Final Report

Management of Venomous Snake Bites - A Systematic Review

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Preface

In the recent years, The Health System Research Institute has taken interest in developing clinical management guidelines for Thailand. As a clinician in academic institution, I become interested in this important activity. Good clinical guideline could not be developed with out evidence-based medicine. A systematic review is one of the most important part of this process through examination of strength of evidence of particular clinical questions.

For fifty years, King Chulalongkorn Memorial Hospital and the Saovabha Memorial Institute have been recognized as leaders in the clinical management of snake bite, and important provider of snake antivenom for Thailand. It is therefore a great opportunity to review all evidence related to clinical management of snake bite, or the lack of it, with a purpose to produce guideline for this unique topic of medicine.

Initially, I planned to limit our scope on the snake of Thailand. But after interactions with Paul Garner and the Cochrane Collaboration Center, I was convinced that it is worthwhile examining evidence from around the world in the same setting, and contribute to the international Cochrane network. This report is part of the ongoing effort in the international scale. Part of this report will be available in the Cochrane library available worldwide in the internet as well.

Issarang Nuchprayoon, MD, Ph.D.

Acknowledgement

I am deeply grateful to Paul Garner and the infectious disease group of Cochrane Collaboration Center, for his interest, in this project from the beginning and his extensive personal guidance on how to do a proper systematic review.

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Many thanks to Dr. Surang Triteeraprapab for her help in translation of this manuscript in to Thai language version, Ms. Kulwadee sai-im for her secretarial help, and the medical students of the Chulalongkorn University who helped retrieving documents for reviews.

Finally, I wish to thank the Health System Research Institute of Thailand for its support of this work and for coordinating this activity and introduction to Paul Garner in the first place. I believe the HSRI has been wise in its investment and stepped in right direction.

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Background

Snake bites are very common in Thailand as well as worldwide. In the United States, venomous snakes account for approximately 8,000 bites annually, resulting in about 9 to 15 fatalities. The majority of deaths occur in children, the elderly, and untreated or mistreated individuals. (Gold and Weingert, 1994). In Australia, twelve deaths attributed to snakebite were reported in 1992-1994 (Sutherland and Leonard, 1995). In Papua New Guinea, the annual incidence of envenoming and the mortality rate were 81.8 and 4.3 per 100,000 respectively (Currie *et al*, 1991).

Snake bite is very important cause of death for people in Africa. In Zimbabwe, the annual incidence were 137 cases of snake bite with 1.8% mortality rate. In Savanna West Africa, it was estimated that more than 20,000 death annually was attributable to snake bites (Theakston, personal communications). In Nigeria, it was estimated that more than 9,000 deaths was from venomous snake bite.

In the Southeast Asia, snakes are one of the important public health problems. In Myanmar (Burma), there were more than 10,000 snake bites annually, with 10% mortality rate. (Myin-Lwin *et al*, 1985) In Thailand, the reported annual incidence of venomous snake bites in 1987 were around 5,000 cases (Junnanod *et al*, 1993) and 20 per cent of these victims were children. This is probably an underreported number. At Chulalongkorn Hospital alone, there were 1760 outpatients visits for snake bites annually, 180 of whom were children.

Venomous snakes can cause fatal bleeding or respiratory failure, and specific for the snake species:

- The venoms of the *Elapidae* family (Cobra, King Cobra, and kraits) can cause respiratory failure due to neuromuscular weakness.
- The venom of the *Viperidae* family (Russell's viper, Green pit viper, and Malayan pit viper) can cause coagulation defect and can result in internal or external bleeding symptoms.
- The Malayan pit viper venom can cause acute renal failure.

In addition to these specific consequences of envenoming, many snake bite wound are accompanied by local reaction ranging from slight swelling to extensive necrosis and infection, which could also be fatal.

There are a series of questions about effectiveness of the various interventions used in snake bites, and these are outlined below.

ANTIVENOM:

An effective snake antivenom helps in neutralizing systemic symptoms, but can result in serious side effects which , if managed properly, are controllable. Snake antivenoms are among the few pharmacologic agents that are in widespread use often without adequate clinical trial (WHO, 1981). Antivenoms are usually made from by hyperimmunization of horses and the purified serum can cause allergic reactions including anaphylaxis, and serum sickness. Throughout the world, there are over 70

antivenom producers; however, due to the high cost of production, prices are high and often unaffordable by many ministries of health in developing countries where there are most needed (Theakston and Warrell, 1991). In addition, not all venomous snake bites cause systemic symptoms; therefore a guideline will be helpful for physicians and health care providers for the management of these patients. Using antivenom only when indicated will minimize side effects and be appropriate for economics.

For Cobra bite, which causes respiratory failure, there are two alternative ways of management. One is to give Cobra antivenom when there is evidence of neuromuscular weakness. The other is to provide ventilator support until the venom clears from the circulation, such as ptosis or respiratory problems. The questions to be answered are whether one method is superior, or more cost-effective than the other.

For Russell's viper (RV), Malayan pit viper (MPV), and Green pit viper (GPV) bite, which cause impairment of coagulation, species-specific antivenom is indicated if systemic bleeding (epistaxis, bleeding per gum, hematemesis, bloody stool, hematuria, remote hematoma, bleeding into central nervous system) occurs. In these cases, there are several laboratory tests for abnormal coagulation including prolonged venous clotting time (VCT), hypofibrinogenemia, prolonged prothrombin time (PT), prolonged activated thromboplastin time (aPTT), althought the best and simplest test is whole blood clotting time (WBCT20) as this can be arried out anywhere in the world. When the blood is incoagulable, the antivenom use is also indicated.

When the type of snake is not known, and the patient developed bleeding symptoms, the antivenom use becomes empirical. A poly-specific antivenom to cover the local snake venom may be necessary although its efficacy has to be assessed. We will make an attempt to review the most reasonable snake bite at each local community.

PREVENTING REACTIONS TO ANTIVENOM

The main problem with antivenom is that foreign animal proteins (from the immunised animal) frequently causes a severe allergic reactions called anaphylaxis, with bronchospasm, laryngeal oedema, and death. Anaphylaxis is treated with adrenalin, but even with prompt treatment the reactions can be fatal.

Different interventions have been proposed, to be given concurrently with antivenom to prevent these adverse reactions occurring. Adrenalin, antihistamines and corticosteroids are potential interventions to reduce the incidence and severity of these anaphylaxis and other allergic effects caused by the antivenom.

The potential for antivenom to cause anaphylaxis will vary with the particular type of antivenom, the process used to concentrate the antivenom, other aspects of the manufacturing process, and the dose given. These factors could therefore influence any protective effects of drugs given with antivenom to prevent anaphylaxis and other allergic reactions. By influencing baseline risk of developing adverse reactions, theoretically these factors could also influence the balance between benefit and harm of giving adrenalin prophylactically.

In this review, we will examine the evidence of benefit and harms when giving adrenalin, antihistamines or corticosteroids routinely with antivenom in patients showing signs of envenoming.

TETANUS ANTITOXIN:

Snake fangs usually cause deep and narrow wounds which are difficult to clean adequately. There is a possibility that an anaerobic condition is created and hence a risk for tetanus. The use of tetanus toxoid (TT) and tetanus antitoxin (TAT) is usually considered. The question is whether either one or both are necessary.

PROPHYLACTIC ANTIBIOTICS:

For the same reason as above, there is a risk of infection from snake bite. In clinical practice, there are cases of infected wound after snake bite, which is slow to heal. Prophylactic antibiotics may prevent these infectious events.

STEROIDS:

The venoms of vipers and cobras cause often local tissue damage, manifested by tissue swelling and necrosis. Biochemical and tissue pathology evidence suggests that snake venom can also induce inflammatory reactions. The use of steroids for reducing or preventing this adverse condition is reviewed.

To date, a few review articles has been published about managing snake bites, but there has been no systematic review published on this subject. We will initially review evidence from randomized comparisons that has been done around the world on various snake bites, and will discuss extensively on the snake that is prevalent in Thailand and Asian countries.

Objectives

1. To compare the safety, effectiveness and effective dose of various snake antivenoms in preventing tissue damage, haemorrhage, need for assisted mechanical ventilation and death.
2. To examine evidence for specific adjunctive interventions, including edrophonium (Cobra), steroids (Viper), prophylactic tetanus toxoid and antibiotics.
3. To evaluate drugs given prophylactically to prevent acute adverse reactions to horse serum antivenom, in relation to anaphylaxis and death.

Materials and Methods

All identified trials were entered into a trials register. The inclusion criteria were then applied to all possible trials independently by two reviewers. Where they disagreed, a third person was asked for an opinion, and a consensus reached.

All included trials were examined by the two reviewers and scored on a pre-defined list of methodological aspects; adequacy of concealment of allocation, generation of allocation sequence, inclusion of all randomised patients, and degree of blinding to intervention either observer blind or double blind. If the diagnostic criteria for inclusion in studies, the randomisation techniques, the outcome criteria for allergic

reactions, or other relevant information was not clearly stated, the authors were contacted for further unpublished information.

The following characteristics of included trials were pre-specified as potential sources of heterogeneity, extracted and tabulated.

- type of snakes
- manufacturer of antivenom
- pre-medication with other drugs before antivenom was given

The pre-specified potential sources of heterogeneity were used to explore possible explanations of variation in effect between trials, and to guide interpretation of the findings.

Differences between the results from individual trials were assessed by visual inspection of the graphs and by a chi-squared test of homogeneity. The presence or absence of heterogeneity was considered before pooling data from more than one trial.

All trials included in this review reported binary outcomes (dichotomous data). The data were entered in to RevMan software and presented as relative risk.

Types of study reviewed

Randomised or pseudo-randomized trials in humans.
The inclusion criteria and search strategy included case reports and observational studies in the assessment of the effectiveness of routine tetanus toxoid vaccination.

Types of participants

Patients envenomed with venomous snake bites in:

Elapidae family: Cobra, King cobra, kraits
Viperidae family: Vipers, Crotalids (Rattlesnakes), Copperheads, Bothrops
Others:, Papuan taipan

Types of interventions

- Antivenom.
  - Mono specific antivenom. This is usually species-specific.
  - Poly-specific antivenom.
- Specific interventions other than antivenom:
  - edrophonium
  - heparin
  - steroids
  - tetanus toxoid
  - antibiotics
- Interventions to reduce allergic reactions of antivenom
  - Adrenaline vs no adrenaline
  - Steroid vs no steroid
  - Antihistamine vs no antihistamines

Types of outcomes

- For Viper snake envenomings
  - Normalization of coagulopathy
  - Evidence of spontaneous bleeding
- For Elapid snake envenomings
  - Need for assisted ventilation
  - Physical measurement of paralysis
- For snake bite wound (any snake)
  - Amputation
  - Wound infection
  - Degree of swelling
- Reactions to antivenom-induced anaphylaxis or allergic reactions
  - Primary
    - Death (from any cause)
    - Anaphylaxis (defined as presence of one or more of the following clinical signs: shock, hypotension, bronchospasm with cyanosis, pulmonary oedema).
  - Secondary
    - Allergic reactions: urticaria, angioedema, bronchospasm.
    - Late allergic reactions: fever, rash, or arthritis more than two weeks after antivenom.

Search strategy

The trials register of The Cochrane Infectious Diseases Group was searched for relevant trials (published, in press or in progress). The topic search term used was "snake bites", and the final search was completed on 21 July 1998. Full details of the CIDG methods and the journals searched are published in *The Cochrane Library* in the section on "Collaborative Review Groups".
The reviewers searched The Cochrane Controlled Trial Register, published on *The Cochrane Library* 1998:(3). This is a compilation of about 131,000 published trials identified by handsearching by various individuals within The Cochrane Collaboration. Full details of the sources and methods used are published in *The Cochrane Library*. *The Cochrane Library* was last checked: 25 July1998

The following databases were also searched: MEDLINE 1966- October 1998, using the following search strategy :

set	Search
001	exp snake bites/
002	randomized controlled trial.pt.
003	randomized controlled trials/
004	controlled clinical trial.pt.
005	random allocation
006	double blind method/
007	single blind method/
008	or/2-7
009	clinical trial.pt.

010 exp clinical trials/
011 (clin$ adj25 trial$).tw.
012 ((singl$ or doubl$ or trebl$ or tripl$) adj25 (blind$ or mas
013 placebos/
014 placebo$.tw.
015 random$.tw.
016 research design/
017 or/9-16
018 comparative study/
019 exp evaluation studies/
020 follow up studies/
021 prospective studies/
022 (control$ or prospectiv$ or volunteer$).tw.
023 or/18-22
024 animal/ not (human/ and animal/)
025 8 or 17 or 23
026 25 not 24
027 1 and 26
028 27

Organizations and individuals working in the field were contacted, and these included: Chulalongkorn Hospital, Thai Red Cross Society which supplies most of the antivenom for Thailand. Members of the advisory Panel supporting this review, and the external referees, were asked to check the completeness of the search strategy, and to identify any additional unpublished, ongoing and planned trials.
In addition, as reports of relevant species of snake are more likely to be published in Thai language, we performed a search in a local database for Thai literature available at the medical library at the Faculty of Medicine, Chulalongkorn University. We also recruited references through the reference list in books and book chapters for a complete listing as well as in dissertations that has been performed in Thailand.
The reviewers also drew on existing reviews of this topic (Gold and Wingert, 1994, Sutherland and Leonard, 1995) , and checked the citations of all the trials identified by the above methods.

Methods of the review

Trials were grouped into those examining interventions for specific snakes, including antivenom and other measures.
Broad interventions relevant to all snake bites, such as prophylactic antibiotics or tetanus toxoid, were examined for all types of bite.

Viper snake bites:

- Comparisons between antivenom from various manufacturers
- Restricted or liberal use of specific antivenom in patients with a history of envenoming
- Comparisons of high and low dose antivenom administration

Elapid snake bites:

- Comparisons between antivenom from various manufacturers

- Comparisons between antivenom versus other pharmacologic agents such as anticholinesterases
- Specific antivenom versus assisted ventilation support in patients with respiratory muscle weakness.

ALL BITES

- Assessment of interventions (antihistamines, epinephrine, and steroid) in reducing antivenom reactions.
- The use of tetanus toxoid (TT)and antitoxin (TAT), examining incidence of tetanus. Because tetanus is a serious but preventable disease, trials may not exist, a broader search strategy including non-randomized reports for tetanus toxoid reports in snake bite will also be conducted.
- The use of prophylactic antibiotics: examine wound infection, deaths as outcomes.
- The use of steroids: outcomes in terms of death and tissue damage was assessed.

Assessment of methodological quality

Each trial selected was critically appraised, by examining for four type of biases: selection bias, performance bias, attrition bias and detection bias.

- For selection bias, each trial was rated whether there is concealment of assignment of treatment into adequate (A), unclear (B), inadequate (C), or that allocation concealment was not used (D) as a criterion to assess validity.
- For performance bias, each trial was rated whether the caring physician was aware of each treatment.
- For attrition bias, each trial was rated whether withdrawal from control group versus intervention group were comparable.
- For detection bias, each trial was rated and whether the evaluator of response is aware of the treatment given.

Data collection

Each trial was systematically reviewed and rated for possible bias and concluded into categories of reliability

Data synthesis

Because the number of trials were expected to be relatively few, we will report the conclusion of each trial and their difference in outcome as related to the difference in possible biases.

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Results

MEDLINE search results

One hundred and forty articles was identified by MEDLINE search for all clinical trial under term: "snake bites". They were listed by years published in Table I. We identified 19 trials that assessed efficacy of specific antivenoms or other therapeutic modalities for specific types of snakes. Other articles were reviews, case reports, epidemiology of snake bites, clinical manifestation of snake bites, laboratory diagnosis of snake bites, pharmacokinetics of antivenoms, or new diagnostic tests. Details of the randomized controlled trials were summarized on table II and discussed by species. Some relevant unrandomized trials were also discussed but not listed in the table.

Year	MEDLINE articles identified	Randomized controlled trials
1995-1998	42	8
1990-1994	28	4
1985-1989	35	5
1978-1984	19	1
1967-1977	16	1
TOTAL 31 years	140	19

Table I. Number of randomized controlled trials identified by years published and MEDLINE articles search result.

Cochrane collaboration search result

There were 4 trials identified in the cochrane library 1997 and 7 in CIDG register as of July 1997. One of these was relevant and not identified in MEDLINE search.

Thai medical database search result

We identified 37 articles under search term "snake". Most of these articles, however, are review articles on management of snake bites. The rest were case reports and epidemiological survey of snake bites from each community. There were no identified trials on management of venomous snake bites.

Individual contact to the past and active researcher at the Chulalongkorn Hospital revealed additional recently published trial on Cobra bites (Pochanukul, 1997), as well as a frequently cited proceeding that escaped MEDLINE database.

Management of Elapid snake envenomings

Cobras

Bites by cobras (genus *Naja)* are the principal cause of snake bite deaths in the Philippines (*Naja naja philippinensis)* and Thailand (*Naja kaouthia)*. Post-synaptic neurotoxins such as neurotoxin from cobras and krait (genus *Bungarus)* are present in most cobras and some elapid snakes binds acetylcholine receptor sites on the motor end-plate, thus produce effects similar to myasthenia gravis. Pre-synaptic neurotoxins present on many kraits venoms inhibits the release of acetyl choline presynaptically. Envenomed patients develop progressive muscle paralysis leading to death from respiratory muscle paralysis. Use of species-specific cobra antivenom produces rapid improvement and prevents deaths. Other than specific cobra antivenoms, anticholinesterase drugs has been assessed in several clinical trials because of the mechanism of actions of these neurotoxins.

A randomized controlled trial in the Philippines (Watt *et al*, 1986) reported the efficacy of intravenous edrophonium (Tensilon ®) in 10 adults envenomed by *Naja naja philippinensis* compared with 10 placebo-treated adults. All patients were given atropine sulphate intravenously before Tensilon or normal saline, followed in 30 minutes by saline or Tensilon in a double-blind crossover design. Responses were assessed by a well-defined criteria for ptosis. The concealment of assignment of treatment was adequate. There was no performance bias or detection bias as the physician or evaluator was aware of each treatment assignment. There was no attrition bias. The conclusion from this study that neurotoxicity of cobra venom could be reversed by edrophonium is convincing; however, its effect is transient.

To assess effectiveness of cobra antivenom and its optimal dose, a comparative trial of different doses of cobra antivenom and edrophonium (Tensilon ®) for the treatment of bites by the Philippines cobra was conducted in a double blind fashion (Watt *et al*, 1989). Three different doses (2, 5, or 10 ampoules) of cobra antivenom (equine) made by laboratories of the Ministry of Health of the Philippines were given intravenously in patients with neurotoxic signs. The efficacy of venom neutralization was assessed by a well-defined oculomotor paralysis at 0, 30, 60, and 120 minutes after antivenom infusion. At 120 minutes, edrophonium was given and the oculomotor response recorded. This trial demontrated that cobra antivenom caused in a definite, but partial, decrease in levels of neurotoxicity even at maximal dose, while addition of edrophonium effectively reversed neurotoxicity. This study was well-designed, and without selection bias, performance bias, or detection bias, because the assignment was well-concealed - neither patients or evaluator was aware of each treatment dose. There was no attrition bias. However, the samples size of this study was quite small and difference between each dose level could not be demonstrated.

In the Thai cobra (*Naja kaouthia)* bite, Pochanukul *et al* (1997) studied the optimal single bolus dose of cobra antivenom followed by artificial respiration. In this quasi-randomized study, patients were randomized to receive 50, 100, or 200 ml of *N. kaouthia* antivenom (equine) followed by ventilatory assistance when respiratory failure developed. These were compared to historical control group: patients in 1981-1985 who were managed by ventilatory assistance alone because antivenom were not

available. Important findings of this study was that there was no difference in the onset of respiratory failure necessitating ventilatory assistance but the duration of respiratory failure is significantly shorter when 100 or 200 ml of antivenom bolus was used. This is the largest trial on neurotoxic snake envenoming reported to date. However, there was a potential of performance bias in this study because the details of randomization process was missing - we were unable to assess how randomization was done and whether randomization was concealed. The number of patient in each group was grossly unequal and thus there was a potential for attrition bias because the number of patient withdrawn from each group was not determined. Detection bias is unlikely because of explicit criteria of ventilatory assistance was employed. In this study, the amount of cobra venom level in each patient was not reported even though the detection method was available (Hanvivatvong *et al*, 1987); therefore the potential for selection bias could not be excluded.

Non randomized trials on the treatment of cobra bites

Trishnanada *et al* (1978) assessed the use of cortocosteriod on five cases of patients with envenoming by cobras. There was no demonstrable clinical responses with dexamethasone 10 mg IV every 30 minutes up to 4 doses. All patients responded after Cobra antivenom was given.

Pochanukul *et al* (1994) reported the use of artificial respiration alone without cobra antivenom in 4 patients. These patients with cobra envenoming needed artificial respiration for 36-72 hours and spontaneously recovered.

Other Elapid snakes and kraits

There were no published controlled trials on the management of King cobra bite. Only one case report was found in a Thai medical database (Karnchanachetanee, 1994). Although King cobra antivenom is available in Thailand, the bite is very rare as the snake prefers undisturbed forest (Cox *et al*, 1998).

There were no published controlled trials on the management of krait bites. This could be due to very few case of bites as these snakes are very inactive during the daytime, with exception of Malayan krait (*Bungarus candidus*) bites, which significantly contribute to snake bite-related fatality in Thailand (Looareesuwan *et al*, 1989), and no antivenom available so far.

Papuan taipan (*Oxyuranus scutellatus canni*) is an important neurotoxic snake in Papua New guinea. Its neurotoxin has not been well characterized. A controlled clinical trial on Edrophonium10 mg compared to saline control, and 3,4 Diaminopyridine (DAP) 10 mg compared to saline control has shown no improvement of neurological response (Trevett *et al*, 1995). Some measurable response was seen when the two agents are used in combination (see table I).

Management of Viper envenomings

Russell's viper (RV, *Daboia russelli*) is found in ten countries of southern Asian peninsula, but prevalent in all parts of Thailand, Myanmar (Burma) and Sri Lanka (Cox *et al*, 1998). In Myanmar, RV is responsible for 85% of venomous snake bites. Numerous studies have been reported related to RV envenoming because of its effect on coagulation, and renal toxicity resulting in acute renal failure. Four clinical trials were available on the management of RV bites, one in Thailand and three other in Myanmar.

In Thailand, RV antivenom was supplied by Thai Government Pharmaceutical Organization (GPO). A clinical trial by Karnchanachetanee *et al* (1994) assessed whether a high dose (100 ml every 6 hours) of RV antivenom is more effective in correction of venous clotting time than a low dose (60 ml every 6 hours) therapy. This study was well-designed, with 15 subjects in each group, well-concealed randomization. However, there was a potential of performance bias in this study, because the caring physician was not blind to the dosage treatment. Most importantly, since RV antigen level measured by ELISA were higher in patients who were randomized to receive high dose RV antivenom, the authors did not conclude that the lower dose schedule was better.

Two randomized controlled trials were conducted in Myanmar to assess whether the use of heparin can improve coagulation recovery in patients treated with RV antivenom. All patients were given monospecific RV antivenom produced by Burmese Pharmaceutical Industry (BPI). In one group, heparin 50 U/kg loading with 10 U/kg/h x 24 hr was compared to normal saline x 24 hr control regimens. In one trial (Lwin *et al*, 1989), 28 confirmed cases of RV bite patients with impending disseminated intravascular clotting (DIC) were recruited. In the other trial (Swe *et al*, 1992), 20 patients with fully developed DIC were recruited. These two studies were well-designed, but there was no indication that the assignment of treatment was concealed. The general clinical data and RV antigen levels were comparable among the two groups. There is a potential of performance and detection bias because physicians and evaluators were unblind to each treatment group, although the laboratory tests used were reliable. There was no attrition bias as no subjects were withdrawn from each group. The authors could not demonstrate the benefit of addition of heparin to the therapy with RV antivenom for patients with RV bite with impending or fully developed DIC.

Another trial in Myanmar was to assess the efficacy of intramuscular RV antivenom as a first aid measure in the field before the patient's arrival at the hospital (Win-Aung *et al*, 1996). The antivenom was given intramuscularly (IM) by trained basic health staff in the villages, 5 ml in each buttock within 2 hours of a bite in the field. This study was not randomized; 34 snake bite victims who were given IM antivenom were compared to 82 victims who were not. The patients' characteristics, including age, sex, length of the snakes responsible, were similar, with mean interval between bite and arrival to the hospital of 3.19 ± 2.5 hours. At the hospital, 40 ml RV antivenom was given if there was a DIC (incoagulable blood) or proteinuria. The clinical outcome endpoints: number of patients with DIC, clinical proteinuria, acute renal

failure, and the venom antigen levels, were reduced in the IM antivenom group. Because this study was not randomized, there was an obvious potential for selection bias and performance bias. There was a possibility of detection bias because the treating physicians were aware, but the objective laboratory evaluations were well-defined and reliable. There was no attrition bias as no subjects were withdrawn from each group. Therefore, the authors concluded that IM antivenom immediately after RV bite may be of value as a first aid measure in the field, and is justified when transport is likely to be delayed.

In India and Sri Lanka, where the prevalent vipers are Russell's viper (*Daboia russelli*) and saw-scaled viper (*Echis carinatus*), polyvalent antivenom (Haffkine biologicals) was used to treat snake bite with prolonged venous clotting time (VCT). To find an optimal dose, a randomized trial was done comparing a high dose protocol (4 ampoules in the 1st hr, 4 in the next 2 hr, then 4 every 3 hrs until VCT normalized) or low dose (2 ampoules instead of 4 at the same schedule)(Thomas and Jacob, 1985). Using time required for VCT to normalize, the low dose was shown to be as effective as the high dose. There was a potential of selection, performance, detection, and attrition biases, as the method of concealing assignment and whether physicians and evaluators were blinded to each treatment group, and withdrawal from the study, was not mentioned in this short report. There was no confirmation of the venom amount or snake species to assess whether the two groups were comparable.

The role of intravenous immunoglobulin (IVIG) in viper bites has been assessed in Sri Lanka (Sellahewa *et al*, 1994), where polyvalent antivenom (Serum Institute of India) was used to treat snake bite with prolonged VCT. Comparisons were made between anti-venom (100 units) alone (control group) and anti-venom with IVIG 1g/kg in a randomized design. Treating physicians were not blinded, and protocol for repeating anti-venom was not specified. The number of subjects was small (8 versus 7) in each group. Patients treated anti-venom+IVIG group required longer time for VCT to normalize than patients treated anti-venom alone, which might be explained by the fact that the former group were given only one dose of anti-venom but multiple dose were used in the control group. The authors concluded that IVIG might reduce requirement for repeat dosing of anti-venom. This study had no selection bias, but had a major performance bias because the time to normalize VCT is related to dose of antivenom used- the confounding factor that was not controlled. Detection and attrition biases were not found.

Malayan pit viper (MPV, *Calloselasma rhodostoma*) is prevalent in Southern part of Thailand and Malaysia. Only one clinical trial for management of Malayan pit viper exists (Warrell *et al*, 1986). This trial compared the efficacy of Malayan pit viper-specific antivenom from three different suppliers, Thai Red Cross (TRC), Thai Government Pharmaceutical Organization (GPO), and Twyford Pharmaceutical (Twy), at the manufacturers recommended dose in a randomized controlled fashion. In this trial, the assignment of treatment was adequately concealed. The general clinical data and MPV antigen were comparable among the three groups. There was a potential of performance and detection bias because physician and evaluator were unblinded to each treatment group, although the laboratory tests used was reliable. There was no attrition bias. With a total number of 46 subjects, it was concluded that Twyford and GPO antivenom were superior to TRC antivenom in safety and activity

against coagulaophathy. Thus Twyford and GPO MPV antivenom is recommended for treating systemic envenoming at a dose of 5 ampoules intravenously.

Green pit viper (GPV, *Trimeresurus popeorum* and *Thrmeresurus albolabris*) is a common cause of snake bites in the central region of Thailand. Bitten victims developed mild coagulopathy from GPV bites (Mitrakul, 1973). Although GPV antivenom has been available in Thailand for more than a decade, there was no published trial on the use of GVP antivenom. All identified reports were descriptive studies and retrospective in nature (Mitrakul, 1982, Rojnakarin *et al*, 1995).

Hump-nosed viper (*Hypnale hypnale*) is a pit viper native to Sri Lanka and southwestern India. The venom of this viper is of low toxicity, rarely causes systemic symptoms, but causes local symptoms including pain, swelling, and induration at the site of the bite. To assess the efficacy of a polyvalent antivenom (Haffkine BioPharmaceuticals, India) on hump-nose viper bite, a randomized controlled trial in Sri Lanka was conducted (Sellahewa *et al*, 1995). The randomization of the bitten patients was well-concealed in relation to those receiving antivenom (31 cases) or saline alone (32 controls) in addition to local wound care. The clinical end-point measured was induration at the bite sites to complete resolution of pain, and swelling. There was no demonstrable efficacy of this polyspecific antivenom. The study was well-designed and had no selection, performance, or attrition biases. However, there was a potential of detection bias because the investigator was aware of the treatment given.

Other Pit viper bites

In the western hemisphere, Pit vipers (subfamily Crotalidae), were the most common causes of venomous snake bites. These includes *Crotalus* (rattlesnakes), *Agkistrodan* (moccasins), and *Sistrurus* (massasaugas and pygmy rattlers) in the North American region, and *Bothrops* and *Lachesis* in Amazon rain forest.

Several trials had been conducted in Brazil (Cordoso et al, 1993; Jorge et al,1995), Colombia (Otero et al,1996, Otero-Patino et al, 1998), and Martinique (Thomas et al,1995),, in management of venomous bites from Bothrop species. In Africa, four trials have been conducted to compare the efficacy of different antivenoms and the role of heparin in the treatment of Carpet viper (*Echis carinatus*) bites (Warrell et al, 1974; Warrell et al, 1976; Warrell et al, 1980, Meyer et al, 1997). In Papua New Guinea, where Papuan Taipan, a deadly neurotoxic snake, is predominant, a trial was conducted to assess the role of edrophonium or 3,4 diaminopyridine in the treatment of this snake bite (Trevett et al, 1995). These trials were listed in the table but were not reviewed here for the interest of brevity.

Management of Snake bite wound

There were no clinical trials on the use of tetanus toxoid (TT) or tetanus antitoxin (TAT) identified. There are case reports of snake bite victims died of tetanus in scatterred in pre-TT era (Warrell *et al*, 1986). In most trials, TT are used in conjunction with general wound care.

One trial was identified that addressed this issue of preventing wound infection. In Ecuador, crotalid snakes are prevalent. In addition to inteference with coagulations, crotalid toxin also causes tissue necrosis, blood extravasation, an ideal environment for bacterial infection, and thus might cause abscess and necrotizing myofasciitis. Use of antibiotics prophylaxis has been controversial. One group of investigators in Ecuador assessed the role of an antiobiotic prophylaxis regimen: Gentamycin 2 mg/kg IV every 8 hrs plus chloramphenicol 12 mg/kg IV every 6 hrs for 24 hrs, compared with no antibiotics (control group) in a randomized fashion after Bothrop snake bites (Kerrigan *et al.* 1997). All patients were given tetanus prophylaxis (tetanus toxoid or antitoxin depending on prior immunization). The 59 patients in antibiotics group were comparable to 55 patients in the control group in age, sex, median from snake bites to hospital arrival, clinical and laboratory signs of envenoming (bleeding from various sites, prolonged prothrombin time, and edema. In both groups, 75% of patients also received antivenom therapy. There was no difference in the outcome; 6 patients (10%) of antibiotics group and 3 patients (5%) of control group developed abscess, which were mostly caused by gram-negative coliform bacteria. Although this was a randomized study, the method of concealment was not reported. There was a potential for performance and detection bias because the investigator was aware of the treatment given. There was no attrition bias for there were no withdrawal from either group of the study. The author was correct in concluding that the prophylactic antibiotics could not be recommended for Bothrop snake bite.

The author has unpublished data on randomized controlled trial of prophylactic antibiotics and oral prednisolone on edema and infection after GPV bites (Nuchprayoon and Lekhakul, 1999). In this study, 90 patients envenomed by GPV were randomly assigned to receive regular wound care alone (control group), addition of antibiotics (Amoxycillin 50 mg/kg/day orally for 3 days), or addition of antibiotics plus steroid (oral prednisolone 1 mg/kg/day orally for 3 days). The outcome following objective measurement of swellling of the limb at the bite site, and any signs of inflammation and infection, was estimated. No beneficial effect of Amoxycillin or oral prednisolone could be demonstrated in this study. Although well-designed and treatment assignment well-concealed, this study had the potential for performance and detection, as patients and physicians were aware of the medications given. There was also a potential for attrition bias, as the number of patients withdrawn from control group was significantly larger than the other two groups. A larger number of patients might be needed to demonstrate the beneficial effects of antibiotics or steroid.

Preventing reactions to antivenom

Two trials met the inclusion criteria. One trial was carried out in Sri Lanka in 105 patients to assess adrenaline against a saline control [Premawardhena, 1999]. Steroid or antihistamine were not used as pre-medication. Acute adverse reaction to the antivenom was graded as mild, moderate or severe. The type of the snake was not mentioned in the study. In this trial, allocation concealment is unclear. The schedule was not known by the physician who make assessment of outcome. Outcome were provided in all randomized patient and analysed by intent to treat analysis. he group receiving adrenalin suffered fewer adverse allergic reactions overall (adrenaline: 6/56;

control; 21/49; RR 0.25, 95% CI 0.11-0.56). No patient suffered severe anaphylaxis. No deaths were recorded.

The investigators also recorded potential adverse effects of adrenalin. No patient developed hypertension (blood pressure >160/100 mmHg), arrhythmia (other than sinus tachycardia), or neurological deficits suggestive of cerebrovascular accidents.

The other trial was conducted in 101 Bothrop snakes bite patients Brazil to assess intramuscular promethazine (an antihistamine) against placebo before antivenom was given (Fan et al. 1999). Adrenaline or steroid was not used as pre-medication. Acute adverse reaction to the antivenom was graded as mild, moderate, or severe. In this trial, allocation concealment is adequate. Outcome were provided in all randomized patient and analysed by intent to treat analysis. There were no difference was shown in allergic reactions overall (promethazine 12/49, placebo 13/52; RR 0.98, 95% CI 0.50 to 1.93). One patient from each treatment group suffered severe anaphylaxis. No deaths were recorded.

Conclusions

There were few, perhaps too few, randomized controlled trials globally to guide clinicians on how to best treat venomous snake bites. No two trials has been on the same issue or similar in methodology to do a meta-analysis. Systematic review of these trials have shown that, apart from a specie-specific antivenom, any medical interventions are rarely of sustained benefit. Each antivenom preparation is different in efficacy. In general, monovalent antivenom is more efficacious than polyvalent antivenom. The need for prophylactic antibiotics in snake bites is still remains to be proven.

Implication for practice

For cobra envenomings, edrophonium is effective in reversing neuromuscular paralysis, but last for a few minutes. Cobra antivenom results in significant, but sometimes partial reversal of neuromuscular paralysis. For Thai cobra, a bolus dose of 100 ml *N.kaouthia* antivenoms is recommended, followed by assisted ventilation, if needed

For Russell's viper envenomings, administration of RV antivenom is the single most important intervention for the patients. The earlier administration, the less likely the patient will develop disseminated intravascular coagulation (DIC). Studies that assess optimal dose of RV antivenom in a randomized controlled fashion are biased and thus inconclusive Titration of RV antivenom dose at 6-hr interval using 20-minute whole blood clotting time (WBCT20) or venous clotting time (VCT) are commonly used. In places where transportation of patients to the hospital is likely to be delayed, intramuscular injection of RV antivenom as soon as possible in the field could help prevent victims from developing DIC. The role of IVIG is still unsettled as the available evidence is biased.

For Malayan pit viper envenomings, administration of MPV antivenom is also the most important intervention. MPV antivenom made by Twyford or the GPO of Thailand are antivenom of choice for these patients. The role of heparin or other pharmacologic agents has not been assessed.

There is not enough evidence to make recommendation on how to manage green pit viper envenomings. It is logical to give GPV antivenom when there is clinical evidence of systemic bleeding or when blood is incoagulable.

The role of tetanus prophylaxis has not been addressed in any randomized controlled trials. However, because of the severity of this disease and the safety of tetanus toxoid, along with the fact that snake fangs and infected snake wounds contains anaerobic bacteria, it make sense to treat snake bite wound as dirty wounds and TT and TAT are indicated accordingly.

Prevention of wound infection was addressed in two trials (one unpublished). Gentamicin plus chloramphenicol did not prevent abscess formation after Bothrops bite. In another trial, amoxicillin was not shown to prevent clinical wound infection following green pit viper bite. It remains to be seen whether other antibiotics regimens has any role in prevention of wound infection in certain snake bites.

Adrenalin has been shown in one trial to be effective in preventing allergic reactions from one antivenom. However, the results are dramatic. Based on these results, we would suggest that for antivenom that causes a similar high incidence (50%) of adverse effect, pre-medication with adrenaline should be a routine practice. If clinicians consider the antivenom they are using or other conditions are different, and that adrenalin is not justified routinely, then they should be challenged to test this in a randomised controlled trial (see below).

Despite its theoretical usefulness, the use of promethazine (a histamine H1-blocker) does not prevent any allergic reaction to horse serum antivenom in a large trial. Therefore, the use of H1-blocker as a pre-medication before antivenom infusion are probably not justified. Corticosteroid have not been assessed whether it can prevent adverse effects of horse serum antivenom.

Implications for research

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Trial Register

Published report on the management of venomous snake bites

Types of Snake envenoming	Geo-graphic area	Comparisons between	Number of subjects	Study Design & Randomization	Outcome Endpoints	Conclusions	Refer-ence
Malayan pit viper (MPV, งูกะปะ, *Calloselasma rhodostoma*) envenoming	Thailand (Trang province)	Mono-specific MPV antivenom from • Thai Red Cross (TRC), • Thai Government Pharmaceutical Organization (GPO), • Twyford Pharmaceutical (Twy).	46, (15 TRC, 15 GPO, 16 Twy)	Randomized controlled trial (unblind)	Time from anti- venom infusion to restoration of blood coagulability	GPO was superior than TRC and Twy.	Warrell *et al.* 1986
Russell's Viper (RV, งูแมวเซา, *Daboia russelli*) envenoming	Thailand (Prachin-buri, central plain)	Mono-specific RV antivenom from GPO at • 60 ml q 6 h, or • 100 ml q 6 h until VCT < 20 minutes	30, (15 each)	Randomized controlled trial (unblind)	Time and volume of anti- venom needed to restoration of blood coagulability by VCT	Inconclusive, because there were significant difference in envenoming (blood venom by ELISA) among the two groups	Karncha-nachetа-nee *et al.* 1994
Russell's Viper (RV, งูแมวเซา, *Daboia russelli)* envenoming	Myanmar (Burma)	Mono-specific RV anti- venom from Burma pharmaceutical industry (BPI) plus • Heparin 50 U/kg loading with 10 U/kg/h x 24 hr • Normal saline x 24 hr	28, (14 each)	Randomized controlled trial (unblind)	• Activated partial thromboplastin time (aPTT) recovery • Fibrinogen conc-entration recovery • Factor V level recovery • Factor X level recovery	Heparin did not significantly improve coagulation recovery after antivenom therapy	Lwin *et al.* 1989.
Russell's Viper (RV, งูแมวเซา, *Daboia russelli)* envenoming with DIC	Myanmar	Mono-specific RV anti- venom from Myanmar pharmaceutical industry (MPI) plus • Heparin 50 U/kg loading with 10 U/kg/h x 24 hr • Normal saline x 24 hr	20, (10 each)	Randomized controlled trial (unblind)	• aPTT recovery • Fibrinogen conc-entration recovery • F V level recovery • F X level recovery	Heparin did not sig-nificantly improve coagulation recovery after antivenom therapy	Swe *et al*, 1992

Types of Snake envenoming	Geo-graphic area	Comparisons between	Number of subjects	Study Design & Randomization	Outcome Endpoints	Conclusions	Refer-ence
Russell's viper (*Daboia russelli*) bites	Myanmar	Monospecific antisera (ASV) 40 ml intravenously (IV) if systemic envenomization (incoagulable blood and/or clinical proteinuria) and other supportive therapy in hospital • ASV 10 ml (5 ml to each buttock) intramuscularly (IM) within 2 hours after bitten in the field, before hospitalization • No prior ASV I.M. before hospitalization (standard treatment only)	116, 34 ASV IM, 82 standard treatment only.	Clinical trial	Prevalence of complications: • Disseminated intravascular coagulation (DIC) • proteinuria, • acute renal failure • systemic bleeding • hypotension • IV ASV received • serum creatinine • proteinuria • venom antigen level • the need peritoneal dialysis.	Reduced number of patients with systemic envenoming complications following DIC and decreased fatality rate of victims who receive ASV IM prior to hospitalization.	Aung *et al*, 1996
Pit viper envenomization (clinical or lab-oratory evidence)	Ecuador (Amazon rain forest)	Tetanus prophylaxis plus • Antibiotics: Gentamicin 1 mg/kg IV for adults; or 2 mg/kg IV for children q8h, and chloramphenicol 12 mg/kg q6h • No antibiotics treatment (control)	114, 59 anti-biotics, 55 control	Prospective, controlled trial	• Incidence of abscesses	Antibiotics do not prevent infectious complications of envenomization and is not cost-effective.	Kerrigan *et al*, 1997
Any snake envenoming that result in prolonged venous clotting time	India	Lyophilized polyvalent antivenom (Haffkine Biopharmaceutical Corp., Bombay) at • 4 ampoules at hr 1,3,6 and then 4 amp q3h • 2 ampoules at hr 1,3,6 and then 4 amp q3h	53, (26 high dose, 27 low dose)	Randomized controlled trial (unblind)	Time from anti- venom infusion to restoration of VCT (<10 min)	No significant difference between high and low dose antivenom therapy	Thomas and Jacob, 1985.
Any snake envenoming that result in prolonged venous clotting time	Sri Lanka	Polyspecific snake anti- venom (AVS, Serum Institute of India, Pune) plus • IVIG 1 g/kg (Sandoz) or • saline	15, (7 AVS+ IVIG, 8 AVS alone)	Randomized controlled trial (unblind)	• Time from anti-venom infusion to restoration of VCT (<10 min) • Need for repeat AVS	AVS+IVIG significantly reduces the need for repeat AVS.	Sellahe-wa *et al*, 1994

Types of Snake envenoming	Geo-graphic area	Comparisons between	Number of subjects	Study Design & Randomization	Outcome Endpoints	Conclusions	Refer-ence
Cobra (งูเห่า, *Naja naja philippinensis*) envenoming	Philip-pines	Atropine 0.6 mg followed by • Edrophonium (Tensilon®) 10 mg vs • normal saline	10	Randomized double-blind crossover placebo-controlled trial	• Duration (seconds) of upper lid retrac-tion maintained during upward gaze • Degree of ptosis (mm iris uncovered)	Edrophonium unequivocally improved neuro-logical outcome, at 5 minutes post injection.	Watts *et al*, 1986.
Cobra (งูเห่า, *Naja naja philippinensis*) envenoming	Philip-pines	Philippine cobra antivenom (Philippine Ministry of health laboratory) at dosage of • 2 vials • 5 vials • 10 vials followed by edrophonium (Tensilon®) at 120 min	8	Randomized double-blinded controlled trial	• Duration (seconds) of upper lid retrac-tion maintained during upward gaze • Degree of ptosis (mm iris uncovered)	No difference in outcome between the three doses of anti-venom; all resulted in partial but modest improvement. Edro-phonium is effective.	Watts *et al*, 1989
Cobra (งูเห่า, *Naja naja kaouthia*) envenoming	Thailand (Central)	Cobra antivenom (Queen Saowabha memorial institute) at a bolus dosage of • no antivenom (gr. I) • 50 ml (gr. II) • 100 ml (gr. III) • 200 ml (gr. IV) followed by assisted ventilation as needed	68; (27 gr.I, 23 gr.II, 10 gr.III, 8 gr.IV)	Randomized trial (group II-IV) with historical control (group I)	• Duration of ventilatory assistance • Duration of hospitalization	Significant decrease in duration of respiratory failure is seen with 100 ml IV bolus Cobra antivenom compared to no or 50 ml.	Pocha-nukul *et al*, 1997
Papuan taipan (*Oxyuranus scutellatus canni*)	Papua New Guinea (central)	One or more of the following regimens 6 hours apart: • Edrophonium (Edro) 10 mg vs saline control • 3,4 Diaminopyridine (DAP) 10 mg vs saline control • Edro + DAP (no control)	11 Edro vs 11 control, 12 DAP vs 6 control, 10 Edro+ DAP	Randomized double-blinded controlled trial (for Edro alone or DAP alone trials)	• Degree of ptosis (mm iris uncovered) • Degree of limitation of lateral gaze • Maximal extent of mouth opening • Size of an evoked compund muscle action potential (CAMP) • peripheral grip strength	Edrophonium or 3,4 DAP alone does not significantly improve neurological out-come. Combined edrophonium and 3,4 DAP produce measurable elec-trophysiological and clinical response.	Trevett *et al*, 1995

Types of Snake envenoming	Geo-graphic area	Comparisons between	Number of subjects	Study Design & Randomization	Outcome Endpoints	Conclusions	Refer-ence
Carpet viper *(Echis carinatus)* bites with incoagulable blood and/or immunological tests of wound aspirate.	Nigeria	All receive *Echis*- specific antivenom 20 ml IV and other necessary supportive treatment plus • low dose heparin (50 units/kg IV followed by 10 units/kg/h infusion for 22 hrs. vs. • no heparin	14, (7 each)	Case-control study	• Clinically • Coagulation tests:; whole blood clotting test, kaolin-cephalin clotting time, platelet count, fibrin degradation products, fibrinogen and clotting factors V, VIII and II	Heparin does not reduce local effects of envenoming. *In vitro, Echis*-induced thrombin is less sensitive to the inhibitory effect of heparin than physiologic thrombin.	Warrell *et al*, 1976
Carpet viper (Saw-scaled viper, *Echis carinatus*) envenoming with uncoagulable blood	Nigeria (and South Africa)	• *Echis*-specific monovalent antivenom (South African Institute of Medical Research, SAIMR) vs • North and West African polyvalent (*bitis-echis-naja*) antivenom (Behringwerke)	46, (23 each)	Randomized controlled trial (unblind)	Time and volume of anti- venom needed to restoration of blood coagulability by VCT	SAIMR antivenom reverse coagulation defects more rapidly and at a lower dosage than Behringwerke antivenom	Warrell *et al.*, 1974
Carpet viper (Saw-scaled viper, *Echis carinatus)* envenoming with uncoagulable blood	Nigeria (and South Africa)	• *Echis*-specific monovalent antivenom (Pasteur, Paris) vs • North and West African polyvalent (*bitis-echis-naja*) antivenom (Behringwerke)	14, (7 each)	Randomized controlled trial (unblind)	Time and volume of anti- venom needed to restoration of blood coagulability by VCT	Pasteur antivenom reverse coagulation defects more rapidly and at a lower dosage than Behringwerke antivenom	Warrell *et al.*, 1980
Carpet viper (Saw-scaled viper, *Echis ocellatus)*	West African savanna (Ghana, Togo, Nigeria)	• ovine *Echis ocellatus*-specific monovalent antivenom (EchiTab®, Therapeutic antibodies Ltd.) vs • Institute Paris Serum (IPSER) Africa polyspecific antivenom	30, (22 Echi-Tab, 17 Ipser Africa)	Randomized controlled trial (unblind)	volume of anti- venom needed to restoration of blood coagulability by WBCT20, Antivenom reactions	EchiTab 1 vial q6h is equally effective as Ipser Africa anti-venom (4 ampoules q6h), but EchiTab causes more frequent allergic reactions.	Merger *et al*, 1997

Types of Snake envenoming	Geo-graphic area	Comparisons between	Number of subjects	Study Design & Randomization	Outcome Endpoints	Conclusions	Refer-ence
Lanced-head vipers (*Bothrop jararaca*) envenoming	Brazil (Sao Paulo)	Brazillian polyspecific *Bothrop* antivenoms made by • Instuto Butantan (Butantan) • Instituto Vital Brazil (Vital) • FundaÇão Ezequiel Dias (FUNED) were given 4 ampoules initially (for 'less severe' patients) and q6hr prn, or 8 ampoules initially (for 'more severe' patients and q6h prn.	39 Butantan, 41 Vital, 41 FUNED	Randomized double-blinded controlled trial, stratified by severity	Time and volume of anti- venom needed to restoration of blood coagulability by VCT	No difference in clinical efficacy between the three types of Bothrop antivenom.	Cardoso *et al*, 1993
Lanced-head vipers (*Bothrop jararaca*) envenoming, mild to moderate cases only	Brazil (Sao Paulo)	Brazillian polyspecific *Bothrop* antivenoms (Butantan)at • 4 ampoules (40 ml) or • 2 ampoules (20 ml)	170, (88 high dose, 82 low dose)	Randomized double-blinded controlled trial	Restoration of VCT at 6, 12 and 24 hour after antivenom therapy	No difference in clinical efficacy between the two doses of Bothrop antivenom.	Jorge *et al*, 1995
Lanced-head vipers (*Bothrop atrox*) envenoming	Colom-bia (Antio-quia and Chocó)	• Polyvalent antivenom (Bothrop-crotalid-lachesid) vs • Monospecific anti-*B. atrox* antivenom prepared by Instito Clodomiro Picado, Univ Costa Rica at the doses of 3 vials for mild, 6 vials for moderate, and 9 vials for severe envenoming initially and 3 vials q12h prn.	39, (20 mono, 19 poly)	Randomized double-blinded controlled trial, stratified by severity	• Cessation of local and gingival bleed-ing at 6 and 12 hr. • Restoration of VCT at 6, 12 and 24 hour after antivenom therapy	No difference in clinical efficacy between the two types of antivenom.	Otero *et al*, 1996
Bothrops lanceolatus envenoming at risk for systemic thrombosis	Martin-ique	During Jun 91- Mar 93 - Aug 94 • Nadroparine (Fraxiparine, FP) vs • Urokinase (UK) + FP with antivenom for severe cases During Mar 93- Aug 94 • all are treated with Monovalent antivenom (Pasteur Merieux serums et vaccins)	50, 6 UK, 7UK+FP, 12 non-randomiz ed FP vs 25 AVS alone	Unrandomized trial (historical control), with randomization only between UK vs UK+FP	• Prevention of severe thrombosis	Urokinase or Fraxparine does not prevent thrombosis. Antivenom effect-ively prevent thrombosis	Thomas *et al*, 1995

Types of Snake envenoming	Geo-graphic area	Comparisons between	Number of subjects	Study Design & Randomization	Outcome Endpoints	Conclusions	Refer-ence
Bothrops sp. envenomings	Colom-bia (Uraba - North-western region)	Antivenom doses were 2, 4, and 6 vials (10 ml/vial) for mild, moderate and severe envenoming, respectively of • Butantan polyspecific, pepsin-digested Bothrops antivenom (gr.A) • Butantan polyspecific, whole IgG Bothrops antivenom by caprylic acid fractionation (gr. B) • Colombian commercial, monovalent, whole igG Bothrops antivenom (gr. C)	79, 30 (gr.A) 27 (gr.B) 22 (gr.C)	Randomized, blinded, clinical trial	• Hemostatic parameters, • Cessation of local and systemic bleeding. • Clearance of venom • Early antivenom reactions (EARs)	Similar in neutralizing Bothrops venom. Whole IgG antivenom produced by caprylic acid fractionation is good for reducing EARs incidence.	Otero-Patino *et al*, 1998

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