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Apparent marked reduction in early antivenom reactions compared to historical controls: Was it prophylaxis or method of administration?

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ABSTRACT

Objective: Serious morbidity and mortality following snakebite injuries are common in tropical regions of the world. Although antivenom administration is clinically effective, it carries an important risk of early anaphylactic reactions, ranging from relatively benign nausea, vomiting, and urticaria to life-threatening angioedema, bronchospasm and hypotension. Currently, no adequately powered study has demonstrated significant benefit from the use of any prophylactic drug. A high rate of anaphylactic reactions observed during a trial of three different antivenoms in Ecuador prompted adoption of premedication with intravenous (IV) hydrocortisone and diphenhydramine together with dilution and slower administration of antivenom.

Design: In a rural mission hospital in Eastern Ecuador, 53 consecutive snakebite victims received a new antivenom regimen in 2004–2006, comprising prophylactic drugs and IV infusion of diluted antivenom over 60 min. They were compared to an historical control cohort of 76 patients treated in 1997–2002 without prophylactic drugs and with IV "push" injection of undiluted antivenom over 10 min. All these patients had incoagulable blood on admission and all were treated with Brazilian Instituto Butantan polyspecific antivenom.

Results: Baseline characteristics of the historical control and premedicated groups were broadly similar. In the historical group, early reaction rates were as follows: 51% of patients had no reaction; 35% had mild reactions; 6% moderate; and 6% severe. In the premedicated/slow IV group, 98% of patients had no reaction; 0 mild; 0 moderate; and 2% severe. The difference in reaction rates was statistically significant ($p < 0.001$).

Conclusions: Premedication with intravenous hydrocortisone and diphenhydramine together with dilution of antivenom and its administration by IV infusion over 60 min appeared to reduce both the frequency and severity of anaphylactic reactions. A randomized blinded controlled trial is needed to confirm these encouraging preliminary findings.

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1. Introduction

Snakebite injuries are an important cause of morbidity and mortality in many tropical developing countries but treatment with antivenom has yet to be standardized. Prompt administration of appropriate antivenom to systemically envenomed patients has been shown to improve the rate of recovery from coagulopathy in several studies of patients envenomed by Asian and South American pit vipers (Reid et al., 1963; Warrell et al., 1986; Cardoso et al., 1993; Smalligan et al., 2004). Antivenom treatment is often associated with early anaphylactic or pyrogenic reactions as well as late, serum-sickness type reactions (Moran et al., 1998). Early anaphylactic reactions range from tachycardia, rigors, chills, vomiting, and urticaria to more serious bronchospasm, dyspnoea, angioedema, hypotension and death (Warrell et al., 1986; Cardoso et al., 1993; Moran et al., 1998). Reaction rates reported in the literature vary widely from 3 to 84% (Malasit et al., 1986; Cardoso et al., 1993). Most authorities agree that these early reactions should be treated by interrupting antivenom infusion and immediate administration of adrenaline, systemic steroids, and an antihistamine. Once the reaction has resolved, however, antivenom treatment should be completed. The development of a protocol that will prevent these serious and sometimes fatal adverse reactions to antivenom administration has remained elusive.

In Ecuador, where the current study took place, national antivenom production is inadequate to meet the demand and antivenom has historically been imported from other countries such as Colombia, Mexico, Costa Rica, and Brazil (Theakston et al., 1995). Smalligan et al. (2004) reported the results of a randomized controlled trial (RCT) of three different antivenoms in 294 snakebite victims in rural Ecuador. All three of these antivenoms were effective in reversing the symptoms of systemic envenoming but were also associated with high rates of anaphylactic reactions ranging from 19 to 73%. Two life-threatening anaphylactic reactions to another imported antivenom (Probiol manufactured in Colombia) prompted the medical staff to change the treatment protocol in two ways: addition of premedication with a combination of hydrocortisone and diphenhydramine and administration of diluted antivenom by a 60 min IV infusion. The nursing and medical staff maintained the same level of documentation, using the same proforma, and employed the same procedures as were used during the earlier randomized controlled trial.

2. Materials and methods

2.1. Ethics

Patients in the historical group or their relatives gave informed consent for admission, investigation, and treatment as outlined in the RCT (Smalligan et al., 2004). Premedicated patients were treated under the standard of care protocol of the hospital at that time and their charts were reviewed retrospectively with confidentiality maintained. This review was approved by the Investigational Review Board of East Tennessee State University with written approval and consent from the medical staff and administration of Hospital Vozandes del Oriente in Ecuador.

2.2. Participants

All participants were patients presenting to Hospital Vozandes del Oriente, Shell, Pastaza, Ecuador with a history of snakebite who had incoagulable blood as determined by a simple 20 min whole blood clotting test (20WBCT) (Warrell et al., 1977; Sano-Martins et al., 1994). The historical control group was the 76 patients randomized to receive Brazilian Instituto Butantan antivenom "Soro Antibotropico" during the RCT carried out between January 1997 and December 2001 (Smalligan et al., 2004). The premedicated/slow IV group consisted of 53 patients admitted between January 2004 and October 2006.

2.3. Data collection

During both phases of this study, all patients had a detailed history, physical examination and other relevant information recorded on the same standard forms. All medical staffs responsible for administering antivenom were familiar with the signs of early anaphylactic reactions and patients were watched carefully for such signs. Patients were evaluated frequently by the medical and nursing staff and important clinical changes were recorded in the individual patient records.

2.4. Classification and grading of allergic reactions

Brown's grading of the severity of anaphylaxis was used to evaluate early antivenom reactions (Brown, 2004): none [0], mild [1] (skin and subcutaneous tissues changes such as generalized erythema, urticaria, periorbital oedema, or angioedema), moderate [2] (features suggesting respiratory, cardiovascular, or gastrointestinal involvement, including dyspnoea, stridor, wheezing, nausea, vomiting, dizziness, diaphoresis, chest or throat tightness, or abdominal pain), or severe [3] (hypoxia, hypotension, or neurological compromise including cyanosis, O_2 saturation < 90 mm Hg, confusion, collapse, or loss of consciousness).

2.5. Treatment protocols

All patients were treated with an initial dose of 20 ml (2 vials) of "Soro Antibotropico" (Instituto Butantan, Sao Paulo, Brazil) antivenom (Theakston and Warrell, 1991). The historical group received a batch with expiry date December 2000 and the premedicated/slow IV group a batch with expiry date May 2005.

In both studies the antivenom was meticulously refrigerated at 4 °C and it remained colorless and with consistent clinical efficacy even past the expiry dates. Nine patients in the historical group received antivenom during the twelve months after the batch's stated expiry date and twenty-six patients of the prophylaxis group received antivenom past the stated expiry date. In neither the control group nor the prophylaxis group was there any significant difference in allergic reaction rates among patients receiving antivenom after the expiry date. Use of recently expired antivenom is