient with significant swelling may also have features of

coagulopathy. Antivenom-associated adverse reactions and anaphylaxis have been reported to occur in 38.5–76% of patients treated in hospitals in Kwazulu-Natal; a fact that treating clinicians should bear cognizance of when administering antivenom (Wood et al., 2009; Moran et al., 1998), being fully prepared for a potentially life-threatening anaphylactic reaction.

The aim of this study was to investigate the incidence and nature of adverse reactions following the administration of SAVP antivenom at our institution.

2. Methods

A retrospective chart review was performed on patients with

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snakebites admitted to Ngwelezana hospital over a 52-month period (January 2016–April 2020). Only those administered antivenom were included. Data was collected on demographics, indication for antivenom, prior history of atopy, adverse reactions to antivenom, and clinical outcomes. Adverse reactions to antivenom included:

- anaphylaxis: all patients requiring adrenaline infusion for hypotension post antivenom administration;
- serum sickness: delayed allergic reaction with rash, joint pain, fever, lymphadenopathy;
- minor skin reactions: e.g. redness, swelling, itchiness.

When indicated, antivenom was given under close monitoring, either in the emergency department or (in the case of children) in theatre under co-supervision of the anaesthetic team. Antivenom was given as per written protocol (Table 1).

A number of protocol deviations occurred, resulting in the addition of intravenous antihistamine and hydrocortisone given prior to antivenom infusion. This practice stems from an older protocol now outdated. The use of these premedication deviations were recorded and analysed as part of this study. The F(ab')₂ equine source South African antivenoms (South African Vaccine Producers, Modderfontein Road, Sandringham, Johannesburg, South Africa) consists of polyvalent which covers nine of the most dangerous South African cytotoxic and neurotoxic snakes and Jameson's mamba found in central Africa (see Table 2), and boomslang monovalent. Ethics approval was obtained from the University of KwaZulu-Natal Biomedical Research Ethics Committee, reference number BCA027/19.

2.1. Statistical analysis

Descriptive statistics were expressed as an average and standard deviation or median and interquartile range where appropriate. The χ^2 test for independence was for comparison of categorical variables. A multivariable logistic regression model was used to analyze any associations linked to adverse reactions from antivenom. An α value of 0.05 was used to indicate statistical significance. Statistical analysis was performed using the R language for statistical computing (version 4.1.3).

3. Results

A total of 758 patients were treated for snakebite in the emergency

Table 1
Protocol for antivenom administration.

1. Ensure indication correct.
2. Consent from patient, parent or guardian.
3. Transfer patient to resuscitation area.
4. Full monitoring (i.e. continuous monitoring of heart rate, oxygen saturation, respiratory rate and blood pressure readings every 2 min)
5. 2× IV lines (large bore) appropriate for age.
• 1 line for Crystalloid- for resuscitation.
• 1 line for Antivenom
6. Premedication.
• Adrenaline IM
• 0.3–0.5 mg in adults
• Half of 0.01 mg/kg in children
• Expect tachycardia, monitor for dysrhythmias
• Monitor for anaphylaxis
7. Antivenom initial dose
• 8–10 vials polyvalent for Cytotoxic or Neurotoxic bites
• 2 vials monovalent antivenom for Boomslang bite
• Dilute in 200 ml normal saline and infuse over 20–30 min (test dose not required)
8. Repeat doses of antivenom as needed
9. Doctor to closely monitor patient
10. Patients to be counselled re: Serum sickness (type III reaction)

Table 2

Envenomations for which polyvalent antivenom and monovalent antivenom is effective.

POLYVALENT ANTIVENOM	
Cytotoxic snakes	Minimum LD50 (estimated mouse) neutralised by 1 ml of SAVP Polyvalent Antivenom
Mozambique spitting cobra (<i>Naja mossambica</i>)	13
Puff adder (<i>Bitis arietans</i>)	67
Gaboon adder (<i>Bitis gabonica</i>)	80
Rinkhals (<i>Hemachatus haemachatus</i>)	33
Neurotoxic snakes	
Forest cobra (<i>Naja melanoleuca</i>)	73
Snouted cobra (<i>Naja annulifera</i>)	27
Cape cobra (<i>Naja nivea</i>)	133
Black mamba (<i>Dendroaspis polylepis</i>)	93
Green mamba (<i>Dendroaspis angusticeps</i>)	20
Jameson's mamba (<i>Dendroaspis jamesoni</i>) – not found in South Africa	53
MONOVALENT ANTIVENOM	
Boomslang (<i>Dispholidus typus</i>)	3200

department over the study period, of which 165 (20.6%) warranted admission to the trauma service. Only 51 patients – 6.7% of all snakebite presentations/33% of all snakebite admissions – received antivenom. Only the polyvalent antivenom was indicated and administered during this period. The demographic breakdown of those patients who received antivenom was as follows: 30 patients (59%) ≥ 13 years (16 males, 14 females, average age 32.5 years, range 15–89); 21 patients (41%) < 13 years (average age 5.5 years, range 1–12). See Fig. 1.

3.1. Indications for antivenom administration

The main indication for antivenom administration was cytotoxicity – 39/51 patients (77%). Among these, the indications were as follows: rapidly progressive swelling – 27/39 (69%); coagulopathic indices in conjunction with swelling (increased INR/low platelets/both) – 9/39 (23%); facial bite with impending airway obstruction – 8/39 (21%). The remaining 12/51 patients (23%) received antivenom for neurotoxicity. See Table 3.

Snakebite-induced compartment syndrome is an uncommon phenomenon and the diagnosis should only be made with caution, ideally after several clinical re-evaluations and compartment pressure measurements. Fasciotomy is very rarely indicated for snakebite victims and carries a high morbidity profile.

3.1.1. Antivenom Dosage

The mean antivenom dose given was 10.14 vials (SD 5.21), with a mean administration duration of 47.86 min (SD 21.46).

3.1.2. Antivenom-associated adverse events

Thirty-one patients (61%) who received antivenom experienced some form of adverse reaction to antivenom administration classified as either a rash, 'serum sickness' (rash and pyrexia), or overt anaphylaxis (hypotension ± bronchospasm). Antivenom-associated anaphylaxis occurred in 47% (24/51) of patients. The incidence of anaphylaxis was

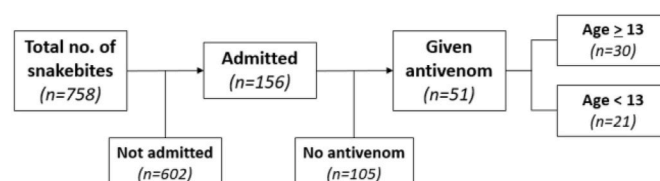


Fig. 1. Study population.

Table 3

Indications for antivenom administration.

Envenomation syndrome	Indication for antivenom	No. of patients (%)
Cytotoxicity (77%)	Rapidly progressive swelling/impending compartment syndrome	27(69)
	Coagulopathy in conjunction with swelling*	9(23)
	Facial bite with impending airway obstruction	8(21)
	Progressive paralysis/respiratory failure	12(23)

Five patients in this group had dual indications: rapidly progressive swelling plus coagulopathy.

higher in children (12/21 [57%]) than in adolescents and adults (12/30 [40%]), although it did not reach statistical significance ($p = 0.055$). Data regarding pre-existing atopy was collected. Only one patient had a history of asthma (a 12 year old boy); this patient developed anaphylaxis from antivenom and required intubation and ventilation for 48 h.

3.1.3. Use of premedicants

Patients were treated without strict adherence to protocol. Eleven patients did not receive intramuscular adrenaline prior to the antivenom infusion. Anaphylaxis occurred in 27% (3/11) patients who did not receive adrenaline pre-medication compared with 50% (19/38) of patients where the protocol was followed; $p = 0.64$. In two patients it was unknown if any pre-medication was given; both had anaphylaxis.

Of the 38 patients receiving adrenaline pre-medication, 27 also had steroid and antihistamine. Thirteen of these 27 patients (48%) developed anaphylaxis compared to nine out of 22 patients who received only adrenaline pre-medication (41%); $p = 0.61$.

Anaphylaxis Incidence related to Antivenom Dosage.

The incidence of anaphylaxis in patients given ≤ 10 ampoules of polyvalent antivenom was 47.6% (10/21) compared with 46.7% (14/30) of patients given > 10 ampoules of antivenom, $p = 0.89$. See Table 4 for a summary of anaphylaxis events.

3.1.3.1. Minor reactions to antivenom. Minor reactions to antivenom were less common. Skin rash occurred in six patients (12%), all of whom had received adrenaline, antihistamine and steroid premedication. Serum sickness type reaction was described in one patient (2%), who also had received all three drugs prior to antivenom administration. Twenty patients (39%) did not develop any allergic reaction following antivenom administration; five of these had received no pre-medication.

Multivariable logistic regression found age ($p = 0.014$) to be a predictor of anaphylaxis, but not adrenaline, antihistamine or steroid pre-medication, and not dose of antivenom given. See Table 5.

Seven of the 24 patients (29%) that developed anaphylaxis required

Table 4

Overview of anaphylaxis events.

	Anaphylaxis (n = 24)	No anaphylaxis (n = 27)	P-value
Age (years)			
<13 (n = 21)	12 (57%)	9 (43%)	$p = 0.055$
≥ 13 (n = 30)	12 (40%)	18 (60%)	
Premedication			
No Adrenaline (n = 11)	3 (27%)	8 (73%)	$p = 0.64$
Adrenaline (n = 38)	19 (50%)	19 (50%)	
Unknown (n = 2)	2		
Adrenaline only (n = 22)	9 (41%)	13 (59%)	$p = 0.611$
Adrenaline, Antihistamine & Steroid (n = 27)	13 (48%)	14 (52%)	
Unknown (n = 2)	2		
Number of Vials of Antivenom			
<10 vials (n = 21)	10 (48%)	11 (52%)	$p = 0.89$
>10 vials (n = 30)	14 (47%)	16 (53%)	

Table 5

Multivariable logistic regression analysis.

Parameter	Odds Ratio	95% CI	p-value
Age	0.943	0.893–0.983	0.013
Adrenaline	11.646	1.033–278.651	0.077
Antihistamine	0.218	0.014–1.963	0.208
Steroid	0.393	0.03–3.326	0.419
Antivenom dose	0.948	0.804–1.108	0.506

intubation for bronchospasm and respiratory difficulty, needing ventilatory support for up to 48 h. No patients suffered cardiac arrest and there were no deaths after the administration of antivenom. All adverse reactions related to the administration of antivenom had resolved by time of discharge, and no patients were followed up after discharge. The hospital stay was similar for patients who did versus did not develop anaphylaxis (9.5 and 8.8 days).

4. Discussion

There have been several studies researching snakebites in the northern KwaZulu-Natal Zululand region of South Africa (Coetzer and Tilbury, 1982; Wood et al., 2009; Blaylock, 2004; Wood et al., 2017). Ngwelezana hospital ranks among the busiest snakebite treatment centres in the country, serving a largely rural population of around 3 million and 18 referral hospitals. This region is a warm, humid, subtropical, low-lying area; and supports a high density and diversity of snake species. However, the majority of species are either non-venomous or medically insignificant, and bites by these snakes require only attention to the wound and analgesia.

The primary aim of this study was to investigate adverse reactions related to the administration of SAVP antivenom. Only 6.7% of patients with snakebites who presented to Ngwelezana Hospital during the reviewed time frame required antivenom. In a previous study from our hospital, antivenom was given to 9% of snakebite patients (Wood et al., 2009). Pattinson et al. (Pattinson et al., 2017) reported on 28 patients that received antivenom, which comprised 12.6% of their cohort.

5. Incidence of anaphylaxis and minor reactions following antivenom administration

Our results demonstrated acute adverse reactions in 61% of the patients who received antivenom. Minor reactions were less common (14%) than anaphylaxis which occurred in nearly half (47%) of patients. Of these patients who developed anaphylaxis, 29% required intubation and ventilatory support for up to 2 days. The incidence of anaphylaxis was higher in children compared to adolescents and adults, although not statistically significant. Multivariable logistic regression did however demonstrate a correlation between age and anaphylaxis. Pattinson et al. (Pattinson et al., 2017) reported an incidence in children of 58%, remarkably consistent with the findings in this study. Wood et al. (Wood et al., 2009) also noted a higher rate of anaphylaxis in children: 37.5% (≤ 10 years), 43% (11–20 years) and zero incidence in patients older than 20 years of age. The high anaphylactic reaction rate is a compelling reason to adhere to correct indications for antivenom administration, for antivenom to be administered by protocol in a high care environment, and attendance by trained medical personnel. Bedside preparation must be thorough in the form of pre-prepared adrenaline infusion and immediate availability of intubation equipment.

5.1. The role of pre-medicant

Our current protocol advises only adrenaline as pre-medication. Morais et al. (Morais, 2018) reviewed the efficacy of premedication for the prevention of adverse reactions to antivenom and concluded from several papers that there is some benefit using adrenaline. A

randomized study from Sri Lanka of 103 patients who received antivenom administration (1998–1999) with or without adrenaline pre-medication showed an 11% incidence of adverse reactions using adrenaline pre-medication compared to 43% observed in control (placebo) patients; $p < 0.0002$ (Premawardhena et al., 1999).

Between 2002 and 2007, an Australian prospective cohort study of 195 found only a marginal reduction (23%–18%) of hypersensitivity reactions with the use of adrenaline, and no reduction with any other drugs. They concluded that there was no value in pre-medication before antivenom infusion (Isbister et al., 2008).

A later (2005–2008) and larger study (1007 patients) in Sri Lanka by de Silva et al. investigated the efficacy of promethazine, hydrocortisone and adrenaline. In this randomized and double-blind, placebo-controlled trial the authors found that pretreatment with low-dose adrenaline reduced the risk of acute severe reactions to snake antivenom by 43%. They found no benefit from the use of an antihistamine or steroid. Furthermore, they found that the co-administration of hydrocortisone counteracted the benefit observed with adrenaline alone (de Silva et al., 2011). This finding may be relevant to our study which showed that adrenaline did not decrease the incidence of adverse reactions, as most of the patients receiving pre-treatment adrenaline also had a steroid administered.

De Silva et al., in 2016 published a review of the prevention and treatment of antivenom-induced adverse effects and concluded that only adrenaline had any reliable reports of decreasing the number of adverse reactions (de Silva et al., 2016). Similar to other studies in the international literature (Morais, 2018; Isbister et al., 2008; de Silva et al., 2011; de Silva et al., 2016), our study showed no benefit from the administration of preventive steroids and antihistamines prior to antivenom administration for adverse reactions (anaphylaxis, rash or serum sickness). Their use was popularized previously in South African guidelines (Wood et al., 2009). Some of our clinicians continue to adhere to this practice, but it is not part of our current protocol and given that steroid and antihistamine have no benefit and steroid may counteract the benefit of adrenaline alone, their current use as a pre-medicant before antivenom administration should be discouraged. At present, only adrenaline has been shown to be safe and effective in the prevention of acute reactions to antivenom with any evidence base.

Be that as it may, if adrenaline does not truly prevent an anaphylactic reaction, its benefit may lie in the blunting of the acute reaction, with a less life-threatening respiratory and haemodynamic collapse, affording the attending clinicians a better opportunity to achieve control.

5.1.1. Administering antivenom in a high-care environment

Despite the inherent dangers associated with antivenom administration, no patient suffered cardiac arrest after its administration, no patient died, and all adverse effects had resolved prior to discharge. This further underlines that antivenom administration is justified when the indication is correct, where monitoring and high care facilities are present, and the treating medical personnel are ready to manage an adverse/anaphylactic reaction. Under these conditions, anaphylaxis may be readily managed, and, if the antivenom infusion has not yet been completed, it may be completed once the anaphylaxis is under control.

5.1.2. Limitations

This study does have several limitations. The small data set makes the study low-powered and decreases the evidence quality. The study and the findings are only relevant and applicable to the treatment of snakebites in South Africa, where the particular above-mentioned polyvalent antivenom is in regular clinical use and cannot be broadly applied to other areas where snakebites are a common clinical problem. Another limitation of this study was the nonadherence to protocol. The addition of steroid and antihistamine as pre-medicants complicated the analysis and, as alluded to, may have negatively impacted the value of adrenaline alone as a pre-medicant. Further studies of adverse reactions with strict adherence to protocols may be of value.

6. Conclusions

The administration of the SAVP polyvalent antivenom to snakebite patients in South Africa carries a significant risk of anaphylaxis (47%). Therefore, strict indications for antivenom use should be adhered to and administration must be as per written protocol in a high-care environment by medical personnel ready to deal with an anaphylactic reaction. The incidence of anaphylaxis appears to be higher in children, and this, coupled with the potential difficulties related to managing a small airway, should prompt extra vigilance when antivenom is being administered to children.

Author contribution

Giles - Conceptualization; Data curation; Formal analysis; Investigation; Methodology; Project administration; Roles/Writing – original draft. SR Cacala - Formal analysis; Investigation; Methodology; Supervision; Writing – review & editing. D Wood - Conceptualization; Supervision; Validation; Writing – review & editing. J Kloppe - Formal analysis; Software; Supervision; GV Oosthuizen - Conceptualization; Formal analysis; Methodology; Project administration; Supervision; Validation; Visualization; Writing – review & editing.

Ethical statement

Ethics approval was obtained from the University of KwaZulu-Natal Biomedical Research Ethics Committee, reference number BCA027/19.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

Data will be made available on request.

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