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Freeze-dried trivalent antivenom for snakebites in the Brazilian Amazon: A study about safety and efficacy

Submission date
27/06/2017

Recruitment status
No longer recruiting

Registration date
07/07/2017

Overall study status
Completed

Last Edited
05/09/2023

Condition category
Injury, Occupational Diseases, Poisoning

[_] Prospectively registered
[X] Protocol
[_] Statistical analysis plan
[X] Results
[X] Individual participant data

Plain English summary of protocol

Background and study aims
Antivenoms (AVs) are the only specific treatment for preventing or reversing most of the snakebite envenomings (poisonous) effects. Bothrops, Lachesis and Crotalus are the most common types of snakebites in Brazil. In tropical areas, a major concern in snakebites treatment effectiveness is due to the failure in liquid AV distribution, because of the lack of an facilities being able to keep the AV cold. To minimize this problem, a freeze-drying process was suggested to improve AV stability. This study compares the safety and efficacy of a trivalent freeze-dried trivalent antivenom (FDTA), and the liquid available standard of care AV provided by the MoH (MoH AV), to treat Bothrops, Lachesis and Crotalus snakebites in the Brazilian Amazon.

Who can participate?
Adults aged 12 to 70 who have Bothrops, Lachesis and Crotalus snakebites.

What does the study involve?
After admission to hospital and examination of the snakebites, participants are randomly allocated to one of two groups. Those in the first group receive the freeze-dried AV therapy. Those in the second group receive the standard level of care AV therapy. After AV therapy, patients are admitted to the hospital ward for close monitoring during 24 hours. Participants are asked to attend the hospital seven and fifteen days after discharge. At follow-up visits, clinical examination was carried out and the s to investigate the venom and assess if there are any late adverse (harmful) reactions to AV therapy.

What are the possible benefits and risks of participating?
There are no notable benefits with participating. There is a risk of reactions after AV therapy such as urticaria (hives), asthma, laryngeal (the area of the throat where voice comes from) edema (swelling), shock, and other complications.

Where is the study run from?
1. Tropical Medicine Foundation Dr. Heitor Vieira Dourado (FMT-HVD) (Brazil)

2. Hospital Geral de Roraima (Brazil)
3. Unidade Mista de Borba (Brazil)

When is the study starting and how long is it expected to run for?
June 2003 to December 2008

Who is funding the study?
Brazilian Army (Brazil)

Who is the main contact?
1. Professor Jacqueline Sachett
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Contact information

Type(s)
Scientific

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Additional identifiers

EudraCT/CTIS number

IRAS number

ClinicalTrials.gov number

Secondary identifying numbers
U1111-1196-9116

Study information

Scientific Title
Safety and efficacy of freeze-dried trivalent antivenom for snakebites in the Brazilian Amazon: An open randomized controlled phase IIb clinical trial

Study objectives
There is safety and efficacy of a freeze-dried trivalent antivenom, and the available AV provided by the MoH, to treat Bothrops, Lachesis and Crotalus snakebites in the Brazilian Amazon.

Ethics approval required
Old ethics approval format

Ethics approval(s)
Research Ethics Committee of the Instituto de Biologia do Exército (IBEx), 18/09/2003

Study design
Prospective randomized open phase IIb trial

Primary study design
Interventional

Secondary study design
Randomised controlled trial

Study setting(s)
Hospital

Study type(s)
Treatment

Participant information sheet
No participant information sheet available

Health condition(s) or problem(s) studied
Snakebites

Interventions

After snakebite envenoming diagnosis, participants are randomly assigned to one of two arms with allocation ratio 1:1. The randomisation list is computer-generated. When a patient is considered to meet the inclusion criteria and had given her/his informed consent, the patient was formally recruited, and the patient's unique ID number was allocated in the Case Report Form (CRF). After admission, a CRF is filled with the patient's unique ID number, gender, area of occurrence of the snakebite (rural or urban), age (in years), ethnicity, education (in years), anatomical region of the bite, and time from bite to medical assistance (in hours). Clinical examination includes the observation of local and systemic manifestations. For Bothrops snakebites, laboratorial characterisation includes clotting time, erythrocyte sedimentation rate, International Normalized Ratio (INR), hemoglobin, leucocyte and platelet counts and plasma levels of fibrinogen, creatinine, urea, lactate dehydrogenase, aspartate transaminase, alanine transaminase and creatine phosphokinase in the plasma. For Lachesis and Crotalus snakebites, laboratory characterization included clotting time, INR and plasma levels of fibrinogen, creatinine, urea, and activities of aspartate transaminase, alanine transaminase and creatine phosphokinase in the plasma.

Twenty minutes after pre-medication with IV hydrocortisone (500 mg), IV cimetidine (300 mg) and oral dexchlorpheniramine (5 mg) (standardized according to local guidelines), AV therapy is given to participants from both arms in a dosage corresponding to mild or moderate envenomation based on the group they are in. Before administration, dissolution was observed visually as the FDTA vials were gently agitated by hand during one minute. AV therapy is given based on randomisation.

Group 1:
Participants in this group receive the freeze-dried trivalent antivenom (FDTA), produced under GMP conditions by Butantan Institute (São Paulo, Brazil) in partnership with Instituto de Biologia do Exército (Rio de Janeiro, Brazil).

Group 2:
Participants receive the standard level of care AV available Bothrops, Bothrops-Lachesis and Bothrops-Crotalus AVs provided by the MoH (MoH AV).

In Brazil, snake AV production is standardised and all the AV production from the three national laboratories (Butantan Institute, Ezequiel Dias Foundation and Vital Brazil Institute) is acquired by the MoH for national distribution free of charge.

Analgesic drugs are given on demand for pain, the bitten limb is nursed in the most comfortable position, blisters were aspirated, necrotic tissue are surgically debrided, abscesses are drained, and antibiotic treatment is given accordingly.

After AV therapy, patients are admitted to the hospital ward for close monitoring during 24 hours. The same laboratorial tests referred above were repeated four hours, 12 hours and 24 hours after AV therapy. Patients are asked to attend the hospital seven and fifteen days after discharge. At follow-up visits, clinical examination is carried out and the and the laboratory tests are repeated, in order to investigate clinical evolution of the envenomations and occurrence of late adverse reaction to AV therapy. If the patient does not present for the follow-up visits, the investigator plans a domiciliary visit at the next day. Patients who do not present to hospital visits and are not found at domiciliary visits are considered lost to follow-up.

Intervention Type
Drug

Phase
Phase II

Drug/device/biological/vaccine name(s)
Freeze-dried trivalent antivenom

Primary outcome measure
Early adverse reactions of AV therapy is measured using the clinical examinations for urticaria, asthma-like crisis, laryngeal edema and shock in the first 24 hours after treatment.

Secondary outcome measures
Presence of late adverse events are measured using clinical examinations (fever, urticarial, arthralgia, adenomegaly, neurological and renal complications at 24 hours until 15 days after treatment.

Overall study start date
20/06/2003

Completion date
15/12/2008

Eligibility

Key inclusion criteria
1. Male and female subjects
2. Aged between 12 and 70 years old
3. Bothrops, Lachesis and Crotalus snakebites are diagnosed using clinical, epidemiological and laboratorial evaluation

Participant type(s)
Patient

Age group
Adult

Sex
Both

Target number of participants
116

Key exclusion criteria
1. Pregnancy or breastfeeding
2. Previous hematological disorders
3. Known immunodeficiencies (HIV, malignancies, chemotherapy or other immunosuppressive treatments)
4. Previous treatment with snake AVs and history of any moderate/severe allergic reaction in the past

5. Presenting with severe snake envenomings, defined for Bothrops and Lachesis as life-threatening snakebites with severe bleeding, hypotension, shock and acute renal failure, and for Crotalus as intense rhabdomyolisis and severe acute renal failure were not included

Date of first enrolment
01/06/2005

Date of final enrolment
30/05/2008

Locations

Countries of recruitment
Brazil

Study participating centre
Tropical Medicine Foundation Dr. Heitor Vieira Dourado (FMT-HVD)
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Study participating centre
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Sponsor information

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Army Institute of Biology

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Sponsor type
Government

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Sponsor type
Government

Website
http://www.pos.uea.edu.br/mtrop/

Organisation
Instituto de Biologia do Exército

Sponsor details
-
Rio de Janeiro
Brazil
-

Sponsor type
Not defined

Website
http://www.ibex.eb.mil.br/

ROR
https://ror.org/02egtfm54

Funder(s)

Funder type
Government

Funder Name
Brazilian Army

Results and Publications

Publication and dissemination plan
Planned submission to Plos Neglected Tropical Diseases, as an Original Article.

Intention to publish date
30/07/2017

Individual participant data (IPD) sharing plan
The datasets generated during and/or analysed during the current study are/will be available upon request from the Corresponding Investigator: Wuelton Marcelo Monteiro at wueltonmm@gmail.com

IPD sharing plan summary
Available on request

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
Results article	Results	27/11/2017		Yes	No
Dataset			05/09/2023	No	No
Protocol file			05/09/2023	No	No