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Haematological evaluation of patients bitten by the jararaca, *Bothrops jararaca*, in Brazil ☆

Marcelo L. Santoro [a,*], Ida S. Sano-Martins [a], Hui W. Fan [b], João L.C. Cardoso [b], R. David G. Theakston [c], David A. Warrell [d], BIASG[1]

[a] *Laboratório de Fisiopatologia, Instituto Butantan, Av. Vital Brazil, 1500, 05503-900 São Paulo, SP, Brazil*
[b] *Hospital Vital Brazil, Institute Butantan, São Paulo, SP, Brazil*
[c] *Alistair Reid Venom Unit, Liverpool School of Tropical Medicine, Liverpool, UK*
[d] *Nuffield Department of Clinical Medicine, University of Oxford, John Radcliffe Hospital, Oxford, UK*

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ABSTRACT

Complete blood counts are used frequently by physicians to assess and manage the development of complications of diseases. We studied 100 patients bitten by *Bothrops jararaca* snakes, and correlated their haematological values with the severity of envenoming and the development of complications. Patients who developed both local and systemic bleeding showed a greater drop in packed cell volume, red blood cell (RBC) count and haemoglobin concentration than those with who did not bleed. No morphological changes in RBCs were seen in blood films. Total white blood cell (WBC) counts were significantly higher in the clinically "more severe" group than in the "less severe" group on admission. Neutrophilic leucocytosis with left shift was present on admission, concurrently with a decrease in eosinophil and lymphocyte counts. These changes tend to become more marked 6 h after antivenom therapy, and are greatest in "more severe" envenoming. Thrombocytopenia on admission is positively associated with the development of systemic bleeding and the severity of envenoming. Thrombocytopenia may also be a useful prognostic indicator for the development of local complications, such as necrosis. The intensity of neutrophilia and eosinopenia might be used to follow the progression of necrosis in victims of snake bite.

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1. Introduction

In Brazil, almost 27,000 snake bites are recorded annually (15 cases per 100,000 population), resulting in more than 100 deaths each year (0.4%) and unknown numbers of permanent sequelae. Almost 90% of them are caused by lance-headed vipers (*Bothrops* and related genera) (Brasil, 2001). In southeastern Brazil, particularly in São Paulo State, *Bothrops jararaca* is responsible for most (97.5%) of the bites (Ribeiro and Jorge, 1997). People bitten by *B. jararaca* frequently manifest local effects at the site of the bite (oedema, ecchymoses, blisters and necrosis) and systemic signs of envenoming such as spontaneous bleeding (gingival bleeding, haematuria and epistaxis) and blood incoagulability (Rosenfeld, 1971).

☆ *Ethical statement*: The authors warrant that the manuscript is an original work, it has not been published before and it was not submitted for publication anywhere. It contains no libelous or other unlawful statements, and it does not infringe on the rights of others. The authors have no relationship with any manufacturers or distributors of products used in this manuscript. This paper reflects our own research and analysis and does so in a truthful and complete manner. All authors have contributed significantly to the execution, analysis and writing of the study reported and co-authors have agreed to submit the manuscript to *Toxicon*. Besides, the manuscript is appropriately placed in the context of prior and existing research.

* Corresponding author. Tel.: +55 11 3726 7222x2163; fax: +55 11 3726 7222x2162.
E-mail address: santoro@butantan.gov.br (M.L. Santoro).

[1] BIASG: Butantan Institute Antivenom Study Group: J.L.C. Cardoso, H.W. Fan, F.O.S. França, M.T. Jorge, R.P. Leite, S.A. Nishioka, A. Avila, I.S. Sano-Martins, S.C. Tomy, M.L. Santoro, A.M. Chudzinski, S.C.B. Castro, A.S. Kamiguti, E.M.A. Kelen, M.H. Hirata, R.M.S. Mirandola, R.D.G. Theakston and D.A. Warrell.

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Deaths are rare and are usually associated with massive haemorrhage, shock and acute renal failure (Amaral et al., 1985, 1986; Kouyoumdjian et al., 1991; Milani et al., 1997). Local necrosis is one of the most serious consequences of *B. jararaca* envenoming, since it may require amputation resulting in permanent disability. Local necrosis and amputation are mostly associated with bites by larger snakes, bites on fingers and legs and use of a tourniquet (Jorge et al., 1999; Ribeiro et al., 2001).

Since most of the snakes responsible are not identified, diagnosis is based on the clinical features. The dose of antivenom administered is usually based on the severity of clinical symptoms and signs on admission to hospital. Patients bitten by *Bothrops* spp. are classified clinically as mildly, moderately or severely envenomed depending on the extent and rate of spreading of local swelling at the site of bite, the occurrence of bleeding and shock (França and Málaque, 2003), although the prognostic significance of these features has not been tested rigorously. In addition, the detection of circulating venom by enzyme-linked immunosorbent assay (ELISA) has also been used to diagnose and prospectively to assess the severity of *Bothrops* envenoming (Theakston et al., 1992). Higher circulating venom levels are certainly found in more severe cases (França et al., 2003; Theakston et al., 1992), but the lack of technical skills and the time taken to obtain the results make it impracticable for use in isolated areas where most bites occur. Simple coagulations tests, including the bedside 20 min whole blood clotting test (20WBCT) (Sano-Martins et al., 1994), can be used to diagnose systemic envenoming and to control the dose of antivenom. Likewise, the complete blood count (CBC) of patients is a practicable and relatively inexpensive tool that may guide supportive treatment. Detailed results of CBC have not yet been reported in victims of *B. jararaca*. We have therefore investigated whether the CBC of patients with clinically "less severe" or "more severe" *Bothrops* envenoming, before and after antivenom therapy, could be used as an ancillary tool to help physicians to predict the occurrence of complications, such as necrosis.

2. Patients and methods

2.1. Patients

The clinical protocol was approved by the hospital ethics committee and all patients gave informed consent to participate in the study (Cardoso et al., 1993). One hundred patients admitted to Hospital Vital Brazil, Instituto Butantan, São Paulo, Brazil, from 1989 to 1991 with a clinical diagnosis of *Bothrops* envenoming, confirmed in some cases by identification of the dead snake or by ELISA immunodiagnosis, were included in this study (Cardoso et al., 1993). The length of *Bothrops* snakes brought by patients was also recorded, in order to allocate them as young (<0.5 m) or adult ($\geqslant 0.5$ m) specimens. According to physical examination on admission, patients were classified as either "less severely" envenomed or "more severely" envenomed group (Cardoso et al., 1993). Severely envenomed patients with massive haemorrhage, haemodynamic disturbances and/or acute renal failure were not included in this investigation, because they were transferred to an intensive care unit of a referral hospital as soon as they received antivenom, and could not be followed up by us. The former group included patients manifesting at least one of the following features: swelling involving one or two segments of the bitten limb, local bleeding and mild systemic (gingival) haemorrhage. The latter group consisted of patients with swelling involving three to five segments of the bitten limb, more pronounced systemic bleeding but with no hypotension or shock. In each group, patients received antivenom produced by Instituto Butantan, Fundação Ezequiel Dias or Institute Vital Brazil (Cardoso et al., 1993), prepared using virtually identical techniques (Raw et al., 1991). The "less severe" and "more severe" groups received, respectively, an initial intravenous bolus dose of 4 (40 mL) or 8 (80 mL) ampoules of *Bothrops* antivenom. Antivenom administration was started as soon as possible after admission. Patients were studied for at least 48 h after antivenom therapy and data were recorded on standard forms (Cardoso et al., 1993). Information included the use of a tourniquet, time between snake bite and admission to hospital, site of the bite, evidence of local bleeding, swelling, bruising, local necrosis and signs of spontaneous systemic bleeding (gingival bleeding, epistaxis, petechiae, ecchymosis and bleeding from gastrointestinal and genitourinary tracts). When early pyrogenic-like or anaphylactic reactions occurred, antivenom administration was interrupted and patients were treated with 1% adrenaline (0.3 mL) subcutaneously and chlorphenamine maleate (10 mg) intravenously. After the symptoms of the reaction had subsided, antivenom administration was completed.

Whenever possible, patients were asked to return 4 weeks after discharge to assess clinical recovery and normalization of laboratory data.

2.2. Blood samples

Blood samples (20 mL) were obtained by venipuncture on admission (T_0), at 6 (T_6), 12 (T_{12}), 24 (T_{24}) and 48 (T_{48}) h after the end of antivenom administration and at follow-up about 4 weeks later (T_{ret}). Blood coagulation status was assessed by the simple bedside 20WBCT (Sano-Martins et al., 1994). CBCs were carried out on samples containing potassium EDTA as anticoagulant and *Bothrops* antivenom (20 μL/mL of blood, in order to halt *in vitro* action of *Bothrops* venom). Haemoglobin concentration, red blood cell (RBC) and white blood cell (WBC) counts were determined in an automated cell counter (CELM Electronics, São Paulo). The packed cell volume (PCV) was determined using a microhaematocrit centrifuge (International Equipment Company, USA). Absolute values (mean corpuscular volume (MCV), mean corpuscular haemoglobin (MCH) and mean corpuscular haemoglobin concentration (MCHC) were calculated as described elsewhere (Dacie and Lewis, 1991). Leucocyte differential counts were performed manually in blood smears stained with panchromatic stain. Platelet counts were determined

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