

Snake antivenom for snake venom induced consumption coagulopathy (Review)

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[Intervention Review]

Snake antivenom for snake venom induced consumption coagulopathy

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Editorial group: Cochrane Injuries Group.

Publication status and date: New, published in Issue 6, 2015.

Review content assessed as up-to-date: 30 January 2015.

Citation: Maduwage K, Buckley NA, de Silva HJ, Lalloo DG, Isbister GK. Snake antivenom for snake venom induced consumption coagulopathy. *Cochrane Database of Systematic Reviews* 2015, Issue 6. Art. No.: CD011428. DOI: 10.1002/14651858.CD011428.pub2.

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ABSTRACT

Background

Snake venom induced consumption coagulopathy is a major systemic effect of envenoming. Observational studies suggest that antivenom improves outcomes for venom induced consumption coagulopathy in some snakebites and not others. However, the effectiveness of snake antivenom in all cases of venom induced consumption coagulopathy is controversial.

Objectives

To assess the effect of snake antivenom as a treatment for venom induced consumption coagulopathy in people with snake bite.

Search methods

The search was done on 30 January 2015. We searched the Cochrane Injuries Group's Specialised Register, the Cochrane Central Register of Controlled Trials (CENTRAL, *The Cochrane Library*), Ovid MEDLINE(R), Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid OLDMEDLINE(R), Embase Classic+Embase (OvidSP), three other sources, clinical trials registers, and we also screened reference lists.

Selection criteria

All completed, published or unpublished, randomised, controlled trials with a placebo or no treatment arm, where snake antivenom was administered for venom induced consumption coagulopathy in humans with snake bites.

Data collection and analysis

Two authors reviewed the identified trials and independently applied the selection criteria.

Main results

No studies met the inclusion criteria for this review.

Authors' conclusions

Randomised placebo-controlled trials are required to investigate the effectiveness of snake antivenom for clinically relevant outcomes in patients with venom induced consumption coagulopathy resulting from snake bite. Although ethically difficult, the routine administration of a treatment that has a significant risk of anaphylaxis cannot continue without strong evidence of benefit.

PLAIN LANGUAGE SUMMARY

Snake antivenoms for treating people who have been bitten by a snake, and have developed abnormal blood clotting

Many snake venoms cause coagulopathy in humans. Coagulopathy is a condition in which the person's blood is unable to clot because the venom causes decreased levels of clotting factors. Coagulopathy increases the risk of bleeding. Antivenom is a treatment used to neutralise venom in people who have been bitten by a snake. There is some evidence from observational studies in humans which suggest that snake antivenom is helpful to people who have been bitten by a snake. However, the use of antivenom has some risks, and can cause allergic reactions.

Antivenom is made by injecting venom into either horses, sheep or goats, and then collecting the animal blood and separating out the specific antibodies to the snake venom. The antivenom is put into a person's vein, so that it can mix with the blood in their body.

The authors of this Cochrane review investigated whether there was evidence that antivenom helped people who had been bitten by a snake and had developed coagulopathy. The authors looked for studies where antivenom was used as a treatment for people who developed coagulopathy after a snake bite, regardless of the type of snake.

The type of study eligible for inclusion in the review was the randomised controlled trial, and the control group needed to receive either a placebo or no antivenom. The review authors did not find any trials meeting this criteria, despite searching all the major international medical reference databases. The databases were searched on 30 January 2015.

Since no relevant randomised controlled trials were identified, this systematic review provides no evidence to help doctors decide if and when to use antivenom for snakebite coagulopathy. The authors say that trials of antivenom are urgently needed so that doctors and patients can fully understand the benefits and risks of antivenom. At the moment doctors make decisions about when to use antivenom based on the results of observational studies, which may not fully describe the effects of antivenom.

BACKGROUND

Description of the condition

Snake envenoming is a major medical problem in tropical areas. The estimated burden of snake bite is approximately 421,000 cases of envenoming with 20,000 fatalities annually, although there may be as many as 1,841,000 envenomings and 94,000 deaths (Kasturiratne 2008).

Venom induced consumption coagulopathy is one of the major clinical manifestations of snake envenoming and may be complicated by fatal haemorrhage (Isbister 2010a). Venom induced consumption coagulopathy has previously been referred to by a number of different terms, including disseminated intravascular coagulation, defibrination syndrome and procoagulant coagulopa-

thy (Isbister 2010b). Venom induced consumption coagulopathy results from the action of snake procoagulant toxins on human coagulation factors causing consumption of these clotting factors leading to multiple factor deficiencies (Isbister 2009a). There are many examples of procoagulant snake toxins that cause venom induced consumption coagulopathy, including prothrombin activators in *Echis carinatus*, *Pseudonaja textilis*, *Notechis scutatus* venoms (Rosing 1992; Joseph 2001; Rosing 2001), factor X activators in *Dabois russelii*, *Bothrops atrox*, *Cerastes cerastes*, *Bungarus*, *Ophiophagus* venom (Tans 2001), factor V activators in *Bothrops atrox*, *Naja naja oxiana* venom (Rosing 2001), thrombin-like enzymes in *Agkistrodon contortrix contortrix* venom (Swenson 2005), and plasminogen activators in *Trimeresurus stejnegeri* venom (Sanchez 2006). Venom induced consumption coagulopathy can result in bleeding if there is trauma, or spontaneous haemorrhage in cases where the venom also contains a haemorrhagin (e.g. *E. carinatus*).

Major haemorrhage in vital organs, such as intracranial haemorrhage, is the most serious issue and is often fatal.

A number of laboratory clotting times and clotting factor studies are used to diagnose and monitor venom induced consumption coagulopathy, including the prothrombin time/international normalised ratio, the activated partial thromboplastin time, and the 20-minute whole blood clotting test. These play a major role in diagnosis, assessment and treatment of venom induced consumption coagulopathy (Isbister 2010a).

Description of the intervention

Antivenom is the primary treatment for snake envenoming (Lalloo 2003; Isbister 2010c). Antivenoms contain polyclonal antibodies raised against one or more snake venoms. They may contain whole immunoglobulins, but more commonly, pepsin or papain digested fragments of immunoglobulins such as F(ab')₂ or Fab. They are made by injecting venom into either horses, sheep or goats, and then collecting blood and separating out the specific antibodies to the snake venom. Intravenously administered antivenom in patients with snake envenoming binds to circulating snake toxins which aims to neutralise or eliminate the toxins and thereby prevent or reverse the clinical effects of envenoming. Monovalent antivenoms are raised against a single snake species, while polyvalent antivenoms are raised against more than one species.

Immediate hypersensitivity reactions to the foreign proteins (immunoglobulins) in snake antivenoms are the major adverse effect of antivenom treatment, including life threatening anaphylaxis (Nuchprayoon 1999; Lalloo 2003; Gawarammana 2004; de Silva 2011; Isbister 2012). Manufacturing protocols and methods of snake antivenoms are different in various regions in the world and the standardisation of snake antivenom production remains problematic.

How the intervention might work

Antibodies in the antivenom bind to the toxic components in snake venom. Early administration of antivenom will bind the circulating procoagulant snake toxins and potentially prevent, delay or lessen the severity of venom induced consumption coagulopathy. In the majority of patients who have already developed venom induced consumption coagulopathy, antivenom is used to neutralise circulating toxins and allow recovery of venom induced consumption coagulopathy. However, the effectiveness and mechanism of action of antivenom in already developed venom induced consumption coagulopathy remains unclear (Isbister 2009b). Recovery of the coagulopathy depends on re-synthesising clotting factors which is not directly affected by antivenom administration (Isbister 2010a).

Why it is important to do this review

Even though snake antivenom is the mainstay of the treatment for snake envenoming, there is controversy regarding the effectiveness of antivenom for venom induced consumption coagulopathy (Isbister 2010a). It is unlikely that antivenom can be administered early enough to prevent venom induced consumption coagulopathy because the procoagulant toxins in snake venoms act rapidly (Isbister 2010a). The more important question is whether the administration of antivenom will speed the recovery of venom induced consumption coagulopathy by inactivating the active toxins to allow re-synthesis of clotting factors (Isbister 2010a). Thus only if further factor consumption is occurring due to significant amounts of circulating pro-coagulant venoms, would antivenom be expected to speed recovery.

Recent observational clinical studies on Australian elapid envenoming indicated that neither early (versus late) antivenom nor higher doses of antivenom (> one vial) were associated with more rapid recovery in venom induced consumption coagulopathy (Allen 2009; Isbister 2009b). In contrast, in *Echis* envenoming in Africa, the use of antivenom does appear to speed the recovery of the coagulopathy (Mion 2013). We aim to examine the clinical trial evidence regarding effectiveness of snake antivenom for venom induced consumption coagulopathy from all snake species.

OBJECTIVES

To assess the effects of antivenom for the recovery from venom induced consumption coagulopathy in people with snake envenoming.

METHODS

Criteria for considering studies for this review

Types of studies

All randomised controlled trials (RCTs) in humans.

Types of participants

People of any age with snake envenoming who have already developed snake venom induced consumption coagulopathy. Diagnosis of venom induced consumption coagulopathy must be based on abnormal results from the 20-minute whole blood clotting test or an elevated international normalised ratio of >2.

Types of interventions

Intravenous administration of snake antivenom regardless of the type of antivenom or the dose. People who were not treated with antivenom were the comparison group.

Types of outcome measures

Primary outcomes

- Mortality

Secondary outcomes

- Major haemorrhages
- Time to improve clotting studies (e.g. time to international normalised ratio <2; time to improve 20-minute whole blood clotting test)
- Immediate systemic hypersensitivity reactions
- Serum sickness

Calculation of information size requirements

Snakebite mortality is very variable and has contributors other than venom induced consumption coagulopathy such as neurotoxicity, myotoxicity and acute renal injury. However, for simplicity we have taken the mortality rate from [Kasturiratne 2008](#), which estimates an overall case-fatality of around 5%. Using G*Power (<http://www.gpower.hhu.de/en.html>), the estimated sample size required in order to show this rate could be halved would require 2504 people in total.

Search methods for identification of studies

In order to reduce publication and retrieval bias we did not restrict our search by language, date or publication status.

Electronic searches

The Cochrane Injuries Group's Trials Search Co-ordinator searched the following:

1. Cochrane Injuries Group Specialised Register (30/01/2015);
2. The Cochrane Central Register of Controlled Trials (*The Cochrane Library*) (issue 1 of 12, 2015);
3. Ovid MEDLINE(R), Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid OLDMEDLINE(R) 1946 to 30/01/2015;
4. Embase Classic + Embase (OvidSP) 1947 to 30/01/2015;
5. ISI Web of Science: Science Citation Index Expanded (1970 to 30/01/2015);

6. ISI Web of Science: Conference Proceedings Citation Index-Science (1990 to 30/01/2015);

7. Toxicology Literature Online (TOXLINE) (<http://toxnet.nlm.nih.gov/cgi-bin/sis/htmlgen?TOXLINE>) (30/01/2015);

8. ClinicalTrials.gov (<https://clinicaltrials.gov/>) (30/01/2015);

9. WHO International Clinical Trials Registry Platform (ICTRP) (<http://apps.who.int/trialsearch/>) (30/01/2015);

10. OpenGrey (<http://www.opengrey.eu/>) (30/01/2015).

We adapted the MEDLINE search strategy illustrated in [Appendix 1](#) as necessary for each of the other databases. We also added search filters, and a modified version of the 'Cochrane Highly Sensitive Search Strategy, for identifying randomised trials in MEDLINE and Embase' ([Lefebvre 2011](#)).

Searching other resources

We searched the reference lists of all relevant studies and contacted experts in the field in order to identify ongoing and completed studies. We also ran a search on Google and Google Scholar restricting the search results from 1947 to present, and reviewed over 500 results to find relevant studies ([Appendix 1](#)).

Data collection and analysis

We performed this systematic review according to the instructions given in the *Cochrane Handbook for Systematic Reviews of Interventions* ([Higgins 2011](#)), and our protocol ([Maduwaige 2014](#)).

Selection of studies

Two authors (KM and GI) independently screened the titles and abstracts of all articles identified by the search strategy. When either or both authors identified the article as possibly being a report that meets the inclusion criteria, we obtained the full text version of the published article. Both authors reviewed the full text of each article to determine if the article meets the inclusion criteria. There were no disagreements between the two authors about the inclusion of studies. We provided details of the included and excluded studies in the appropriate tables within the review.

The two authors independently reviewed each article that met the inclusion criteria, and extracted data from the article onto a standard data extraction form. We then compared these data forms, which were consistent with each other.

Data extraction and management

Two authors (KM and GI) extracted data on the following items onto a standard form.

- General information about the article (title of the article, source, publication year, years the study was conducted, language of publication, etc.).

- Clinical trial characteristics: design, diagnostic ascertainment, standard care provided, randomisation, allocation concealment, interventions, drop-out and lost to follow up rates, definitions of outcomes, and methods of outcome assessment.

- Patients: inclusion and exclusion criteria, sample size, baseline characteristics (e.g. age of the patients, past history of bleeding, anticoagulant therapy or coagulation disorders, clinical severity on enrolment, etc.).

- Interventions: type of antivenom (polyvalent or monovalent), manufacturer, dose of antivenom (number of vials or mg), duration of administration, timing of administration of antivenom after the bite.

- Outcomes: mortality, major haemorrhage (according to the definition by the International Society on Thrombosis and Haemostasis), time to improved clotting function defined as either the time to international normalised ratio <2 or time until a negative result of the 20-minute whole blood clotting test, length of hospital stay, systemic hypersensitivity reactions.

Assessment of risk of bias in included studies

In the future if studies are included in this review, two authors (KM and GI) will independently assess the included studies for risk of bias in the following areas. We will assess risk of bias using the suggested domains and guidance provided in the Cochrane Collaboration's tool for assessing risk of bias (Higgins 2011). We will assess random sequence generation (selection bias), allocation concealment (selection bias), blinding of participants and personnel (performance bias), blinding of outcome assessment (detection bias), incomplete outcome data (attrition bias), selective reporting (reporting bias), and other sources of bias (in particular, funding source). If there is insufficient information we will initially judge domains as "unclear risk" and will attempt to clarify the risk of bias by contacting the study authors. We plan to include all studies irrespective of the risk of bias; however, we plan to perform a sensitivity analysis. If the sensitivity analysis shows substantial differences, we will present alternative estimates that exclude studies with high or unclear risk of bias.

Sequence generation of the randomisation process

- Low risk: using random number tables, computer random number generation, coin tossing, stratified or block randomisation, shuffling cards or envelopes, throwing dice, drawing lots or other valid methods

- High risk: "quasi" randomisation, date of birth, day of visit, identification number or record results, alternate allocation

- Unclear risk: not described or not enough information to make a clear judgment

Allocation concealment

- Low risk: allocation concealment is described and would not allow either the investigator or participants to know or influence treatment group assignment at the time of study entry

- Acceptable methods include central randomisation (phone, web, pharmacy) or sequentially numbered, opaque sealed envelopes

- High risk: the method of allocation is not concealed (e.g. random sequence known to staff in advance, envelopes or packaging without all safeguards or a non-randomised and predictable sequence)

- Unclear risk: trial either did not describe the method of allocation concealment or reported an approach that clearly was not adequate

Blinding of participants and personnel

- Low risk: blinding, and unlikely that the blinding could have been broken, or no blinding, or incomplete blinding but outcome unlikely to be influenced

- High risk: no blinding, incomplete or broken blinding and outcome likely to be influenced

- Unclear risk: not described or not enough information to make a clear judgment

Blinding of outcome assessment

- Low risk: blinding of outcome assessors was clearly maintained, or no blinding but measurements unlikely to be influenced

- High risk: no blinding, or broken blinding, and measurements likely to be influenced

- Unclear risk: not described or not enough information to make a clear judgment

Intention-to-treat analysis

- Low risk: specifically reported that intention-to-treat analysis was undertaken by the authors, or report that makes it unmistakable that intention-to-treat was undertaken for the primary analysis

- High risk: no report of an intention-to-treat analysis being conducted

- Unclear risk: not described or not enough information to make a clear judgment

Incomplete outcome data

- Low risk: no missing data, reasons for missing data not related to outcomes, missing data balanced across groups and proportion missing or plausible effect size not enough to have clinically relevant effects

- High risk: reasons related to outcome and imbalance in number or reasons, proportions missing or plausible effect size

enough to have clinically relevant effect, “as treated” analysis with substantial departure from allocation, inappropriate use of imputation

- Unclear risk: not described or not enough information to make a clear judgment

Selectiveness of outcome reporting

- Low risk: method is available and all pre-specified outcomes of interest are reported in the pre-specified way, protocol not available but it is clear that all pre-specified and expected outcomes of interest are reported
- High risk: outcomes not reported as pre-specified or expected e.g. missing, added, subset, unexpected measurement or methods. Outcomes reported are incomplete and cannot enter a meta-analysis
- Unclear risk: not described or not enough information to make a clear judgment

Reporting bias

We will interpret our results cautiously and with an awareness of the likelihood of reporting bias. We will consider using funnel plots.

Other sources of bias

- Low risk: studies appear to be free of other sources of bias such as imprecision (e.g. small sample size), diversity (e.g. inadequate dose, unusual population)
- High risk: baseline imbalance, non-randomised studies, recruitment bias in cluster-randomised trials, inadequate power and/or implausible sample size calculation, early stopping of trial (based on interim analysis of efficacy)
- Unclear risk: not described or not enough information to make a clear judgment

Measures of treatment effect

Dichotomous data

We planned to present dichotomous data outcomes as risk ratios (RRs) with 95% confidence intervals (CIs) for individual trials.

Continuous data

We planned to present continuous data outcomes with mean differences (MDs) and 95% CIs. We planned to calculate the mean difference if possible as these results are easier for clinicians and readers to interpret; and use standardised mean differences (SMDs) when different scales are used in the trials.

Ordinal data

We planned to report the types of adverse events and complications.

Unit of analysis issues

Individual participants are the unit of analysis. To answer our primary question (does antivenom improve venom induced consumption coagulopathy compared to no antivenom treatment) we planned to initially simply combine all active intervention groups of the study into a single group and compare their outcomes to the control groups(s) not receiving antivenom. We may also explore comparison of doses or types of antivenom (post-hoc).

Dealing with missing data

In the future if studies are included in this review, we will contact the authors of the original studies if essential data are missing from their trial reports. If we receive no reply after eight weeks, we will extract the available data from the published reports. We will assess the missing data and attrition rates for each of the included studies and report the number of participants who are included in the final analysis as a proportion of all participants in the study.

Assessment of heterogeneity

In the future if studies are included in this review, we will evaluate statistical heterogeneity using the Chi² test to assess for heterogeneity between trials, and the I² statistic for quantifying heterogeneity across studies (roughly interpreted as follows: 0 to 30%: probably not important; 31 to 60%: may represent moderate heterogeneity; 61 to 75%: may represent substantial heterogeneity; 76 to 100%: very considerable heterogeneity) as outlined in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). We expect considerable heterogeneity due to considerable variation across trials in setting, snake, intervention and outcomes. We intend to use a random-effects model to account for this heterogeneity in any summary estimates of effect. We may also (post-hoc) look for plausible explanations of heterogeneity. We will discuss the implications of heterogeneity and how they relate to external validity in the discussion.

Assessment of reporting biases

Systematic difference between reported and unreported findings are referred to as reporting bias. We will include selective outcome reporting assessment as part of the ‘Risk of bias table’ and also under ‘Intention-to-treat analysis’.

We will assess publication biases by using funnel plots when there are at least 10 studies included in the meta-analysis.

Data synthesis

In the future if studies are included in this review, we will analyse the data using the Cochrane Collaboration statistical software [Review Manager](#). We will express results for dichotomous outcomes as RRs with 95% CIs and continuous outcomes as MDs. We will present data in a 'Summary of findings' table according to Grading of Recommendations Assessment, Development and Evaluation (GRADE) guidelines as well as the method described in the *Cochrane Handbook for Systematic Reviews of Interventions* ([Higgins 2011](#)). The table will include mortality, major haemorrhages, time to improved clotting (e.g. time to international normalised ratio <2 or time to normalised result of the 20-min whole blood clotting test), immediate systemic hypersensitivity reactions and serum sickness as outcomes.

We planned to present dichotomous outcomes such as mortality, number of haemorrhages, number of immediate type hypersensitivity reactions, and number of cases of serum sickness as RRs with 95% CIs for individual trials. For dichotomous data meta-analysis we planned to use a Mantel-Haenszel random-effects model. For continuous outcomes (e.g. time to improve clotting studies) that have been recorded as MDs, SMDs or standard deviations (SDs) with 95% CIs, we planned to use an inverse variance random-effects model. If we were to find two or more studies assessing the same outcomes we will perform meta-analysis. If meta-analysis is not possible we will write a narrative summary of the study findings and follow alternative methods as described in the *Cochrane Handbook for Systematic Reviews of Interventions* ([Higgins 2011](#)).

Subgroup analysis and investigation of heterogeneity

Where possible (if sufficient data and information are available) we will perform subgroup analysis based on the following factors, which are thought to affect outcomes after venom induced consumption coagulopathy:

1. type of snake envenoming (elapids and viperids);
2. type of snake antivenoms;
3. dose of antivenom.

Sensitivity analysis

In the future if studies are included in this review, we will restrict sensitivity analyses to include studies with both adequate allocation concealment and blinded outcome assessment.

RESULTS

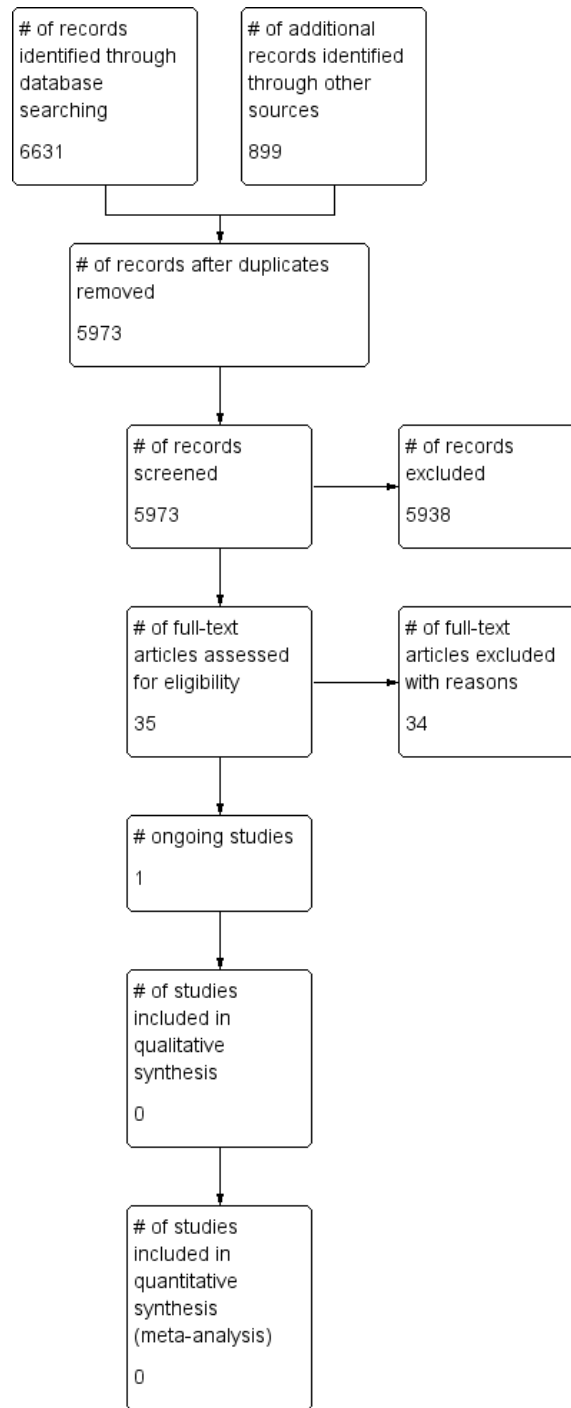
Description of studies

We did not find any studies for inclusion in this review. There is one ongoing trial (NCT01864200).

Results of the search

The search retrieved 7530 records and after duplicates were removed we screened 5973 records ([Figure 1](#)). The search identified one ongoing study, and the results will be included in the review when they become available.

Figure 1. Study flow diagram.



Included studies

There are no studies included in this review.

Excluded studies

We excluded 34 of 35 studies after reviewing the full text report. See [Characteristics of excluded studies](#). One ongoing study was identified.

Risk of bias in included studies

There are no studies included in this review.

Effects of interventions

There are no studies included in this review.

DISCUSSION

Summary of main results

We were unable to identify any placebo randomised controlled trials of snake antivenom for venom induced consumption coagulopathy meeting the inclusion criteria. We identified one ongoing trial. There were 32 published and two ongoing studies comparing two or more different antivenoms or comparing different doses of antivenoms for venom induced consumption coagulopathy. Few non-randomised trials including comparison groups without antivenom showed that antivenom was effective for envenoming by some snakes (e.g. *Echis* species in Africa), but not others (e.g. Australian elapids) ([Isbister 2010a](#); [Mion 2013](#)).

Overall completeness and applicability of evidence

There is a lack of evidence to support or refute a benefit of antivenom for venom induced consumption coagulopathy.

Quality of the evidence

There was no evidence to assess the quality of the evidence.

Potential biases in the review process

There are no studies included in this review.

Agreements and disagreements with other studies or reviews

The results of this review agree with the conclusion of a systematic review article that also examined RCTs comparing the effects of different antivenoms (n=14) and different doses of antivenom (n=5) ([Maduwage 2014a](#)). If antivenom was always highly effective in shortening the duration of VICC it might be expected that differences would also be seen commonly in such trials. In nine of 14 studies, the authors concluded equal effectiveness (or ineffectiveness) of two or three antivenoms, and four of five studies investigating different doses or dosing regimens concluded equal effectiveness. Even the six RCTs that concluded a difference between doses or antivenoms, lacked a strong statistical basis for this conclusion (i.e. the difference was not based on intention to treat analysis; three of these trials were very small and lacked the statistical power to support the significance of the differences observed ([Warrell 1974](#); [Warrell 1980](#); [Dart 2001](#)), and the others did a post-hoc analysis (a selected time point, sub-group, outcome, or statistical technique that had not been pre-specified) ([Ariaratnam 2001](#); [Smalligan 2007](#); [Abubakar 2010](#)).

AUTHORS' CONCLUSIONS

Implications for practice

There are no completed placebo randomised controlled trials of antivenom for venom induced consumption coagulopathy and therefore nothing from this systematic review provides evidence to help clinicians in deciding to use antivenom for venom induced consumption coagulopathy. The effectiveness of administration of antivenom for venom induced consumption coagulopathy will continue to be based on observational studies until placebo randomised controlled trials are undertaken.

Implications for research

Significant mortality and morbidity is associated with snake envenoming ([Kasturiratne 2008](#)) so effective treatments are desperately required. Antivenom was introduced for the treatment of snake envenoming over a century ago and its clinical use has been based on in vitro and in vivo animal studies of efficacy, small observational studies and clinical experience. As confirmed in this review there has never been a placebo randomised controlled trial

to demonstrate clinical effectiveness for venom induced consumption coagulopathy. This raises some difficult clinical questions regarding the use of a treatment known to have significant adverse effects (e.g. severe anaphylaxis; Nuchprayoon 1999) where there is no good evidence demonstrating benefit.

Undertaking placebo randomised controlled trials of snake antivenom is a challenge to clinical research and regarded as potentially highly unethical by many clinicians and experts (Gerardo 2014). Such a suggestion would be regarded by some as similar to doing a placebo controlled trial of insulin for diabetes mellitus, such is the overwhelming belief in the benefit of antivenom therapy. Therein lies the inescapable ethical dilemma. How do we undertake the appropriate placebo controlled trial of antivenom to demonstrate clinical effectiveness, if it is regarded as unethical to not give antivenom to some patients.

Well designed observational studies have demonstrated that for some snakes there appears to be a clear benefit of antivenom, speeding the recovery of coagulopathy in *Echis ocellatus* envenoming (Mion 2013), but for others there is little or no benefit, such as Australasian elapids (Isbister 2009b). There is substantial *in vitro* and *in vivo* evidence that antivenom binds toxins and that antivenom can neutralise the procoagulant and anticoagulant effects of venoms (Isbister 2009a). However, it is essential to translate pre-clinical efficacy studies into clinical effectiveness studies (Isbister 2010c), and understand that antivenom may be beneficial for some snake and some clinical syndromes, but not others.

There are a number of precedents where placebo randomised controlled trials have been commenced or completed for different antivenoms. The ongoing study identified in this review is a good example of such a trial. Details of the ethical considerations for this trial have been published (Gerardo 2014). A recently published placebo randomised controlled trial of antivenom for red-back spider bite showed no benefit despite decades of belief that it

was effective (Isbister 2014). Again, this study required sufficient evidence to justify ethically undertaking a study with a placebo. In envenoming that causes coagulopathy, the safety of this approach could be ensured by first performing observational studies that demonstrate the time to recovery of clotting factors is not strongly influenced by time to antivenom or dose for a particular snake.

The way forward for developing evidence for antivenom treatment in venom induced consumption coagulopathy will be to use novel study designs to introduce placebo arms. For example, undertaking a placebo controlled trial of early antivenom, where all patients will get antivenom at some stage. Such studies will be challenging but are essential to providing sufficient evidence of benefit for a treatment with severe adverse reactions.

A parallel way forward for developing evidence for antivenom treatment in venom induced consumption coagulopathy might be to examine the use of early (on arrival) versus delayed (after blood test results are returned) antivenom. Such studies will be challenging, not least because of the considerable heterogeneity of clinical features of envenoming by a particular species, but are essential to providing evidence that there is a benefit for this treatment that outweighs the considerable risk of severe adverse reactions.

ACKNOWLEDGEMENTS

We would like to acknowledge the Cochrane Injuries Group editors for their advice and support.

This project was supported by the UK National Institute for Health Research, through Cochrane Infrastructure funding to the Cochrane Injuries Group. The views and opinions expressed are those of the authors and do not necessarily reflect those of the Systematic Reviews Programme, NIHR, NHS or the Department of Health.

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Ariaratnam 2001 {published data only}

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Boyer 2013 {published data only}

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Abubakar 2010	No placebo control group. Compared two different antivenoms.
Ariaratnam 2001	No placebo control group. Compared two different antivenoms.
Boyer 2013	No placebo control group. Compared two different antivenoms.
Bush 2014	No placebo control group. Compared two different antivenoms.
Cardoso 1993	No placebo control group. Compared three different antivenoms
Cherian 1998	No placebo control group. Compared two different doses of antivenom
Dart 2001	No placebo control group. Compared two different doses of antivenom
Isbister 2013	No placebo control group. Compared antivenom versus antivenom with fresh frozen plasma
Jorge 1995	No placebo control group. Compared two different doses of antivenom
Karnchanachetanee 1994	No placebo control group. Compared two different doses of antivenom
Kothari 2001	No placebo control group. Compared two different doses of antivenom
Meyer 1997	No placebo control group. Compared two different antivenoms.
Myint-Lwin 1989	No placebo control group. Compared antivenom versus antivenom with heparin
NCT00639951	No placebo control group. Compared two different doses of antivenom. Ongoing study
NCT00868309	No placebo control group. Compared two different antivenoms. Ongoing study
Otero 1996	No placebo control group. Compared two different antivenoms.
Otero 1999	No placebo control group. Compared two different antivenoms.
Otero 2006	No placebo control group. Compared two different antivenoms.
Otero-Patino 1998	No placebo control group. Compared three different antivenoms
Otero-Patino 2012	No placebo control group. Compared two different antivenoms.
Pardal 2004	No placebo control group. Compared two different antivenoms.

(Continued)

Paul 2003	No placebo control group. Compared antivenom versus antivenom with heparin
Paul 2004	No placebo control group. Compared two different doses of antivenom
Paul 2007	No placebo control group. Compared antivenom versus antivenom with heparin
Sellahewa 1994	No placebo control group. Compared antivenom versus antivenom with intravenous immunoglobulin
Shah 1986	No placebo control group. Compared antivenom versus antivenom with heparin
Smalligan 2004	No placebo control group. Compared three different antivenoms
Srimannarayana 2004	No placebo control group. Compared three different doses of antivenom
Tariang 1999	No placebo control group. Compared two different doses of antivenom
Thomas 1985	No placebo control group. Compared two different doses of antivenom
Warrell 1974	No placebo control group. Compared two different antivenoms.
Warrell 1976	No placebo control group. Compared antivenom versus antivenom with heparin
Warrell 1980	No placebo control group. Compared two different antivenoms.
Warrell 1986	No placebo control group. Compared two different doses of antivenom

Characteristics of ongoing studies [ordered by study ID]

NCT01864200

Trial name or title	A Randomized, Double-Blind, Placebo-Controlled Study Comparing CroFab® Versus Placebo With Rescue Treatment for Copperhead Snake Envenomation (Copperhead RCT)
Methods	A Randomized, Double-Blind, Placebo-Controlled Study
Participants	<p>Inclusion Criteria:</p> <ul style="list-style-type: none">• Envenomation by a copperhead snake. A snake identified by one of the following means: i. Snake or photograph of snake brought to Emergency Department; ii. Patient chooses copperhead from an array of snake photographs; iii. Patient envenomated in an area where only copperheads are endemic; iv. Patient envenomated by a captive copperhead snake• Completion of informed consent and eligibility confirmation within 24 hours of envenomation• Envenomation on only one extremity, distal to the elbow or knee• Clinical evidence of mild or moderate venom effect (limb swelling and/or tenderness) is present (Venom effects need not be progressing.)• Patient willing and able to complete follow-up schedule of assessments• Patient is able to read, comprehend and sign the IRB approved consent document(s)

	<ul style="list-style-type: none"> ● Patient is able to read and comprehend the written assessment tools (e.g. DASH, SF-36, etc.) ● Patient is ≥ 14 years of age ● Patient is sober, competent, and able to complete verbal and written informed consent <p>Exclusion Criteria:</p> <ul style="list-style-type: none"> ● Patient has clinical evidence of severe venom effect as defined by meeting any one of the following parameters: i. Swelling to an entire extremity (all major joints affected). Lower extremity: i. swelling crossing hip joint. Upper extremity: swelling crossing shoulder joint; ii. INR > 2.0; iii. Platelets $< 50,000$ cells/μL; iv. Fibrinogen < 50 mg/dL Compartment syndrome; vi. Systolic Blood Pressure < 90 mmHg; vii. More than minimal bleeding; viii. Investigator's clinical discretion ● Patient has already received antivenom for the management of the current envenomation ● Patient is pregnant or breastfeeding ● Patient is a prisoner ● Patient has a distracting injury or condition with acute pain or functional impairment, and/or is unable to make a reliable self-report of functionality status based solely on the condition of interest <ul style="list-style-type: none"> ● Patient had a previous snake envenomation to any body area in the 30 days prior to screening/enrolment, regardless of whether antivenom was administered for the previous envenomation ● Patient had an acute traumatic event, surgery, an acute medical event, or exacerbation of a pre-existing medical or surgical condition affecting the envenomated extremity within the 30 days prior to screening/enrolment ● Patient has participated in a clinical study involving an investigational pharmaceutical product or device within the 3 months prior to screening that may have impact on clinical outcomes of snakebite <ul style="list-style-type: none"> ● Patient has previously participated in this clinical study ● Patient has a known history of hypersensitivity to any components of CroFab®, or to papaya or papain ● Patient is otherwise unsuitable for inclusion in this study, based on the opinion of the investigator
Interventions	Crotilidae polyvalent immune fab (ovine) and placebo
Outcomes	Patient Specific Functional Scale at Day 14
Starting date	July 2013
Contact information	Anna Temu: anna.temu@btgplc.com
Notes	This study completed in March 2015. Its results will be included in this review when published

DATA AND ANALYSES

This review has no analyses.

APPENDICES

Appendix I. Search strategies

Cochrane Injuries Group Specialised Register & Cochrane Central Register of Controlled Trials (*The Cochrane Library*)

#1MESH DESCRIPTOR Snakes

#2MESH DESCRIPTOR Boidae

#3MESH DESCRIPTOR colubridae EXPLODE ALL TREES

#4MESH DESCRIPTOR elapidae EXPLODE ALL TREES

#5MESH DESCRIPTOR Viperidae EXPLODE ALL TREES

#6(snake* or viper*):TI,AB,KY

#7MESH DESCRIPTOR Snake Venoms EXPLODE ALL TREES

#8MESH DESCRIPTOR Elapid Venoms EXPLODE ALL TREES

#9MESH DESCRIPTOR Viper Venoms EXPLODE ALL TREES

#10(snake venom*):TI,AB,KY

#11((venom* or bite*) adj3 snake*):TI,AB,KY

#12((envenomation or venom-induced or antivenom* or antivenin*)):TI,AB,KY

#13(snake adj3 poisonous):TI,AB,KY

#14MESH DESCRIPTOR Antivenins EXPLODE ALL TREES

#15#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14

#16* NOT INMEDLINE NOT INEMBASE

#17#15 AND #16

Ovid MEDLINE(R), Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid OLDMEDLINE(R)

1. exp snakes/ or exp boidae/ or exp colubridae/ or exp elapidae/ or exp viperidae/

2. (snake* or viper*).ab,ti.

3. exp snake venoms/ or exp elapid venoms/

4. snake venoms.mp.

5. ((venom* or bite*) adj3 snake*).ab,ti.

6. (envenomation or venom-induced or antivenom* or antivenin*).ab,ti.

7. (snake adj3 poisonous).ab,ti.

8. exp Antivenins/

9. exp Viper Venoms/

10. 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9

11. randomi?ed.ab,ti.

12. randomized controlled trial.pt.

13. controlled clinical trial.pt.

14. placebo.ab.

15. clinical trials as topic.sh.

16. randomly.ab.

17. trial.ti.

18. Comparative Study/

19. 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18

20. (animals not (humans and animals)).sh.

21. 19 not 20

22. 10 and 21

Embase Classic + Embase (OvidSP)

1. exp snakes/ or exp boidae/ or exp colubridae/ or exp elapidae/ or exp viperidae/
2. (snake* or viper*).ab,ti.
3. exp snake venoms/ or exp elapid venoms/
4. snake venoms.mp.
5. ((venom* or bite*) adj3 snake*).ab,ti.
6. (envenomation or venom-induced or antivenom* or antivenin*).ab,ti.
7. (snake adj3 poisonous).ab,ti.
8. exp Antivenins/
9. exp Viper Venoms/
10. 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9
11. exp Randomized Controlled Trial/
12. exp controlled clinical trial/
13. exp controlled study/
14. comparative study/
15. randomi?ed.ab,ti.
16. placebo.ab.
17. *Clinical Trial/
18. exp major clinical study/
19. randomly.ab.
20. (trial or study).ti.
21. 11 or 12 or 13 or 15 or 16 or 17 or 18 or 19 or 20
22. exp animal/ not (exp human/ and exp animal/)
23. 21 not 22
24. 10 and 23

ISI Web of Science: Science Citation Index Expanded & Conference Proceedings Citation Index-Science

#11#10 AND #7 AND #6

#10#9 OR #8

#9TS=(envenomation or venom-induced or antivenom* or antivenin*)

#8TS=(venom* or bite* or poisonous or poison)

#7TS=(snake* OR boidae OR colubridae OR elapidae OR viperidae OR viper*)

#6#5 AND #4

#5TS=(human*)

#4#3 OR #2 OR #1

#3TS=((singl* OR doubl* OR trebl* OR tripl*) SAME (blind* OR mask*))

#2TS=(controlled clinical trial OR controlled trial OR clinical trial OR placebo)

#1TS=(randomised OR randomized OR randomly OR random order OR random sequence OR random allocation OR randomly allocated OR at random OR randomized controlled trial)

Toxnet (toxicology data network)

antivenom* OR antivenin* OR venom-induced OR envenomation

OpenGrey

(antivenom* OR antivenin* OR venom-induced OR envenomation) AND (poison* OR bite* OR venom* OR venom-induced)

WHO International Clinical Trials Registry Platform (ICTRP)

Title:(poison* OR bite* OR venom* OR venom-induced)

AND

Condition:(antivenom* OR antivenin* OR venom-induced OR envenomation)

AND

Recruitment status: ALL

Clinicaltrials.gov

Snake antivenom for snake venom induced consumption coagulopathy (Review)
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(antivenom* OR antivenin* OR venom-induced OR envenomation) AND (poison* OR bite* OR venom* OR venom-induced)

Google and Google Scholar

snake envenoming OR snake envenomation OR coagulopathy OR venom induced OR coagulation abnormalities OR snake antivenom OR snake antivenin AND (randomized controlled trial or randomised controlled trial).

CONTRIBUTIONS OF AUTHORS

All authors contributed to this protocol.

DECLARATIONS OF INTEREST

All authors: none known.

SOURCES OF SUPPORT

Internal sources

- Library services, University of Newcastle, NSW, Australia.
Support to find the references for the review.

External sources

- No sources of support supplied