Communication/Comunicação

Comparative evaluation of adverse effects in the use of powder trivalent antivenom and liquid antivenoms in *Bothrops* snake bites

Avaliação comparativa de efeitos adversos no uso do soro antiofídico trivalente liofilizado e soros antiofídicos líquidos no acidente botrópico

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ABSTRACT

Introduction: Snake bite, a problem in public health, generally occurs where there is no electric power. **Methods:** A comparative clinical study was conducted with 102 victims of *Bothrops* snake bite, from the State of Amazonas, Brazil; 58 victims were treated with liofilizated trivalent antivenom serum (SATL) and 44 victims treated with liquid bivalent and monovalent antivenom serum (SAMBL). **Results:** 17% (10/58) of patients presented adverse effects with the SATL and 25% (11/44) with the SAMBL. **Conclusions:** There was no statistic difference in number of adverse effects between the two types of snake bite antivenom.

Keywords: *Bothrops*. Antivenoms. Adverse effects.

RESUMO

Introdução: Acidente ofídico, problema de Saúde Pública, é mais frequente onde não há energia elétrica. **Métodos:** Foi realizado estudo clínico comparativo com 102 vítimas de acidente botrópico, do Estado do Amazonas, Brasil; 58 vítimas tratadas com soro antiofídico trivalente liofilizado (SATL) e 44 vítimas tratadas com soro antiofídico monovalente e bivalente líquido (SAMBL). **Resultados:** A comparação entre os tipos de soro demonstrou 17% (10/58) de indivíduos com eventos adversos com o uso de SATL e 25% (11/44) com o uso dos SAMBL. **Conclusões:** Não houve diferença estatística na quantidade de reações adversas entre os dois tipos de soros antiofídicos.

Palavras-chaves: *Bothrops*. Soro antiofídico. Efeitos adversos.

In Brazil, snake bite is a problem in public health[1]; generally, it occurs where there is no electric power, far from hospitals, for example, in forests of the Amazon Region, in field activities, and in communities of people of indigenous origin[2-4], where this study was conducted. The registers of the Brazilian Health Ministry list about 20,000 victims of snake bite per year in the Brazilian territory. This statistic number is not exact, as many snake bites occur where there is no health unit to handle the notification. Many times, the victims allow the snake bites to naturally heal without antivenoms and in some cases with significant complications[5-7]. They lose fingers, legs, hands, and arms, and they cannot work as well as they could before the snake bite. They have serious complications such as infections, kidney failure and death[8]. In these distant regions, because of the lack of electric power, it is impossible to conserve the liquid antivenom in low temperature between 2^0C and 8^0C, as recommended.

This evaluation is a clinical study to verify the safety of the Brazilian powder trivalent antivenom compared with the Brazilian liquid antivenom, made by the Butantan Institute, in the State of São Paulo, Brazil and the Ezequiel Dias Foundation (*Fundação Ezequiel Dias* - FUNED) and Vital Brazil Institute (*Instituto Vital Brasil* - IVB). The powder trivalent antivenom was also made in the Butantan Institute in association with the Biological Institute of Brazilian Army, in Rio de Janeiro (*Instituto de Biologia do Exército* - IBEx). Thus, Butantan Institute handled the final industrial production and the IBEx performed the clinical study.

The SATL was produced by the Butantan Institute in association with the IBEx. A prospective study was realized to compare the adverse effects between two antivenoms. During the 6 years of comparative study, the powder antivenom was revalidated after analysis and emission of the Butantan Institute certification to perform the analysis without interruption. To be considered for inclusion in the project, the patients had to have only light to moderate snake bite damages. We considered that during this phase, the severe envenoming could be a variable to confuse the results. The participants in the study should not be pregnant and had to be between 12 and 70 years of age; this selection of age was to avoid the exclusion of victims in rural work[5] and to exclude immunological vulnerability and others diseases commonly found outside this range (i.e., those previous snake bite treatments and who are free from allergic effects caused by horsehairs and other horse proteins). In the case of the victims of the *Bothrops* snake bite, the participants to be treated with liquid or powered antivenom were chosen randomly after diagnosis of envenoming, after explanation about the project and after signing the informed consent form. The clinical experiment was considered a simple blind study, that is, only the health workers knew which antivenom was being used. The patients were not informed; they knew only that they were participating in a project comparing two kinds of antivenom. The protocol of this study was approved by the Research Ethics Committee of the Army Biology Institute (*Instituto de Biologia do Exército*), Rio de Janeiro, and it was sent to National Ethical Committee. The guidelines for human experimentation of the National Health Council were followed in the conduct of clinical research. The Pearsons χ^2 test was used to statistic analysis of results[9]. The patients were treated in *Dr. Heitor Vieira Dourado* - Tropical Medicine Foundation (*Fundação de Medicina Tropical Dr. Heitor Vieira Dourado* - FMT-HVD).

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After the use of antagonists of alpha-1 and alpha-2 receptors (cimetidine 300mg IV and dexchlorpheniramine 10ml oral route and hydrocortisone 500mg IV), according to snake bite degree (e.g., light snake bite = two flasks of SATL or four to six ampoules of SAMBL; moderate snake bite = four flasks of SATL or eight to twelve ampoules of SAMBL), the antivenom injection was done under medical supervision to permit the detection of adverse effects, in accordance to the objective of this study. The snake bite victims were hospitalized for a period of 24h or more. After this, if there were no complications to justify further confinement in the hospital, the victim was sent home with instructions to return on the seventh day and after the fifteenth day after the snake bite. On those occasions, they were evaluated for delayed adverse effects. The quantitative and qualitative registers of detected effects were presented by graphs of comparative analysis between the SATL and the SAMBL **(Figure 1)**.

The distribution of snake bite victims according by characteristic of antivenom was 57% (58/102) to SATL and 43% (44/102) to SAMBL, the ratio of patients were equals (0.5) to both groups of patients, SATL (p-value=0.09, CI=95%) and SAMBL (p-value=0.9, CI=95%).

When the adverse effects between the antivenoms are compared, there are 17% (n=58) of persons with adverse effects with the SATL and 25% (n=44) with the SAMBL (p-value=0.47, CI=99%), the ratio of adverse effects is equal to both in statistic analysis. Although the total number of evaluated victims is only 102 persons, it is possible to say that to this moment (Project Phase II) and in these cases, that the SATL is as safe as SAMBL because had no statistic difference in number of adverse effects between the two antivenoms, as described in **Figure 2** . The more frequent adverse effects with the SATL were urticaria, pruritus, facial rubor and vomiting; with the SAMBL the more frequent adverse effects were pruritus, urticaria, vomiting and headache **(Figure 1)**. In according of literature[10-12], the adverse effects presented in this study were expected to occur and could be controlled with other medicines, as soon as they appeared. It was not reason to stop the treatment with both antivenoms (SATL and SAMBL). To urticaria it was 31.3% with SATL and 30.8% with SAMBL (p-value=1), to pruritus it was 25% with SATL and 38.5% with SAMBL (p-value=0.58) and to others adverse effects it was 43.8% to SATL and 30.8% to SAMBL (p-value=0.63), there was no statistic significance between the two, although there was good tolerance to both antivenoms **(Figure 2)**.

There were no more adverse effects in the SATL, which was made with three different immunoglobulins, in agreement with the experiences in India[13]. We believed that this antivenom can be used when the genus of snake is not known. In the economic aspect, it is clear that the SATL is better than the SAMBL, as it could be used until eight years, eleven months and seven days after fabrication, after revalidation of the study. The SATL was safe for the *Bothrops* snake bite. The epidemiological, clinical and therapeutic aspects were studied, and the SATL is viable with priority to the regions where access is difficult due to the long distances from the public health unit. Every patient who used the SATL went home without complications and as evaluated until 15 days after the specific therapy. There was

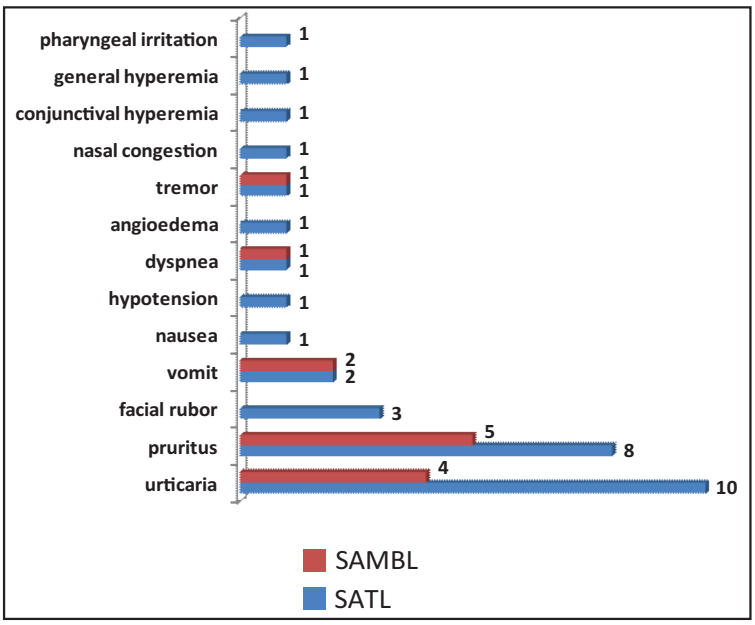

FIGURE 1 - Distribution of adverse effects by type of antivenom (SAMBL and SATL).

SAMBL: liquid bivalent and monovalent antivenom serum; **SATL:** liofilizated trivalent antivenom serum.

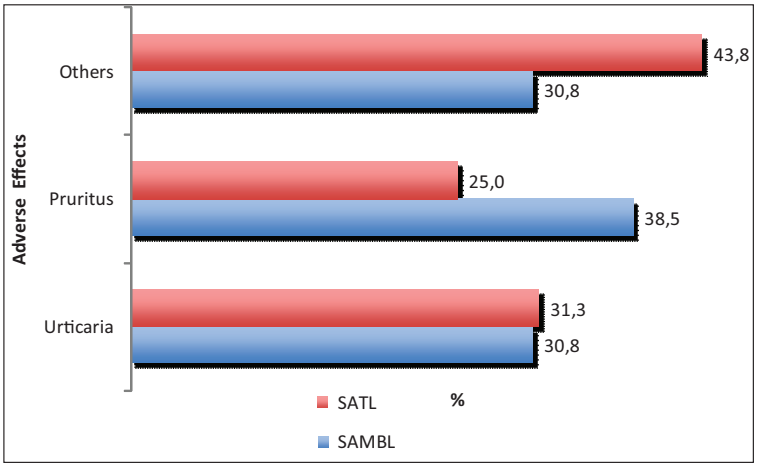

FIGURE 2- Distribution of urticaria, pruritus and others adverse effects by type of antivenom (SAMBL and SATL).

SAMBL: liquid bivalent and monovalent antivenom serum; **SATL:** liofilized trivalent antivenom serum; **NS:** no significance

no difference in the safety between both antivenoms (SATL and SAMBL). It is necessary to make the SATL in Brazil because it is more economic for the government and is better to the people living long distances from the public health unit. The SATL was used for almost nine years after its production and the SAMBL used until three years after the efficacy was determined.

The principal objective is to the Amazon Region, where there are important epidemiological characteristics, such as when the public health unit is far from the primary forest and agriculture regions, when there is no electric power to conserve the liquid antivenom in cold temperatures (2^0C to 8^0C), and because there are the three genera of snakes (*Chrotalus*, *Bothrops* and *Lachesis*) in the Amazon Region and sometimes it is difficult to distinguish the snake after the bite.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

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