Parallel infusion of hydrocortisone ± chlorpheniramine bolus injection to prevent acute adverse reactions to antivenom for snakebites

A randomised, double-blind, placebo-controlled study

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ABSTRACT

Objective: To investigate the efficacy of continuous infusion of hydrocortisone with or without chlorpheniramine bolus against early adverse reactions to polyspecific antivenom.

Design and setting: Prospective, double-blind, randomised, placebo-controlled trial at General Hospital, Anuradhapura, Sri Lanka.

Subjects: 52 patients with snake envenoming were randomised to receive infusion of hydrocortisone (Group A), hydrocortisone with chlorpheniramine bolus (Group B) or placebo (Group C) during the administration of antivenom.

Intervention: Hydrocortisone 1000 mg in 300 mL of normal saline infusion was started 5 min before and continued for 30 min after antivenom. Chlorpheniramine 10 mg intravenous bolus dose was given 5 min after commencement of antivenom.

Main outcome measures: Occurrence and severity of adverse reactions to antivenom.

Results: Adverse reactions were observed in 80% (12/15) of Group A, 52% (11/21) of Group B, and 81% (13/16) of Group C. Reactions were mild or moderate except in two patients. A significant reduction in the number of adverse reactions was seen in Group B compared with the placebo group (difference, 29 percentage points; 95% CI, 0.2 to 58 percentage points). There was no significant difference between Group A and the placebo group.

Conclusion: Prophylaxis with a parallel hydrocortisone infusion alone is ineffective in reducing the occurrence of acute adverse reaction to antivenom serum, but combining it with chlorpheniramine seems efficacious.

MJA 2004; 180: 20–23

SNAKEBITES ARE A major health problem in some parts of Sri Lanka.[1] In 2000, 32 303 snakebites were reported from all over the island, with 0.6% of the victims dying.[2] The efficacy of antivenom treatment for snakebite is widely accepted.[3,4]

Unfortunately, adverse reactions to antivenom are common in Sri Lanka, despite the development of more purified products.[4,5] A study in Colombia has shown a reduction of early antivenom reactions in *Bothrops* snakebite by using antivenom which contains whole IgG, produced by caprylic acid fractionation, compared with antivenom produced by the conventional pepsin-digested method.[5] Similarly, a very low antivenom reaction rate (4%) is reported in Australia against a wide spectrum of antivenoms, including those for red-back spider, stonefish and snake envenoming, possibly because of the improved quality of the product and premedication with adrenaline.[6,7] However, the situation in Sri Lanka is different — the management of adverse reactions to antivenom is an inseparable part of the management of snake envenoming, as there are no alternative forms of antivenom available. In Sri Lanka, the prevalence of anaphylactic or anaphylactoid reactions and pyogenic reactions to antivenom ranges from 68% to 81%.[1,3,4]

Lacking proper guidelines for reducing reactions, physicians have adopted empirical practices. In Sri Lanka, one popular treatment is an infusion of hydrocortisone 1000 mg in 500 mL of saline. This practice has not been tested scientifically, and safety and efficacy of very high doses of hydrocortisone are unknown. Other methods that have been tried include prophylactic administration of the antihistamine chlorpheniramine, which has no significant benefit in *Bothrops* snakebite,[8] and prophylaxis using hydrocortisone and chlorpheniramine, which has not been proven beneficial.[1,4]

Our aim was to evaluate the administration of hydrocortisone as an infusion, with or without a bolus of chlorpheniramine, to prevent early adverse reactions to antivenom.

For editorial comment, see page 5.

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METHODS

We conducted a randomised, double-blind, placebo-controlled trial during April and May 2002 in General Hospital, Anuradhapura, situated in the

North Central Province of Sri Lanka. Patients older than 12 years with snakebite and evidence of envenoming requiring polyvalent antivenom therapy were eligible for the trial. Patients who had already received hydrocortisone, antihistamines or adrenaline as prophylaxis were excluded.

Treatment

All patients received antivenom (lyophilised polyvalent enzyme-refined, manufactured in India by Vins Bioproduct Limited, Mumbai, Batch no. AVS30-2001). Ten vials dissolved in 500 mL of normal saline were infused over 1 hour.

Patients also received one of the following treatment regimens.

(A) Hydrocortisone + Placebo: Hydrocortisone 1000 mg in 300 mL normal saline was infused, beginning 5 min before and continuing for 30 min after antivenom infusion. Normal saline (5 mL) was given as an intravenous bolus 5 min after the commencement of antivenom.

(B) Hydrocortisone + Chlorpheniramine: Hydrocortisone 1000 mg in 300 mL of normal saline was infused, beginning 5 min before and continuing for 30 min after antivenom infusion. Chlorpheniramine 10 mg in 5 mL was given as an intravenous bolus 5 min after the commencement of antivenom.

(C) Placebo + Placebo: Normal saline (300 mL) was infused, beginning 5 min before and continuing for 30 min after antivenom infusion. Normal saline (5 mL) was given as an intravenous bolus 5 min after commencement of antivenom.

Randomisation

Patients who fulfilled the eligibility criteria were randomly allocated to receive one of the three treatments. The random allocation was based on a random table and was preplanned at a different centre (Faculty of Medicine, Peradeniya, Sri Lanka). The treatment regimens (A, B, C) were clearly typed and each of these was sealed in a separate bare white envelope. These envelopes were brought to the investigating centre (General Hospital, Anuradhapura).

1: Scoring system for assessing severity of envenomation

A score from 1 to 3 was given according to the degree of involvement of each system, and these were summed to give the overall score.

Haematotoxicity	
Positive whole blood clotting test at 20 min (WBCT20)	1
Positive repeated WBCT20	2
Spontaneous bleeding	3
Neurotoxicity	
Weakness of eye and facial muscles	1
Generalised muscle weakness	2
Respiratory muscle weakness leading to mechanical ventilation	3
Local swelling	
Swelling confined to bite site	1
Swelling spreading to half the limb	2
Associated necrosis and gangrene	3
Renal	
Elevated serum creatinine	1
Associated oliguria	2
Peritoneal dialysis in acute renal failure	3
Cardiac	
Presence of electrocardiographic change	1

Two teams were identified in the management of each patient: the treatment team, and the investigating team. The investigating team and the patient were blinded to the treatment. One member of the treatment team randomly selected an envelope. The treatment team carried out the treatment according to the instructions given in the envelope, while the investigating team monitored adverse reactions. One trained member from the investigating team evaluated the reactions of all the patients, to eliminate inter-observer variability.

Data collected

Patients: The patients' age and sex, any previous history of eczema, catarrh, urticaria and other medical conditions were recorded. A history of allergy to food or drugs was taken.

Snakes: The snakes were identified either by studying the dead snake if it was produced or by showing formalin-preserved specimens of snakes to the victim and witnesses. If both these methods failed, clinical features were used to guess the type of envenoming and the snake. Dead snakes were preserved in formalin for secondary confirmation by a herpetologist at the Faculty of Medicine, Peradeniya.

Envenoming: Severity of envenoming was assessed by a scoring system devised by the investigation team (Box 1). Total severity score was calculated for each patient and for each group (A, B, C), for comparison of groups.

Antivenom reactions: Pulse, blood pressure, temperature, auscultatory signs of lungs and allergic reactions were monitored at 5-min intervals for 15 min, then at 15-min intervals for 2 hours, and thereafter 4 hourly for 48 hours.

Reactions were categorised as mild, moderate, or severe,[1] and patients were assessed as having mild, moderate or severe reactions according to the worst reaction observed during the 48 hours. Fever, rigor, sweating, itching, urticaria, abdominal pain and increased body temperature were considered mild reactions. Cough, rhonchi, dyspnoea, lowering of blood pressure to between 120/90 and 80/60 mmHg, and tachycardia between 80 and 120/min were considered moderate reactions. Severe reactions were defined as cold clammy skin, central cyanosis, tachycardia above 120/min, low volume pulse, and hypotension below 80/60 mmHg.

The time of the initial reaction was recorded. Reactions to antivenom were treated by stopping the infusion temporarily and administering either 0.25 mL (mild reactions) or 0.5 mL (moderate and severe reactions) of 1:1000 adrenaline subcutaneously.

Statistical analysis

To compare the proportions of patients who developed reactions for the different types of treatment regimens, the standard errors were calculated for the differences in observed proportions. Those comparisons were done taking two treatment groups at a time. The Kruskal–Wallis test was used to compare the distributions of reactions to different treatment regimens. Where there were three proportions, they were compared row-wise.[9]

Ethical approval

Ethical approval was obtained from the Research and Ethical Committee of the Faculty of Medicine, University of Peradeniya, Sri Lanka. Informed written consent was obtained from all participants.

RESULTS

We recruited 75 patients, but 23 were excluded because of previous treatment. Fifty-two consenting patients were randomised: 15 to treatment A (hydrocortisone and placebo), 21 to treatment B (hydrocortisone and chlorpheniramine), and 16 to treatment C (placebo and placebo). The three groups were similar in age and sex, and in the snakes and severity of envenoming (Box 2).

Urticaria, tachycardia and hypotension were more common in group C than in the other groups (Box 3). Boxes 4 and 5 show the rates of adverse reactions to antivenom and the comparison between groups. Severe reactions were observed in two patients (one each in Groups A and C); these patients developed cold clammy skin and hypotension 15 min after the commencement of antivenom infusion. All other reactions were classed as mild or moderate. There was no significant difference in the total reaction rates with hydrocortisone infusion alone (Box 4). However, compared with placebo, there were significantly fewer adverse reactions when hydrocortisone infusion was combined with chlorpheniramine. Furthermore, there was no significant difference in severity of reactions between the different treatment regimens (Box 5). Twenty-one patients (40% of the whole group) who developed moderate to severe reactions to antivenom were successfully treated with subcutaneous adrenaline 0.5 mL (1:1000 solution).

None of the patients died. One patient went into acute renal failure despite antivenom treatment. No adverse reactions to hydrocortisone (eg, peptic pain and gastrointestinal haemorrhages) or chlorpheniramine (eg, drowsiness) were observed.

2: Characteristics of the snakebite patients

	Treatment A (*n*=15)	Treatment B (*n*=21)	Treatment C (*n*=16)	Overall (*n*=52)
Mean age (SD)	36.5 (13.3)	34.6 (16.7)	39.9 (12.7)	36.8 (14.5)
Number of men (%)	11 (73%)	16 (76%)	9 (56%)	36 (69%)
Type of snake				
Russell's viper	12 (80%)	17 (81%)	13 (81%)	42 (81%)
Common krait	2 (13%)	3 (14%)	3 (19%)	8 (15%)
Uncertain	1 (7%)	1 (5%)	0	2 (4%)
Mean severity score	21.32	17.71	14.75	

Treatments: A, hydrocortisone and placebo; B, hydrocortisone and chlorpheniramine; C, placebo and placebo. There were no significant differences between the groups (row-wise analysis: mean age ANOVA $F = 0.604$, $P = 0.55$; proportions of men $\chi^2 = 1.816$, df = 2, $P = 0.394$; mean severity Kruskal–Wallis $\chi^2 = 2.237$, df = 2, $P = 0.311$).

DISCUSSION

We tested the use of a hydrocortisone infusion in parallel with antivenom, as this is a common practice in Sri Lanka. We found hydrocortisone infusion alone was ineffective, but addition of a chlorpheniramine 10 mg intravenous bolus to the regimen seems to reduce the total adverse reaction rate by 29 percentage points (95% CI, 0.2–58 percentage points; $P = 0.04$ compared with placebo).

Use of low-dose subcutaneous adrenaline immediately before administration of antivenom significantly reduces acute adverse reactions.[10] However, there is a risk of intracerebral haemorrhage in some patients.[11,12] Additionally, there are limitations to the use of adrenaline, particularly in children, pregnant mothers and patients with heart disease, because of adrenaline's non-specific adrenoceptor agonist effect with low therapeutic index, which could cause cardiac dysrhythmia and uterine vasoconstriction causing fetal distress.[13]

Pretreatment with hydrocortisone and chlorpheniramine (antihistamine) has been a common practice in Sri Lanka. Hydrocortisone is recommended in allergy because of its inhibitory effect on cytokine release.[13] It is commonly administered as an intravenous bolus, because of its pharmacokinetics, but continuous infusion is practised in replacement therapy in adrenal insufficiency.[13] Adverse reactions are common with prolonged use, but short courses are fairly safe.[13] Chlorpheniramine is a well-known histamine H_1 receptor blocker. Although ineffective alone in prophylaxis for antivenom reactions, it has proven benefit in resolving reactions.[1,14] This

3: Reactions to antivenom and time from antivenom infusion to reaction

	Treatment A (*n*=15)				Treatment B (*n*=21)				Treatment C (*n*=16)			
	Mean time	Patients			Mean time	Patients			Mean time	Patients		
Reaction	(min)	No.	%	(95% CI)	(min)	No.	%	(95% CI)	(min)	No.	%	(95% CI)
Hypotension (< 120/80 mmHg)	43	5	33%	(30%–36%)	26	8	38%	(36%–40%)	22	9	56%	(55%–58%)
Tachycardia (> 80/min)	42	5	33%	(30%–36%)	18	7	33%	(31%–36%)	16	10	63%	(60%–65%)
Rigors	90	1	7%	(2%–12%)	38	6	29%	(26%–31%)	16	3	19%	(15%–23%)
Itching	25	10	67%	(64%–70%)	16	10	48%	(47%–49%)	13	10	63%	(60%–65%)
Urticaria	32	10	67%	(64%–70%)	19	8	38%	(36%–40%)	15	12	75%	(72%–78%)
Dyspnoea	15	2	13%	(9%–18%)	—	0	—	—	16	5	31%	(28%–34%)

Treatments: A, hydrocortisone and placebo; B, hydrocortisone and chlorpheniramine; C, placebo and placebo.

4: Differences between treatment regimens in proportions of reactions to antivenom

Treatments	Percentage point difference	95% CI
A – B	28	–2 to 57
A – C	–1	–29 to 27
B – C	–29	–58 to –0.2*

Treatments: A, hydrocortisone and placebo; B, hydrocortisone and chlorpheniramine; C, placebo and placebo. * $P = 0.04$.

observation is consistent with the pharmacological action of antihistamines, which counter the effects of released histamine due to mast cell degranulation.[13]

Our results are consistent with antihistamine being able to prevent reactions only after histamine has been released by mast cell degranulation. This process may be complemented by hydrocortisone, but, as we did not test chlorpheniramine alone, we cannot determine this. However, comparison between groups A and B indicated a reduction of 28 percentage points in the reactions due to chlorpheniramine ($P = 0.07$). The small sample size would have contributed to the result not reaching significance.

The study was designed to recruit a larger sample, and was conducted in the centre at which the highest number of snakebites are recorded in Sri Lanka. Unfortunately, many patients had to be excluded because of prior antivenom and other drug therapy at local hospitals. Furthermore, the incidence of snakebite dropped during the study period because of the early cessation of a seasonal pattern of biting. The time constraints of the investigating author also led to a smaller sample recruitment.

There were no significant differences between the three treatment groups when reactions were categorised as "no reaction", "mild" and "moderate and severe" (Box 5). Thus, the benefits of treatment B appeared only as a lower overall reaction rate (Box 4).

What is the applicability and clinical relevance of these observations to current practice? Our observations reject infusion of hydrocortisone in a larger dose as an effective measure against reactions to antivenom. However, other potential benefits of steroids, such as prevention of late reactions (eg, serum sickness) were not tested.

Despite the benefit we observed, we believe it is premature to routinely administer hydrocortisone and chlorpheniramine. Further studies are needed to unravel the possibility of a synergistic effect of both drugs. Similarly, utility of this treatment combined with pretreatment with adrenaline to reduce the moderate to severe reactions would be a new approach worth testing.

ACKNOWLEDGEMENT

The authors greatly appreciate the assistance received from the medical staff of the General Hospital Anuradhapura to conduct this study.

COMPETING INTERESTS

None identified.

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(Received 25 Mar 2003, accepted 1 Oct 2003) ❑

5: Severity of reactions to antivenom

	Treatment A ($n=15$)	Treatment B ($n=21$)	Treatment C ($n=16$)	Total ($n=52$)	χ^2	P*
No reaction	3 (20%)	10 (48%)	3 (19%)	16 (31%)	4.70	0.095
Mild reactions	7 (47%)	4 (19%)	4 (25%)	15 (29%)	3.419	0.181
Moderate and severe reactions	5 (33%)	7 (33%)	9 (56%)	21 (40%)	2.416	0.299
All reactions	12 (80%)	11 (52%)	13 (81%)	36 (69%)	—	—

Treatments: A, hydrocortisone and placebo; B, hydrocortisone and chlorpheniramine; C, placebo and placebo. Mild reactions were rigor, itching, urticaria; moderate/severe reactions were hypotension, tachycardia, and dyspnoea. * Comparison of three proportions (row-wise), df = 2.