Interventions for the symptoms and signs resulting from jellyfish stings (Review)

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[Intervention Review]

Interventions for the symptoms and signs resulting from jellyfish stings

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ABSTRACT

Background

Jellyfish envenomations are common amongst temperate coastal regions and vary in severity depending on the species. Stings result in a variety of symptoms and signs, including pain, dermatological reactions and, in some species, Irukandji syndrome (including abdominal/back/chest pain, tachycardia, hypertension, sweating, piloerection, agitation and sometimes cardiac complications). Many treatments have been suggested for the symptoms and signs of jellyfish stings. However, it is unclear which interventions are most effective.

Objectives

To determine the benefits and harms associated with the use of any intervention, in both adults and children, for the treatment of jellyfish stings, as assessed from randomised trials.

Search methods

We searched the following electronic databases in October 2012 and again in October 2013: the Cochrane Central Register of Controlled Trials (CENTRAL;*The Cochrane Library*, Issue 9, 2013); MEDLINE via Ovid SP (1948 to 22 October 2013); EMBASE via Ovid SP (1980 to 21 October 2013); and Web of Science (all databases; 1899 to 21 October 2013). We also searched reference lists from eligible studies and guidelines, conference proceedings and the World Health Organization (WHO) International Clinical Trials Registry Platform (ICTRP) and contacted content experts to identify trials.

Selection criteria

We included randomised controlled trials that compared any intervention(s) to active and/or non-active controls for the treatment of symptoms and signs of jellyfish sting envenomation. No language, publication date or publication status restrictions were applied.

Data collection and analysis

Two review authors independently conducted study selection and data extraction and assessed risk of bias using a standardised form. Disagreements were resolved by consensus with a third review author when necessary.

Main results

We included seven trials with a total of 435 participants. Three trials focused on *Physalia* (Bluebottle) jellyfish, one trial on *Carukia* jellyfish and three on *Carybdea alata* (Hawaiian box) jellyfish. Two ongoing trials were identified.

Six of the seven trials were judged as having high risk of bias. Blinding was not feasible in four of the included trials because of the nature of the interventions. A wide range of interventions were assessed across trials, and a wide range of outcomes were measured. We reported results from the two trials for which data were available and reported the effects of interventions according to our definition of primary or secondary outcomes.

Hot water immersion was superior to ice packs in achieving clinically significant (at least 50%) pain relief at 10 minutes (one trial, 96 participants, risk ratio (RR) 1.66, 95% confidence interval (CI) 1.01 to 2.72; low-quality evidence) and 20 minutes (one trial, 88 participants, RR 2.66, 95% CI 1.71 to 4.15; low-quality evidence). No statistically significant differences between hot water immersion and ice packs were demonstrated for dermatological outcomes.

Treatment with vinegar or Adolph's meat tenderizer compared with hot water made skin appear worse (one trial, 25 participants, RR 0.31, 95% CI 0.14 to 0.72; low-quality evidence).

Adverse events due to treatment were not reported in any trial.

Authors' conclusions

This review located a small number of trials that assessed a variety of different interventions applied in different ways and in different settings. Although heat appears to be an effective treatment for *Physalia* (Bluebottle) stings, this evidence is based on a single trial of low-quality evidence. It is still unclear what type of application, temperature, duration of treatment and type of water (salt or fresh) constitute the most effective treatment. In addition, these results may not apply to other species of jellyfish with different envenomation characteristics. Future research should further assess the most effective interventions using standardised research methodology.

PLAIN LANGUAGE SUMMARY

Treatment for jellyfish stings

Jellyfish stings are common in temperate coastal regions around the world. Specialised stinging cells on the jellyfish called *nematocysts* produce the sting. The stings of different jellyfish species produce different symptoms of varying severity. Milder symptoms include pain and skin reactions such as redness and itching at the site of the sting.

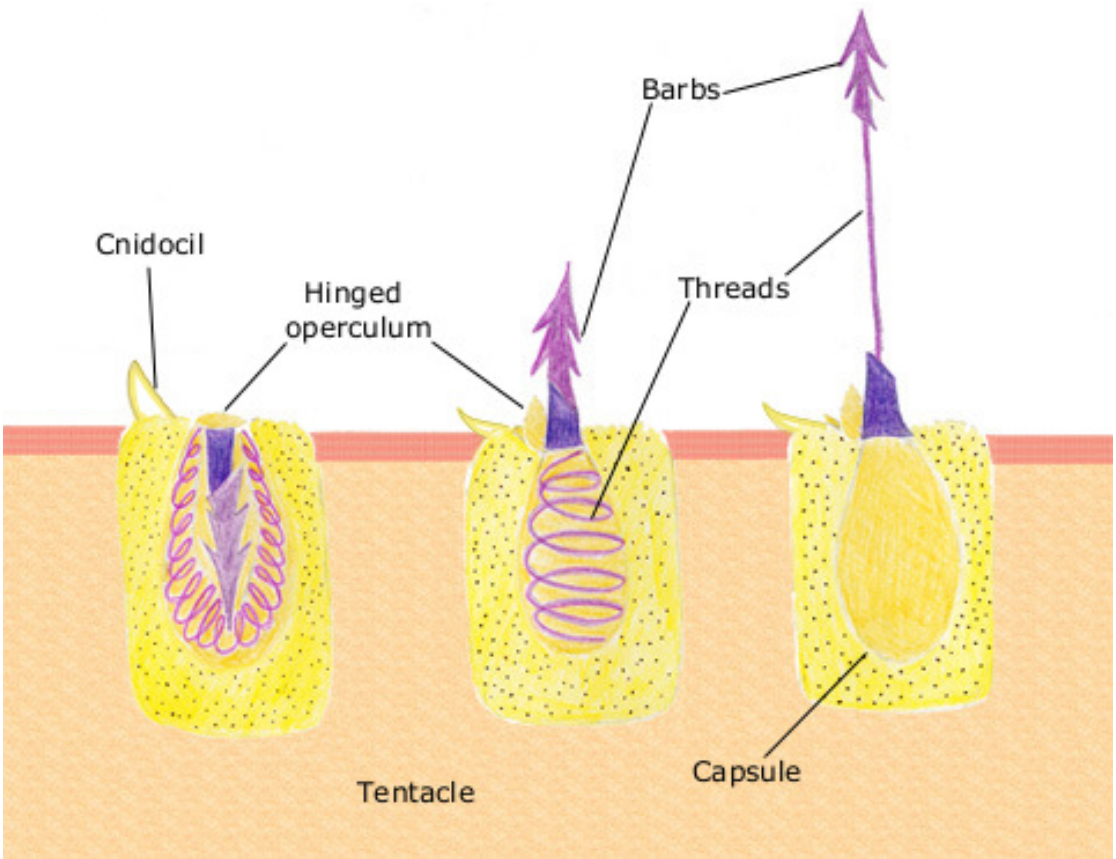
This review identified seven trials on the treatment of jellyfish stings primarily involving two jellyfish species-*Physalia* (Bluebottle) and *Carybdea alata* (Hawaiian box) jellyfish-as well as two trials that are in progress. Many different types of treatments were tested in these trials. Large variation was observed between the duration of treatment among trials. Evidence of limited quality from a single study suggested that hot water immersion relieved pain. This evidence may not apply to other species of jellyfish because of large variability in the effects of stings. Further research should be conducted to help practitioners better understand the most effective treatments for jellyfish stings.

BACKGROUND

Description of the condition

Jellyfish are free-swimming marine invertebrates. All jellyfish possess specialised stinging cells called *nematocysts* (Lotan 1996). Nematocysts are triggered by physical or chemical stimuli (or both), after which a barb is fired and venom is injected into the victim (see Figure 1). Because of the number of nematocysts that may discharge during a 'jellyfish sting' and the potential toxicity of the venom, a jellyfish sting may produce a range of signs and symptoms of varying severity.

Figure 1. Nematocyst discharge from http://commons.wikimedia.org/wiki/File:Nematocyst˙discharge.png



Humans typically come into contact only with surface-dwelling jellyfish species found in temperate coastal regions. As most jellyfish stings go unreported, it is difficult to obtain accurate incidence statistics. Between 2010 and 2011, 40,000 cases of marine sting emergency care around Australia were reported by Surf Life Saving Australia (SLSA 2011). This represented a 30% rise in the number of cases from the previous year (SLSA 2011). Cubozoan or box

jellyfish, in particular, the family Chirodropid, which includes the Indo-Pacific box jellyfish (*Chironex fleckeri*), are considered the most dangerous of jellyfish. *Chironex fleckeri* (the major box jellyfish) has caused more than 70 deaths in the past century, most among young children in remote areas (Tintinalli 2010). Deaths are also rarely caused by *Physalia physalis*, known as the Portuguese man-of-war, or Bluebottle (Stein 1989).

Envenomation usually results in immediate stinging pain and a range of skin reactions, including erythema, urticaria, wheals, vesicular formation, hypo/hyperpigmentation and/or superficial necrosis at the site of contact (Tintinalli 2010; Winter 2007). The pain of a jellyfish sting may be severe and may last for several weeks. Delayed hypersensitivity skin reactions may occur (O'Reilly 2001), as well as more permanent skin markings, including scarring and colour changes (Tintinalli 2010). Cubozoan or box jellyfish, in particular, *Carukia barnesi*, may cause Irukandji syndrome, which is characterised by pain and redness at the site of the sting, followed by generalised severe abdominal, back or chest pain, as well as autonomic features such as tachycardia, hypertension, sweating, piloerection, agitation and, uncommonly, heart complications (myocardial depression with or without pulmonary oedema) (Currie 2005; Huynh 2003). Severe anaphylactic reactions to jellyfish stings are extremely rare (Williamson 1996).

Description of the intervention

Therapy ideally consists of deactivation of attached nematocysts, neutralisation of venom effects and provision of symptomatic relief (including pain relief) and supportive care. The mechanism of action for most 'jellyfish sting' interventions is poorly defined, and some interventions may potentially perform more than one function, for example, deactivation of attached nematocysts, while providing symptomatic relief.

Currently, the Australian Resuscitation Council recommends (1) the use of vinegar in tropical Australia or a cold pack/ice if vinegar is unavailable for the treatment of jellyfish stings and (2) hot water for stings in non-tropical regions or for obvious Bluebottle stings (ARC 2010).

Why it is important to do this review

Jellyfish stings are a significant cause of morbidity and less frequently mortality. Current treatment options are not clearly defined or evidence-based. Therefore, it is important that effective evidence-based treatments are identified.

OBJECTIVES

To determine the benefits and harms associated with the use of any intervention, in both adults and children, for the treatment of jellyfish stings, as assessed from randomised trials.

METHODS

Criteria for considering studies for this review

Types of studies

We included randomised controlled trials (RCTs), as these give the best quality evidence for assessing the effectiveness of an intervention. No language, publication date or publication status restrictions were applied.

Types of participants

For the purpose of this review, anyone who reported being stung by any jellyfish was eligible for inclusion. We considered all age groups. We decided to take a pragmatic approach to trial conduct, and so visual identification of the offending jellyfish by an independent observer was not required. We considered all trial participants presenting with any symptoms, not just those who presented with pain. No baseline thresholds of pain or any other symptoms were required for inclusion in the review.

Types of interventions

We included any intervention given at any dose, duration or intensity. Studies in which more than one intervention was provided, the control group needed to receive a similar intervention for consistency across trial groups. For example, if the trial compared warm water to cold water treatment but the warm water group also received vinegar treatment, then the cold water group must also have received vinegar treatment.

Types of outcome measures

Primary outcomes

- Number of participants obtaining 50% maximum possible pain relief within six hours, as documented on a pain scale such as the visual analogue scale.
- Adverse events due to treatment: number of adverse event withdrawals, number of participants with any serious adverse event (defined as death or any event that is life-threatening, requires inpatient hospitalisation or prolongation of existing hospitalisation, results in persistent or significant disability/incapacity or requires intervention to prevent permanent impairment or damage) and number of participants with a minor adverse event (defined as an adverse event that does not qualify as serious) at one day and at one week.

Secondary outcomes

- Number of participants obtaining 50% maximum possible pain relief at zero to one hour, one to six hours, six hours to one day and one day to one week, as documented on a validated pain scale.
- Median time to re-medication with the same intervention.
- Percentage re-medicating with the same intervention at zero to one hour, one to six hours, six hours to one day and one day to one week.
- Percentage requiring supportive care, for example, dressings, oxygen supplementation or positive-pressure ventilation, at one day.
- Percentage requiring hospital treatment, as inpatient or outpatient, including emergency department visits, at one day.
- Percentage with dermatological signs, for example, scarring, hyperpigmentation or delayed hypersensitivity, at one week.
- All-cause mortality: number of participants dead, irrespective of cause, at one month.

Search methods for identification of studies

Electronic searches

We searched the following electronic databases in October 2012 and then again in October 2013: the Cochrane Central Register of Controlled Trials (CENTRAL; *The Cochrane Library,* Issue 9, 2013); MEDLINE via Ovid SP (1948 to 22 October 2013); EMBASE via Ovid SP (1980 to 21 October 2013); and the Web of Science (all databases; 1899 to 21 October 2013). We searched for both published and unpublished data and placed no limits on language or years.

Our search strategies for CENTRAL, MEDLINE, EMBASE and Web of Science are provided in Appendix 1, Appendix 2, Appendix 3 and Appendix 4. For the MEDLINE search, we ran the subject search with the Cochrane Highly Sensitive Search Strategy (CHSSS) for identifying randomised trials in MEDLINE: sensitivity-maximising version (2008 revision), as referenced in Chapter 6 and detailed in Box 6.4.a-d (c for Ovid) of the *Cochrane Handbook for Systematic Reviews of Interventions* Version 5.1 [updated March 2011] (Higgins 2011). This search was then adapted for all other electronic databases.

We also searched the World Health Organization (WHO) International Clinical Trials Registry Platform (ICTRP) to look for relevant ongoing trials (October 2013) (apps.who.int/trialsearch/).

Searching other resources

We searched the reference lists of eligible studies and relevant guidelines such as the "Australian Resuscitation Council Guidelines to Envenomation-Jellyfish Stings" (ARC 2010) and "International Life Saving Federation Policy Statement-Statements on Marine Envenomation" (ILSF 2000) (October 2013), contacted content experts and authors (October 2012) and performed text-word searches of one relevant conference proceeding, the "International Jellyfish Bloom Symposium" (October 2013).

Data collection and analysis

Methods used for data collection and analysis are as summarised in the protocol (Li 2012).

Selection of studies

Two review authors (LL and RGM) independently determined study eligibility by screening study titles, abstracts and full-text articles. When areas of uncertainty were identified while reading the full text, we attempted to contact the original authors of the study through email or letter to ask for clarification. All disagreements between the two review authors were resolved by discussion and by consensus agreement involving a third review author (ACW), when required. Studies were included or excluded only once a consensus was reached. The review authors were not blinded throughout the selection process. The search included all studies, irrespective of language. Studies that were not published in English were translated so review authors could determine their eligibility.

Data extraction and management

Two review authors (LL and RGM) extracted data from each study independently using a standardised data extraction form (available on request from the authors). Disagreements were resolved by discussion and by consensus agreement involving a third review author (ACW), when required. The review authors were not blinded for this procedure.

We extracted the following data.

- General information: study author(s), title, source, contact address, year of study, country of study, language of publication, year of publication, any author conflicts of interest, study setting (e.g. hospital emergency department, general practice, at the beach).
- Study characteristics and eligibility for review: trial design, randomisation method, recruiting method, duration of trial, trial location, length of follow-up, any obvious concerns of bias.
- Participants: inclusion and exclusion criteria, age, gender, comorbidities, total number of participants, country of origin, number of dropouts or withdrawals and the reasons, if recorded.
- Interventions: number of participants for each intervention, a detailed description of the interventions and comparison interventions, including, when relevant, the type, dose, concentration and duration of application.
- Outcomes: specific outcomes reported, assessment instruments used, scoring range when appropriate.

All data collection and management were performed using Review Manager (RevMan) 5.2 software (RevMan 2013).
For required information that was unclear or missing, we attempted to contact the authors of the trial via email or letter to ask for clarification.

Assessment of risk of bias in included studies

We assessed risk of bias using the suggested domains and guidance provided in The Cochrane Collaboration's tool for assessing risk of bias, as detailed in Section 8.5 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). In particular, we assessed the following domains: 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). For domains initially judged as 'unclear risk', we attempted to clarify the risk of bias by contacting the study authors.
We planned to include all studies, irrespective of the risk of bias. However, we also planned to perform a sensitivity analysis. If the sensitivity analysis showed substantial differences, we planned to exclude from the review studies with high risk of bias.

Measures of treatment effect

We conducted data analysis according to the guidelines presented in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011).

Dichotomous data

We presented dichotomous data results as a summary risk ratio (RR), with 95% confidence intervals (CIs) and, when relevant, risk difference (RD), number needed to treat to produce an additional beneficial outcome (NNTb) and number needed to treat to prevent an event (NNTp).

Continuous data

We presented continuous data results as a mean difference (MD) with 95% CIs if outcomes were measured in the same way between studies. We used the standardised mean difference (SMD) to combine studies that measured the same outcome using different methods.

Unit of analysis issues

We planned to analyse any cluster-randomised trials after taking into account the clustering effect to prevent unit of analysis errors, as detailed in Chapter 16 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). For cross-over trials, we made use of only the first study period.

Dealing with missing data

We analysed data for all participants in the group to which they were allocated, regardless of whether they received the allocated intervention. When the original reports did not analyse the participants in the group to which they were randomised and sufficient information was provided in the study, we attempted to restore participants to the correct group for the purposes of meta-analysis (i.e. we conducted intention-to-treat (ITT) analysis when it was possible to do so). When missing data was suspected, we contacted study authors to seek clarification and/or obtain the missing data. When ITT analysis was not possible, we used per-protocol analysis.

Assessment of heterogeneity

We assessed heterogeneity amongst studies, when appropriate, using the I^2 statistic and Cochran Q statistics. When substantial heterogeneity was detected (statistical heterogeneity of I^2 greater than 50% or Chi^2 P value less than 0.10, or clinical heterogeneity of different interventions or participant characteristics), we explored it by prespecified subgroup analysis.

Assessment of reporting biases

We planned to use a funnel plot to check for publication bias when more than 10 studies were included in the analysis. When reporting bias was suspected because of missing data, we attempted to contact study authors to ask that they provide the data.

Data synthesis

We conducted data analysis using Review Manager software (version 5.2). We used random-effects meta-analysis to analyse studies that were judged sufficiently similar. Trials that compared similar interventions, populations and outcomes were considered sufficiently similar. We intended to stratify jellyfish species into Bluebottles (*Physalia species*), box jellyfish that do not cause Irukandji syndrome (such as the major box jellyfish *Chironex fleckeri)*, jellyfish that cause the Irukandji syndrome, and other jellyfish. We considered a P value of 0.05 or less as statistically significant.

Subgroup analysis and investigation of heterogeneity

It was expected *a priori* that the following areas may cause a difference in outcomes, so we planned to carry out the following subgroup analyses when applicable.

- Studies with low risk of bias compared with studies with high risk of bias. For this subgroup analysis, we identified high risk of bias as one or more domains on the risk of bias tool

judged as 'high risk', as advised in Chapter 8 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). We planned to categorise all remaining trials as having low risk of bias for this analysis.

- Severity of a sting: mild/moderate (not requiring hospitalisation) versus severe (requiring hospitalisation).
- Co-interventions used (e.g. one study may assess the efficacy of warm water with analgesics as a co-intervention, and another may assess the efficacy of warm water with psychosocial support as a co-intervention).
- Participants' age group: children (aged 18 years or younger) compared with adults (aged 19 to 64 years) and the more aged population (aged 65 and older).
- Type of jellyfish (as venoms and sting reactions vary between different species of jellyfish).

We planned to assess differences among subgroups by testing for interaction.

Sensitivity analysis

We planned to carry out sensitivity analysis if unpublished studies, studies with data missing and studies published only as abstracts were included in a meta-analysis. Regardless of the outcome of sensitivity analysis, we planned to place all results into the review, even if they were not included in the final analysis.

RESULTS

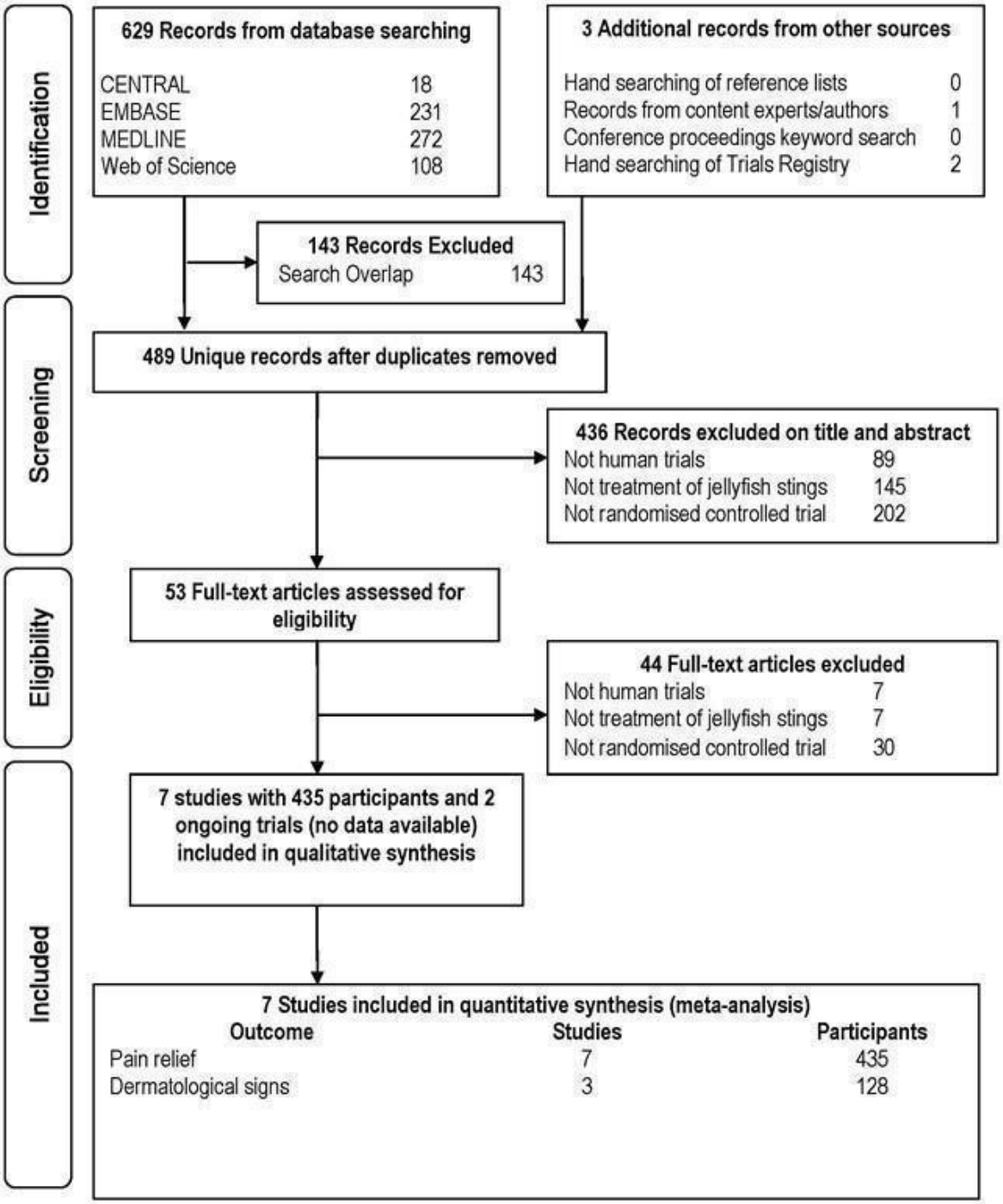
Description of studies

We included seven studies with a total of 435 participants (Bowra 2002; Loten 2006; McCullagh 2012; Nomura 2002; Thomas 2001a; Thomas 2001b; Turner 1980) and identified two ongoing trials (EUCTR 2008; Isbister 2005).
Please see: Characteristics of included studies; Characteristics of excluded studies; and Characteristics of ongoing studies.

Results of the search

The process of identifying reports of randomised clinical trials for inclusion in the review is outlined in Figure 2 (study flow diagram).

Figure 2. Study flow diagram for identification of randomised trials of treatments for jellyfish stings.



Electronic searches of the Cochrane Central Register of Controlled Trials (n = 18), EMBASE (n = 231), MEDLINE (n = 272) and Web of Science (n = 108) identified a total of 629 publications. Three additional publications were identified by content experts and trial registry searching. Searching of conference proceedings and reference lists produced no extra records. After exclusion of duplicates, 489 unique records remained. Of these, 436 were excluded after reviewing titles and abstracts and of the remaining 53 publications, which were assessed after reviewing their full texts, a further 44 were excluded. Therefore, a total of seven completed trials (Bowra 2002; Loten 2006; McCullagh 2012; Nomura 2002; Thomas 2001a; Thomas 2001b; Turner 1980) and two ongoing trials (EUCTR 2008; Isbister 2005) were included in the review. One completed trial was available as an abstract only (Bowra 2002), although the unpublished paper was later provided to us by the authors. The remaining six completed trials were published in four different journals. No data were available for the two ongoing trials (EUCTR 2008; Isbister 2005).

There were no major disagreements requiring adjudication between authors of this review.

Included studies

Included trials assessed a wide range of treatments including:

- Bowra 2002 compared hot water showers with ice packs in 54 participants.
- Loten 2006 compared hot water immersion with ice packs in 96 participants.
- McCullagh 2012 compared parenteral magnesium sulphate versus placebo in 39 participants.
- Nomura 2002 compared hot fresh water versus a combined comparator of acetic acid or Adolph's (papain) meat tenderizer (analysed as a single comparator) in 30 participants (one sting to each arm of participant; one intervention per arm).
- Thomas 2001a conducted a three-arm trial comparing vinegar & chemical hot packs, vinegar & chemical cold packs and vinegar & air-temperature packs in 133 participants.
- Thomas 2001b conducted a four-arm trial comparing vinegar & fresh water, vinegar & seawater, vinegar & Sting-Aid and vinegar & Adolph's meat tenderizer in 63 participants.
- Turner 1980 conducted a four-arm trial comparing vinegar, methylated spirits, Stingose and saltwater in 20 participants (two stings to each arm of a participant; two interventions per arm).

Two trials recruited healthy participants and applied jellyfish stings in a laboratory setting (Nomura 2002; Turner 1980); the remaining trials recruited people accidentally stung in beach settings (Bowra 2002; Loten 2006; McCullagh 2012; Thomas 2001a; Thomas 2001b).

Four trials were performed in Australia (Bowra 2002; Loten 2006; McCullagh 2012; Turner 1980), and three were performed in the United States of America (Nomura 2002; Thomas 2001a; Thomas 2001b). Three of the Australian trials involved *Physalia* (Bluebottle) jellyfish, the remaining Australian trial (McCullagh 2012) involved *Carukia* jellyfish and all three American trials examined *Carybdea alata* (Hawaiian box) jellyfish.

Risk of bias in included studies

Six of seven trials were judged as having high risk in at least one domain, as shown in Figure 3 and Figure 4. As such, six trials were judged to be at high risk of bias, and McCullagh 2012 was judged to be at low risk of bias. In particular, Nomura 2002, Thomas 2001a, Thomas 2001b and Turner 1980 used randomisation techniques that may have caused selection bias.

Figure 3. Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.

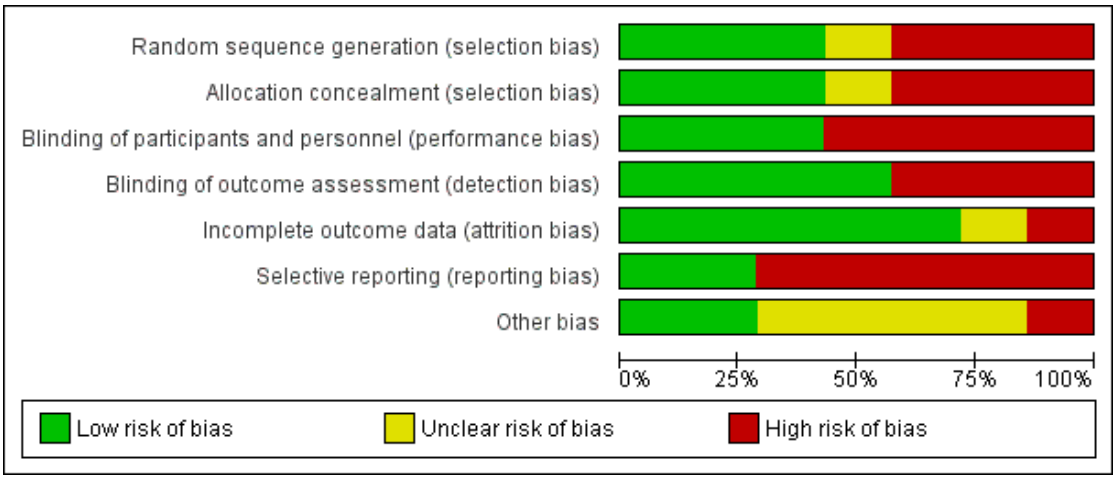
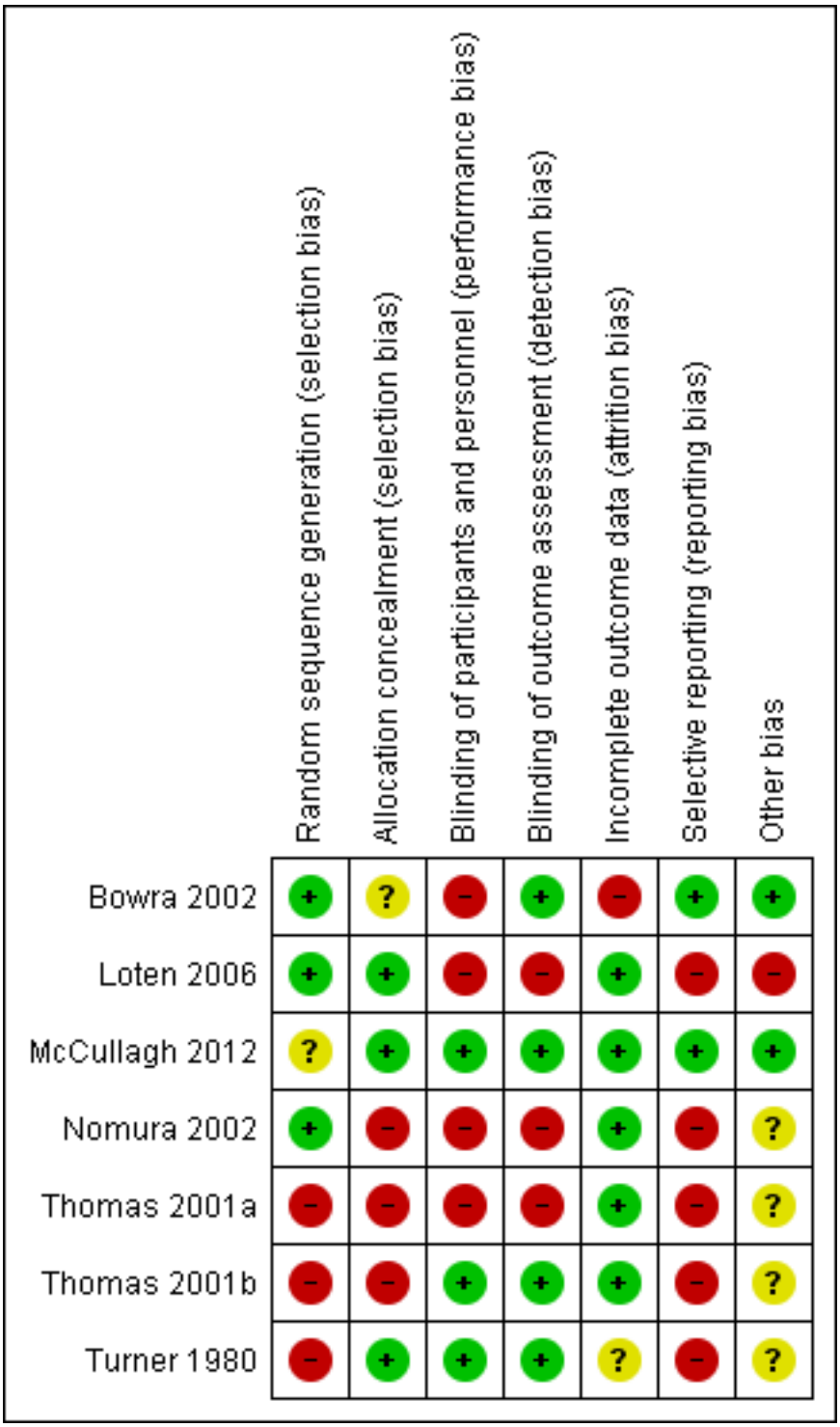


Figure 4. Risk of bias summary: review authors' judgements about each risk of bias item for each included study.



Of note, many trials (Bowra 2002; Loten 2006; Nomura 2002; Thomas 2001a) were unable to blind participants and personnel due to the nature of the treatments, for example, a hot shower compared with ice application.

Effects of interventions

Interventions and data presentation varied greatly across trials and therefore meta-analysis was not possible for our outcomes. We have included the results of only two trials (Loten 2006, Nomura 2002) in our review, as the remaining trials did not report the effects of interventions according to our definition of primary or secondary outcomes.

Primary outcomes

50% maximum possible pain relief: More people reported clinically significant (at least 50%) pain relief with hot water immersion compared with ice packs at 10 minutes (one trial, 96 participants, RR 1.66, 95% CI 1.01 to 2.72; Analysis 1.1.1) and 20 minutes (one trial, 88 participants, RR 2.66, 95% CI 1.71 to 4.15; Analysis 1.1.2) (Analysis 1.1). The NNTb for hot water was 4.7 at 10 minutes and 1.8 at 20 minutes (Table 1).

Adverse events due to treatment: Outcome was not reported in any trial.

Secondary outcomes

Median time to re-medication: Outcome was not reported in any trial.

Percentage re-medicating: Outcome was not reported in any trial.

Percentage requiring supportive care: Outcome was not reported in any trial.

Percentage requiring hospital treatment: Outcome was not reported in any trial.

Percentage with dermatological signs: Treatment with vinegar or Adolph's meat tenderizer compared with hot water immersion made skin appear worse by subjective judgement (one trial, 25 participants, RR 0.31, 95% CI 0.14 to 0.72) (Analysis 2.1). When hot water immersion was compared with ice packs, no significant differences were noted at 24 hours or later in itchiness (one trial, 83 participants, RR 1.03, 95% CI 0.62 to 1.71) (Analysis 2.2), red mark or minor rash (one trial, 83 participants, RR 1.03, 95% CI 0.62 to 1.71) (Analysis 2.3), raised and red/wheal reaction (one trial, 83 participants, RR 0.71, 95% CI 0.32 to 1.58) (Analysis 2.4) or bullous reaction (one trial, 83 participants, RR 0.98, 95% CI 0.06 to 15.09) (Analysis 2.5).

All-cause mortality: Outcome was not reported in any trial.

DISCUSSION

Summary of main results

We identified seven completed trials of 435 participants in which the only investigated jellyfish species were *Physalia* (Bluebottle), *Carybdea alata* (Hawaiian box) and the *Carukia* species. A wide range of treatments were used, and this precluded meta-analysis. Two ongoing trials were also identified.

Few direct comparisons of interventions could be made, but hot water immersion may be the most effective treatment for pain (data from a single trial). Hot water immersion seems to result in a better dermatological appearance compared with vinegar and Adolph's meat tenderizer but not compared with ice packs (data from one trial comparing hot water and vinegar/Adolph's and another trial comparing hot water and ice packs. This is not a pooled comparison). See summary of findings Table 1.

Overall completeness and applicability of evidence

Only a small number of trials were identified as eligible for inclusion in this review. In addition, the sample sizes of these trials were small. Interventions and data presentation varied greatly across trials and therefore meta-analysis was not possible for our outcomes.

Quality of the evidence

Most trials were judged as high risk in at least one domain and thus were judged as high risk overall. Blinding of participants, personnel and outcome assessment is clearly a difficult task for researchers in this field because of the differences between interventions and the subjective nature of outcomes such as pain. This predisposes trials to performance and/or detection bias. The included trials offer several examples of how these difficulties may be overcome. For example, McCullagh 2012 used identically appearing infusions prepared in a different location for both intervention and control groups. Bowra 2002 offers a good example of how detection bias may be reduced: "Subjects were asked to score their pain from zero to ten using standardised questions... they were then asked to place a mark at the appropriate point on a visual analogue scale... research assistants were advised to offer advice or opinions at no time regarding the two treatments offered".

The quality of evidence for each outcome is summarised in the summary of findings (Table 1), which presents all outcomes examined as having low quality of evidence. Data for all outcomes were obtained from single trials only. The quality of evidence may be improved by addressing areas of high risk of bias when possible.

Potential biases in the review process

The strengths of this review include its broad inclusion criteria and comprehensive literature search with no limits on language, year

or publication status. In particular, attempts were made to contact study authors to gain further information, and ongoing trials were also identified. Searching and data extraction and analysis were undertaken by two independent review authors, and arbitration was provided by a third review author. However, we were not always able to make contact with authors or to access the data that we required. Our review is therefore limited by the available data as well as the limited number of trials found.

Agreements and disagreements with other studies or reviews

We made a concerted effort to locate all available randomised trials, including unpublished data and ongoing trials. A recently published review (Ward 2012) located only six randomised trials compared with the seven completed and two ongoing identified in our review. Unlike in our review, Ward et al also included lower-quality evidence such as case series in their analyses. Although Ward 2012 focused only on jellyfish stings in North America and Hawaii, our review took a global approach. Despite this, the conclusions of Ward 2012 are similar to our own.

AUTHORS' CONCLUSIONS

Implications for practice

Low-quality evidence suggests that hot water application is effective in relieving the pain of *Physalia* (Bluebottle) stings. Our findings cannot be extended to other species of jellyfish because of absent reporting of standardised outcomes from the remaining studies included in the review. Further clinical research is required to determine the most effective treatments.

Implications for research

With regard to analgesia, it is unclear whether heat alone is sufficient to cause a beneficial effect (in which case heat packs may be of use), or if the effects are unique to hot water immersion. It is also unclear what temperature, duration of treatment and type of water (salt or fresh) are most effective. Future research should consider these factors, as well as the timing and duration of treatments, blinding of study personnel and the use of standardised outcomes. Researchers may also focus on other species of jellyfish, especially those whose stings are potentially life threatening, such as the *Chironex fleckeri* species, to better clarify variations in treatment guidelines for different envenomations. In particular, further trials could focus on vinegar as an intervention by using the aforementioned factors to produce higher-quality evidence, as vinegar is widely used as an intervention for *Chironex fleckeri* envenomations.

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* *Indicates the major publication for the study*

CHARACTERISTICS OF STUDIES

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

Bowra 2002

Methods	Randomised controlled cross-over trial; two-arm study
Participants	A total of 54 participants aged > seven years accidentally stung at Manly Beach, Sydney, Australia, by *Physalia* (Bluebottle) jellyfish (identified by the victim or when the sting occurred during a recognised Bluebottle swarm). The study took place from December 2000 to Febrary 2001. Participants were excluded if unable to identify the causative jellyfish, had already been stung and treated earlier the same day, informed consent was not obtained, potential contraindications were present (e.g. temperature-induced urticaria) or required more urgent medical treatment
Interventions	• Hot shower for 10 minutes (water temperature set to the maximum level tolerable), then if pain unrelieved, cross-over to ice pack for up to another 10 minutes (27 participants) • Ice pack for 10 minutes (freezer bag applied directly to the skin), then if pain unrelieved, cross-over to hot shower for up to another 10 minutes (27 participants)
Outcomes	• Initial pain as assessed by a visual analogue scale • Cessation of pain • Pain as assessed by a visual analogue scale at 10 minutes, 20 minutes and 24 hours • Exacerbation of symptoms or adverse reactions • Requirement for higher-level care
Notes	Authors contacted on 23 March 2012 for further details on trial data including • Raw data on participants' VAS scores • Authors' definition of 'pain-free' when describing participant results

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote from unpublished paper: "Subjects were randomly allocated to hot shower or ice pack therapy using a computer-generated randomisation table" Comment: Computer-generated randomisation is an appropriate method used for allocation
Allocation concealment (selection bias)	Unclear risk	Comment: Allocation concealment is unknown; it is not mentioned how the allocations were hidden, except that they were computer-generated

Bowra 2002 (*Continued*)

Blinding of participants and personnel (performance bias)	High risk	Quote: "Subjects were randomised to a maximum of 10 minutes of either ice pack or hot shower" Comment: Blinding of participants and personnel to hot shower and ice pack interventions would not be possible
Blinding of outcome assessment (detection bias)	Low risk	Quote: "Subjects were asked to score their pain from zero to ten using standardised questions... they were then asked to place a mark at the appropriate point on a visual analogue scale... research assistants were advised to offer advice or opinions at no time regarding the two treatments offered"; "Results were blinded for statistical analysis" Comment: Standardised outcome assessment performed by independent research assistants, who were specifically told not to indicate any preference
Incomplete outcome data (attrition bias)	High risk	Quote: "24-hour follow up data was obtained for 32 subjects" Comment: Fifty-four participants were enrolled; therefore there was loss to follow-up although no incomplete data for the other outcomes
Selective reporting (reporting bias)	Low risk	The following outcomes listed in the Methods section were reported in the Results section: initial pain as assessed by a visual analogue scale; cessation of pain; pain as assessed by a visual analogue scale at 10 minutes, 20 minutes and 24 hours; exacerbation of symptoms or adverse reactions and requirement for higher-level care. Note: that this information was found in the draft paper
Other bias	Low risk	Comment: funding source not stated, although no proprietary products were used

Loten 2006

Methods	Randomised controlled trial; two-arm study
Participants	Total of 96 participants aged > eight years presenting with apparent Bluebottle stings at a beach setting in Newcastle, Australia, by *Physalia* (Bluebottle) jellyfish. Participants had immediate localised pain with observation of a Bluebottle OR the linear wheal and flare reaction caused by Bluebottle stings Participants were excluded if the sting was to the eye, or if they appeared sufficiently unwell that an ambulance was required
Interventions	• Hot water (45°C) via hose to truncal stings or bucket immersion for limb stings for 20 minutes (49 participants) • Ice pack (-4°C) application for as long as tolerable within a 20-minute period (47 participants)
Outcomes	• Pain as assessed by a visual analogue scale (measured as clinically important pain relief predefined as > 16-mm decrease for an initial VAS from 0 to 33 mm, > 33-mm decrease for an initial VAS from 34 to 66 mm and > 48-mm decrease for an initial VAS from 67 to 100 mm) • Presence of radiating pain, generalised pain, nausea/vomiting or respiratory symptoms • Follow-up after 24 hours on systemic symptoms, persistent pain, itchiness or rash
Notes	Authors contacted on 29 June 2012, via email for further details on trial data including • Data on the result of persistent pain on follow-up

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Quote: "Randomisation was in blocks of six (AABABB, BABAAB etc.)… using a computer-generated sequence of random numbers" Comment: Sequence generation was adequate for randomisation
Allocation concealment (selection bias)	Low risk	Quote: "Participants were randomised to receive either hot water immersion or ice packs, using sequentially numbered sealed envelopes containing the study documents stamped with either 'warm' or 'cold' to indicate treatment… to ensure allocation concealment, the envelopes were not opened until after the patient consented" Comment: Allocation concealment was adequate for this trial

Blinding of participants and personnel (performance bias)	High risk	Quote: "[Subjects] were randomised to receive either hot water immersion or ice packs...Blinding of the patients or investigators was not possible due to the types of treatments" Comment: Blinding of participants and personnel to hot water immersion and ice pack interventions would not be possible
Blinding of outcome assessment (detection bias)	High risk	Quote: "[Subjects] were randomised to receive either hot water immersion or ice packs...Blinding of the patients or investigators was not possible due to the types of treatments" Comment: Blinding of outcome assessment to hot water immersion and ice pack interventions would not be possible
Incomplete outcome data (attrition bias)	Low risk	Quote: "All randomly assigned patients underwent their designated treatment and completed a VAS at 10 minutes, but eight patients did not remain for the 20 minutes" Comment: Attritions/exclusions were adequately described (although no reasons were reported), as were patients lost to follow-up. Data for withdrawn participants were used when available. Withdrawn participants were re-included into the follow-up at 24 hours
Selective reporting (reporting bias)	High risk	Comment: Results section of the study reports primary and secondary outcomes but does not mention persistent pain in follow-up (which was mentioned as a secondary outcome in the Methods) Author states via contact that follow-up with participants was difficult, and that only a few cases of persistent pain occurred
Other bias	High risk	Quote: "The trial was stopped at the halfway interim analysis because hot water immersion was shown to be effective at 20 minutes (P = 0.002)" Comment: There is potential early stopping bias of an interim analysis with no prespecified formal stopping rules Comment: funding source stated as "partially funded by a Margaret Mitchell grant

		(Newcastle Mater Hospital Internal Grant) and a donation from the NSW Surf Life Saving Council"-low risk of bias. In addition, no proprietary products were used

McCullagh 2012

Methods	Randomised controlled trial; two-arm study
Participants	Total of 39 participants aged > 16 years presenting to Cairns Base Hospital (CBH) with signs and symptoms of Irukandji syndrome who required one dose of parenteral opoid analgesia Participants were excluded if they had hypersensitivity to any component in the study protocol, neuromuscular disorders, unable or unwilling to consent, significant hypotension (< 100 mmHg systolic), known or suspected hypocalcaemia, cardiac conduction defect or renal failure (creatinine > 0.2 mmol/L)
Interventions	• Active infusion: 50 mmol of magnesium as magnesium sulphate made up to 500 mL with normal saline • Placebo infusion: 500 mL of normal saline
Outcomes	• Comparison of total analgesic requirements (as defined by MED) between the two groups • Length of stay MED (morphine equivalent dose) was defined as the comparative analgesic doses given; MED was 10 mg morphine = 100 mg pethidine = 100 mcg fentanyl. The total dose of all analgesia administered, both by PCA and as a parenteral injection, including doses given before enrolment into the trial, used during the participant stay, was calculated and converted into MED
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Quote: "Study drug infusions were prepared and randomised by CBH pharmacy department and stored in the ED" Comment: It is unclear how the randomisation sequence was generated, but it is likely to be low risk of bias
Allocation concealment (selection bias)	Low risk	Quote: "Study drug infusions were prepared and randomised by CBH pharmacy department and stored in the ED... Individual bag identification numbers were sealed in envelopes and this was stored in

		the CBH ED. On enrolling a patient a single envelope was randomly selected, and the bag identified was then used in the study. No one involved in the study was aware of the contents of the bag" Comment: Allocation was unknown to study staff other than those in the pharmacy
Blinding of participants and personnel (performance bias)	Low risk	Quote: "Study drug infusions were prepared and randomised by CBH pharmacy department and stored in the ED... No one involved in the study was aware of the contents of the bag... Placebo infusion contained 500ml of normal saline. Active infusion contained 50 mmol of magnesium as magnesium sulphate made up to 500ml with normal saline" Comment: Allocation to active treatment or placebo was unknown to study staff and participants. Use of identically appearing placebo would have ensured blinding
Blinding of outcome assessment (detection bias)	Low risk	Outcomes of the study were clinical and would have been collected by clinical staff (doctors and nurses). As the clinical staff were unaware of which treatment arm a person was in, outcome assessment was blinded
Incomplete outcome data (attrition bias)	Low risk	Quote: "Thirty-nine patients were enrolled in the study... Once randomised no patients were lost or excluded from the trial" Comment: no loss of participants
Selective reporting (reporting bias)	Low risk	All outcome measures stated in the Methods section were reported in the Results
Other bias	Low risk	Quote: "Competing interests-None declared" Comment: non-commercial product, and no competing interests declared

Nomura 2002

Methods	Randomised controlled trial; three-arm study (however, two of the interventions-vinegar and Adolph's meat tenderizer-were counted as one comparison against hot water)
Participants	A total of 30 healthy adult volunteers (physicians, nurses, clinical assistants, medical students) deliberately stung on each arm in a laboratory setting in Hawaii, USA, with *Carybdea alata* (Hawaiian box jellyfish) Volunteers were excluded if they had multiple allergies, previous allergic reaction to marine envenomation, history of easy scarring, complication-prone dermatological conditions, pregnancy or severe illness
Interventions	• Hot fresh water (40°C to 41°C) application for 20 minutes, after which participants could choose to receive another treatment (30 forearms; 30 participants) • Acetic acid 5% (household vinegar) or papain (Adolph's) meat tenderizer in 4:1 ratio with water for 20 minutes (30 forearms; 30 participants)
Outcomes	• Pain as assessed by a visual analogue scale • Subjective judgement of which arm was more painful at each measurement and whether pain had increased, decreased or stayed the same • Subjective judgement on visual appearance of forearms
Notes	Authors contacted via email on 13 June, 24 June 2012, then by mail on 26 June 2012, for further details on trial data including • Raw data on participants' VAS scores • Clarification on whether an "average VAS score" is referring to the mean or the median • Standard deviation for average VAS scores recorded • Clarification on the definition of a 'visibly worse' appearance of forearms

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Comparison treatments were randomised (using a coin flip) to either 5% acetic acid (household vinegar) or papain meat tenderizer paste (Adolph's meat tenderizer)… the arm receiving the hot-water treatment was also randomised using a coin-flip" Comment: Coin flips were adequate for randomisation
Allocation concealment (selection bias)	High risk	Comment: It is not stated whether it is the same individual performing the coin flip and handing out the intervention. It may be possible for an individual to change the result of the coin flip should it not give their desired intervention

Nomura 2002 (*Continued*)

Blinding of participants and personnel (performance bias)	High risk	Quote: "...blinding of study subjects to the treatments they received was not possible for obvious reasons" Comment: Blinding of participants and personnel to hot water immersion versus vinegar or Adolph's would not be possible
Blinding of outcome assessment (detection bias)	High risk	Quote: "...blinding of study subjects to the treatments they received was not possible for obvious reasons" Comment: Blinding of outcome assessment to hot water immersion versus vinegar or Adolph's would not be possible
Incomplete outcome data (attrition bias)	Low risk	Quote: "Thirty subject runs were completed. Five of the subject runs received only unilateral stings despite having a tentacle placed on both arms. (One tentacle was nonfunctional). These 5 subject runs were excluded from analysis because of a lack of paired VAS scores" Comment: Attritions/exclusions from analysis were adequately reported with reasons. Exclusion of the five participants is unlikely to cause bias to the results
Selective reporting (reporting bias)	High risk	Details are lacking in the report, including the VAS recorded by individual participants, results at other time points and results of any cross-over treatments
Other bias	Unclear risk	Comment: funding source not stated

Thomas 2001a

Methods	Quasi-randomised controlled trial; three-arm study
Participants	Total of 133 participants (adult or child) accidentally stung at a beach setting in Hawaii, USA, by *Carybdea alata* (Hawaiian box jellyfish) and not requiring ambulance assistance Participants were excluded if ambulance was required (respiratory distress, altered consciousness, uncontrollable pain, widespread rash, stings to eyes or victim request)
Interventions	• Vinegar and chemical hot packs (maximum temperature 43°C) • Vinegar and chemical cold packs (minimum temperature 5.5°C) • Vinegar and air temperature packs All interventions were applied for 15 minutes

Thomas 2001a (*Continued*)

Outcomes	• Pain as assessed by visual analogue scale
Notes	Authors contacted via email on 13 June 2012, then by mail on 26 June 2012, for further details on trial data including • Numbers of participants originally randomly assigned to the hot, cold and air-temperature pack arms • Raw data on participants' VAS scores • Clarification on whether an 'estimated average pain score' is referring to the mean or the median

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	Quote: "…the workers selected the type of pack applied in a random manner by reaching into a box containing an approximately equal number of the three types of packs and choosing the first one at hand" Comment: Choosing packs randomly from a container does not provide equal probability of choosing any intervention each time and is not sufficiently randomly assigned
Allocation concealment (selection bias)	High risk	It may be easy for a worker to see which pack he or she is picking up from the container. There is potential for an intervention to be switched by a worker (i.e. a pack may be thrown back into the container and another option chosen)
Blinding of participants and personnel (performance bias)	High risk	Quote: "...blinding the researcher as to whether he or she was using hot, cold or air-temperature packs was difficult since as soon as the pack was activated, its temperature change, or lack thereof, was noticeable instantly by touch" Comment: Blinding of participants and personnel to hot, cold and air-temperature packs would not be possible
Blinding of outcome assessment (detection bias)	High risk	Quote: "...blinding the researcher as to whether he or she was using hot, cold or air-temperature packs was difficult since as soon as the pack was activated, its temperature change, or lack thereof, was noticeable instantly by touch"

Thomas 2001a (*Continued*)

		Comment: Blinding of outcome assessments to hot, cold and air-temperature packs would not be possible
Incomplete outcome data (attrition bias)	Low risk	Quote: "...the most reliable results are those from the pain score at 5 minutes. After that, two different analytic methods were used, one which considered only the data actually collected, and another method in which missing pain scores were imputed with the last pain score recorded" Comment: Attritions/exclusions were adequately described (but not all reasons were given). Data from withdrawn participants were included in the final analysis
Selective reporting (reporting bias)	High risk	Quote: "A binary outcome was also constructed, depending on whether the participant experienced complete cessation of pain or not...Since there was no participants in the neutral group (the reference group) who reported a final score of 0, the definition of cessation of pain was widened to include a final pain score of 10" Comment: Criteria for measuring the binary outcome were changed after the trial was completed
Other bias	Unclear risk	Comment: funding source not stated. Hot, cold and air-temperature packs were provided by the same company (Kwik-Heat and Kwik-Kold) and therefore were unlikely to affect results

Thomas 2001b

Methods	Quasi-randomised controlled trial; four-arm study
Participants	Total of 63 participants aged > seven years accidentally stung at a beach setting in Hawaii, USA, by *Carybdea alata* (Hawaiian box jellyfish) Participants were excluded if they required emergency assistance
Interventions	• Vinegar and fresh water • Vinegar and seawater • Vinegar and sting-aid (aluminium sulphate) • Vinegar and Adolph's meat tenderiser (one part to four parts tap water) All interventions were sprayed for 15 minutes

Thomas 2001b (*Continued*)

Outcomes	• Pain as assessed by visual analogue scale
Notes	Authors contacted via email on 13 June 2012, then by mail on 26 June 2012, for further details on trial data including • Raw data on participants' VAS scores • Clarification on whether an 'estimated average pain score' is referring to the mean or the median • Was it at all possible to tell a difference between interventions by smell, residue left on the skin or another mechanism?

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	High risk	Quote: "Each patient…was sprayed with vinegar. Immediately after the liberal spraying, the researchers sprayed one of four solutions in unmarked, opaque spray bottles labelled A, B, C, and D. Field workers chose one of the four bottles randomly by reaching into a container and choosing the first one at hand" Comment: Choosing packs randomly from a container does not provide equal probability of choosing any intervention each time
Allocation concealment (selection bias)	High risk	It may be easy for a worker to see which pack he or she is picking up from the container. There is potential for an intervention to be switched by a worker (i.e. a pack may be thrown back into the container and another option chosen)
Blinding of participants and personnel (performance bias)	Low risk	Quote: "...researchers sprayed one of four solutions in unmarked, opaque spray bottles..." Comment: An effort was made to maintain blinding. The authors were contacted regarding whether the interventions could be discerned by smell or site. As quoted from the author's email reply: "opaque spray bottles were filled...when sprayed on the skin, the 4 solutions looked similar and had no odour..."
Blinding of outcome assessment (detection bias)	Low risk	Quote: "...researchers sprayed one of four solutions in unmarked, opaque spray bottles..."

Thomas 2001b (*Continued*)

		Comment: An effort was made to maintain blinding. The authors were contacted regarding whether the interventions could be discerned by smell or site. As quoted from the author's email reply: "opaque spray bottles were filled...when sprayed on the skin, the 4 solutions looked similar and had no odour..."
Incomplete outcome data (attrition bias)	Low risk	Quote: "Starting at the 5-minute pain score, two different analytic methods were used: one which considered only the data actually collected, and another method in which missing pain scores were imputed with the last pain score recorded" Comment: Attritions/exclusions were adequately described (but not all reasons were given). Data from withdrawn participants were included in the final analysis
Selective reporting (reporting bias)	High risk	Quote: "A binary outcome was also constructed, depending on whether the participant experienced complete cessation of pain or not...only 4 of the 62 participants reported a final pain score of "0"...Because of this low number, the definition of cessation of pain was widened to include a final pain score of 10, which then included 16 participants" Comment: Criteria for measuring the binary outcome were changed after the trial was completed
Other bias	Unclear risk	Comment: funding source not stated

Turner 1980

Methods	Quasi-randomised controlled trial; four-arm study
Participants	Total of 20 healthy adult volunteers deliberately stung a total of four times (two places on each arm) in a laboratory setting in Sydney, Australia, with *Physalia* (Bluebottle)
Interventions	• Vinegar • Methylated spirits • Stingose (aluminium sulphate) • Salt water Interventions were applied simultaneously two minutes after the sting for an unknown duration

Turner 1980 (*Continued*)

Outcomes	• Pain (categorised as most painful and most relief) • Skin reaction (size of wheal; categorised as most reaction and most relief)
Notes	Authors contacted via email on 2 June 2012, then again on 24 June 2012, for further details on trial data including • Randomisation technique for interventions • Any quantitative data on pain measurements or skin reactions

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	High risk	Quote: "...treatment sites were rotated in different subjects" Comment: All four interventions were applied simultaneously to participants each time in a rotating fashion; therefore, it was not a completely random process
Allocation concealment (selection bias)	Low risk	Quote: "The test solutions were assigned a number and subjects and observers did not know which solution was applied to which quadrant" Comment: The author states via contact that the following steps were taken to maintain allocation concealment and blinding • Containers were stopped by a dropper • Containers were handled briefly to remove dropper • Observers took the next solution for each participant to avoid using the same solution each time • Solutions were applied simultaneously and containers kept together to confuse smells
Blinding of participants and personnel (performance bias)	Low risk	Quote: "The test solutions were assigned a number and subjects and observers did not know which solution was applied to which quadrant" Comment: Steps were also taken by the author as mentioned above to maintain blinding of participants and personnel
Blinding of outcome assessment (detection bias)	Low risk	Quote: "The test solutions were assigned a number and subjects and observers did not know which solution was applied to which

Turner 1980 (*Continued*)

		quadrant" Comment: Steps were also taken by the author as mentioned above to maintain blinding of outcome assessment
Incomplete outcome data (attrition bias)	Unclear risk	Comment: Attrition/exclusions were not mentioned in the article
Selective reporting (reporting bias)	High risk	Quote: "Subjective assessments of pain were made at treatment...skin reaction was also assessed at five minutes and 15 minutes" Comment: Pain and skin reactions were rated as the number of times they were rated most or least painful reaction. Results were not clearly represented in the paper
Other bias	Unclear risk	Comment: funding source not stated

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

Study	Reason for exclusion
Auerbach 1997	Not randomised controlled trial
Bailey 2003	Not randomised controlled trial
Birsa 2010	Not randomised controlled trial
Bonham 2004	Not randomised controlled trial
Boulware 2006	Not treatment of jellyfish stings
Burnett 1983	Not human trial
Burnett 1990	Not randomised controlled trial
Burnett 2005	Not treatment of jellyfish stings
Burnett 2009	Not randomised controlled trial
Caritg Monfort 2008	Not randomised controlled trial
Currie 1993	Not randomised controlled trial
Currie 1995	Not treatment of jellyfish stings

(*Continued*)

Exton 1988	Not randomised controlled trial
Exton 1989	Not human trial
Fenner 2001	Not randomised controlled trial
Fenner 2003	Not randomised controlled trial
Fenner 2010	Not treatment of jellyfish stings
Fernando 2001	Not treatment of jellyfish stings
Fisher 1984	Not randomised controlled trial
Garcia Sanchon 1996	Not randomised controlled trial
Habermehl 1990	Not randomised controlled trial
Halstead 1987	Not randomised controlled trial
Hartwick 1980	Not human trial
Henderson 1980	Not human trial
Hillman 1996	Not randomised controlled trial
Isbister 2001	Not randomised controlled trial
Isbister 2004	Not randomised controlled trial
Jacobs 2008	Not randomised controlled trial
Kimball 2004	Not treatment of jellyfish stings
Landow 2000	Not randomised controlled trial
Levine 1996	Not randomised controlled trial
Little 2002	Not randomised controlled trial
Little 2004	Not randomised controlled trial
Little 2008	Not randomised controlled trial
Lopez 2000	Not randomised controlled trial
Mianzan 2001	Not human trial
Ohtaki 1990	Not treatment of jellyfish stings

(*Continued*)

Prestwich 2007	Not randomised controlled trial
Schmidt 2001	Not randomised controlled trial
Seymour 2002	Not human trial
Sutherland 1990	Not randomised controlled trial
Taylor 2007	Not randomised controlled trial
Tonseth 2009	Not randomised controlled trial
Winter 2009	Not human trial

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

EUCTR 2008

Trial name or title	Efficiency of a jellyfish sting inhibitor sun lotion and protocols for jellyfish sting pain relief
Methods	Randomised controlled trial Two objectives are investigated. The main objective is to study the effectiveness of a sun lotion containing a specific jellyfish sting inhibitor versus regular sun lotions as controls (two-arm study) The secondary objective is to investigate the effectiveness of hot/cold immersion for the treatment of Jellyfish stings versus local pain relief from prescription-free pharmaceutical drugs (three-arm study)
Participants	Healthy patients > 18 years of age deliberately stung by jellyfish (*Cyanea* sp) Patients were excluded if there was a history of certain allergic reactions or history of unusual adverse reaction to insects, jellyfish or other types of stings. The following were also excluded • People with atopic diseases • Pregnancy • People who suffer from skin diseases in testing regions or whose inner forearms are too hairy to allow for interpretation of the test • People who have used any medical or cosmetic product on either arm for 48 hours before start of experiment • People taking antihistamines or steroids • People with medical conditions that the investigator believes pose risks that would prohibit participating • People with history of keloid formation • People with allergy to lidocaine or other local pain substances
Interventions	Two areas studied • Degree of pain reduction in test participants using a specific jellyfish (*Cnidaria*) sting inhibitor and repellant lotion, compared to control subjects protected by a normal water repellant sunscreen or no sun lotion at all • Jellyfish-exposed parts are then treated for pain relief with hot therapy, cold therapy or a commercially available Xylocain Liniment 3% (lidocaine 30 mg)

EUCTR 2008 (*Continued*)

Outcomes	Primary outcome: clinically important reduction in pain as measured by the VAS scale Secondary outcome: number of nematocysts fired with protection versus no protection
Starting date	Date of registration: 31 March 2008
Contact information	No contact information provided
Notes	No data available

Isbister 2005

Trial name or title	A randomised controlled trial of hot water (45.C) immersion versus ice packs for *Chironex fleckeri* stings
Methods	Randomised controlled trial; two-arm study
Participants	All patients > eight years presenting with a major box jellyfish (*Chironex fleckeri*) sting Participant exclusion criteria: severe envenoming requiring resuscitation or antivenom, a sting clinically consistent with Irukandji syndrome and not *C. fleckeri*, stings to the eye, an initial abnormal ECG, initial hypotension: systolic BP < 90mmHg
Interventions	• Hot water immersion at 45°Celsius for 30 minutes • Ice packs for 30 minutes
Outcomes	Primary outcome • Reduction in pain defined on the visual analogue scale (VAS) as "much better" or clinically significant according to a modification of Bird and Dickson Secondary outcomes • Cross-over to the alternate treatment • Repeat treatment for recurrent/ongoing pain • Use of opiate analgesia • LOS in ED • Development of regional/radiating pain • Frequency of systemic features • Proportion of recurrent pain at 1 hour, 24 hours • Proportion with papular urticaria at seven to 10 days
Starting date	Originally anticipated to start on 1 October 2005
Contact information	Dr Geoffrey Isbister gsbite@ferntree.com
Notes	No data available

DATA AND ANALYSES

Comparison 1. 50% maximum possible pain relief

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Clinically significant (at least 50%) pain relief (VAS scale)	1		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
1.1 Hot water versus ice packs at 10 minutes	1	96	Risk Ratio (M-H, Random, 95% CI)	1.66 [1.01, 2.72]
1.2 Hot water versus ice packs at 20 minutes	1	88	Risk Ratio (M-H, Random, 95% CI)	2.66 [1.71, 4.15]

Comparison 2. Dermatological signs

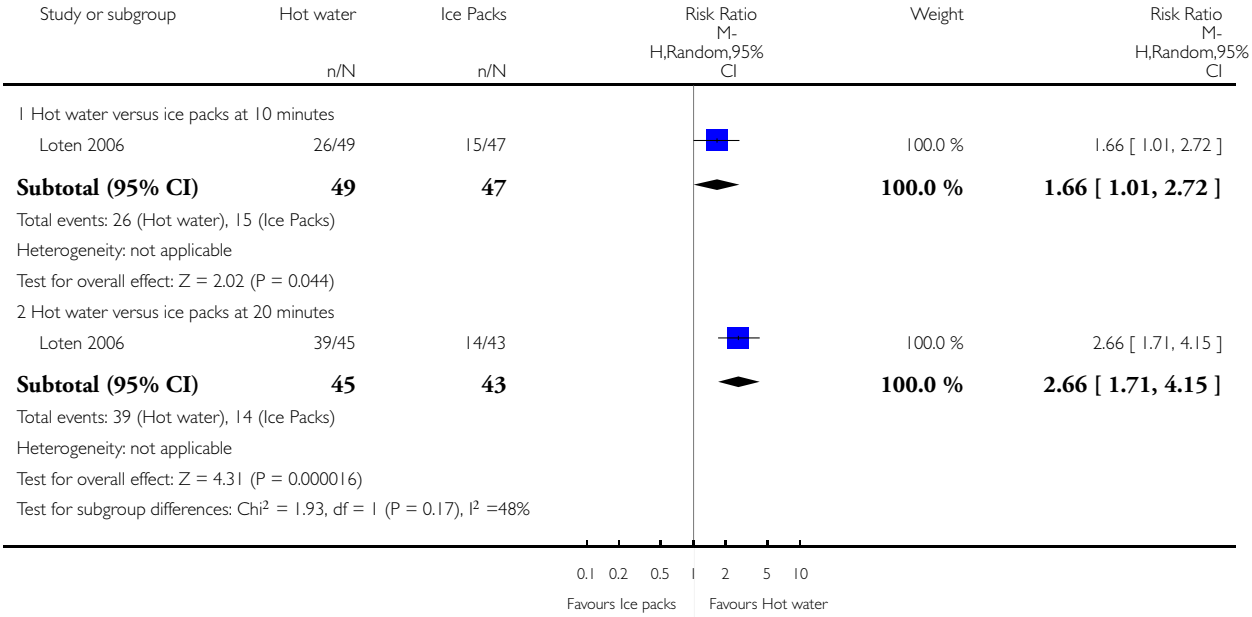
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Visibly worse appearance after treatment compared between interventions	1		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
1.1 Hot water versus vinegar and Adolph's meat tenderizer	1	50	Risk Ratio (M-H, Random, 95% CI)	0.31 [0.14, 0.72]
2 Itchiness 24 hours or later	1		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
2.1 Hot water versus Ice packs	1	83	Risk Ratio (M-H, Random, 95% CI)	1.03 [0.62, 1.71]
3 Red mark or minor rash 24 hours or later	1		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
3.1 Hot water versus Ice packs	1	83	Risk Ratio (M-H, Random, 95% CI)	1.03 [0.62, 1.71]
4 Raised and red/wheal reaction 24 hours or later	1		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
4.1 Hot water versus Ice packs	1	83	Risk Ratio (M-H, Random, 95% CI)	0.71 [0.32, 1.58]
5 Bullous reaction 24 hours or later	1		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
5.1 Hot water versus Ice packs	1	83	Risk Ratio (M-H, Random, 95% CI)	0.98 [0.06, 15.09]

Analysis 1.1. Comparison 1 50% maximum possible pain relief, Outcome 1 Clinically significant (at least 50%) pain relief (VAS scale).

Review: Interventions for the symptoms and signs resulting from jellyfish stings

Comparison: 1 50% maximum possible pain relief

Outcome: 1 Clinically significant (at least 50%) pain relief (VAS scale)

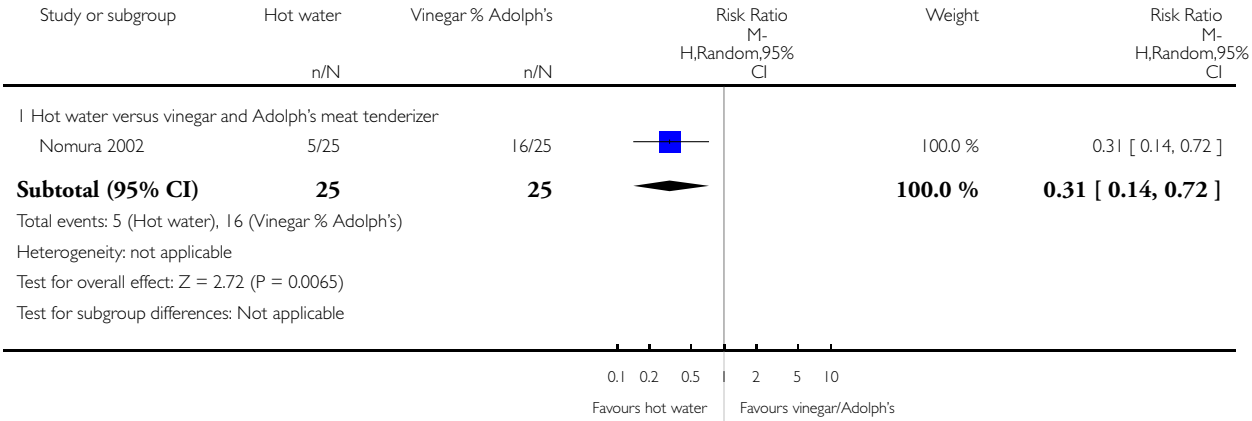


Analysis 2.1. Comparison 2 Dermatological signs, Outcome 1 Visibly worse appearance after treatment compared between interventions.

Review: Interventions for the symptoms and signs resulting from jellyfish stings

Comparison: 2 Dermatological signs

Outcome: 1 Visibly worse appearance after treatment compared between interventions

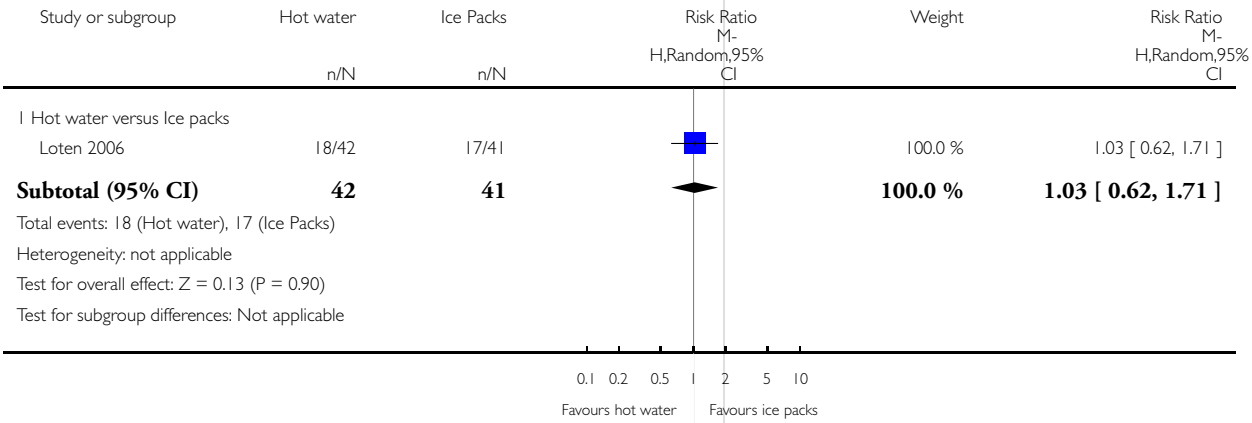


Analysis 2.2. Comparison 2 Dermatological signs, Outcome 2 Itchiness 24 hours or later.

Review: Interventions for the symptoms and signs resulting from jellyfish stings

Comparison: 2 Dermatological signs

Outcome: 2 Itchiness 24 hours or later

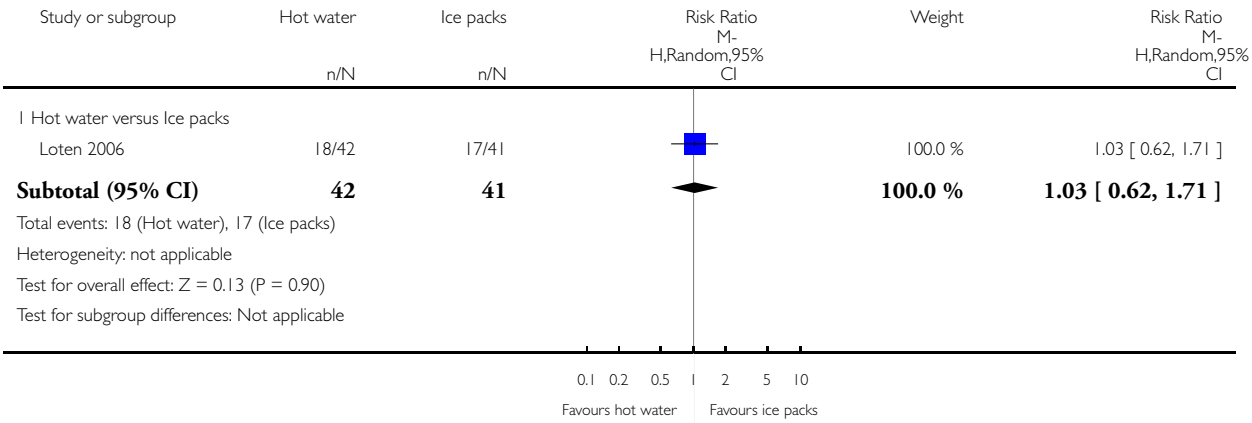


Analysis 2.3. Comparison 2 Dermatological signs, Outcome 3 Red mark or minor rash 24 hours or later.

Review: Interventions for the symptoms and signs resulting from jellyfish stings

Comparison: 2 Dermatological signs

Outcome: 3 Red mark or minor rash 24 hours or later

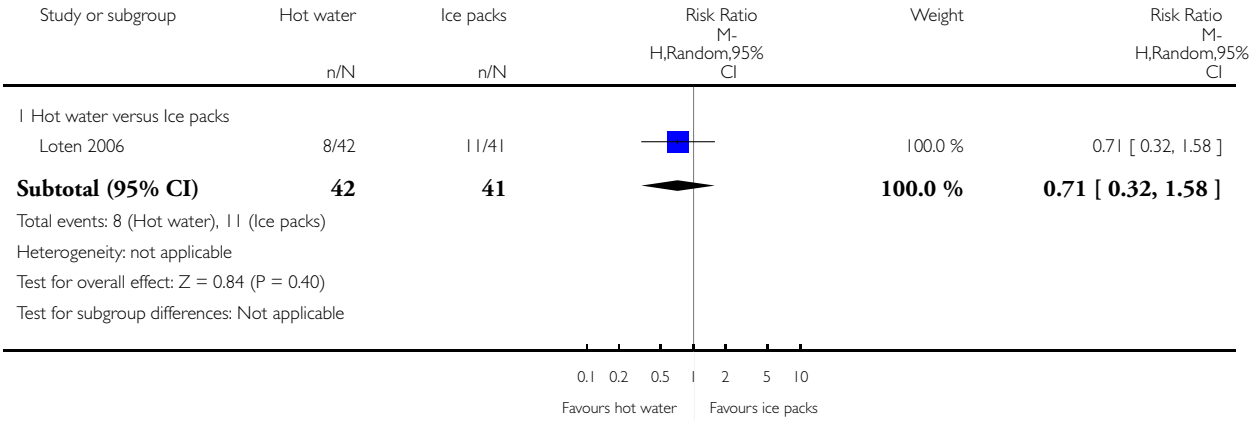


Analysis 2.4. Comparison 2 Dermatological signs, Outcome 4 Raised and red/wheal reaction 24 hours or later.

Review: Interventions for the symptoms and signs resulting from jellyfish stings

Comparison: 2 Dermatological signs

Outcome: 4 Raised and red/wheal reaction 24 hours or later

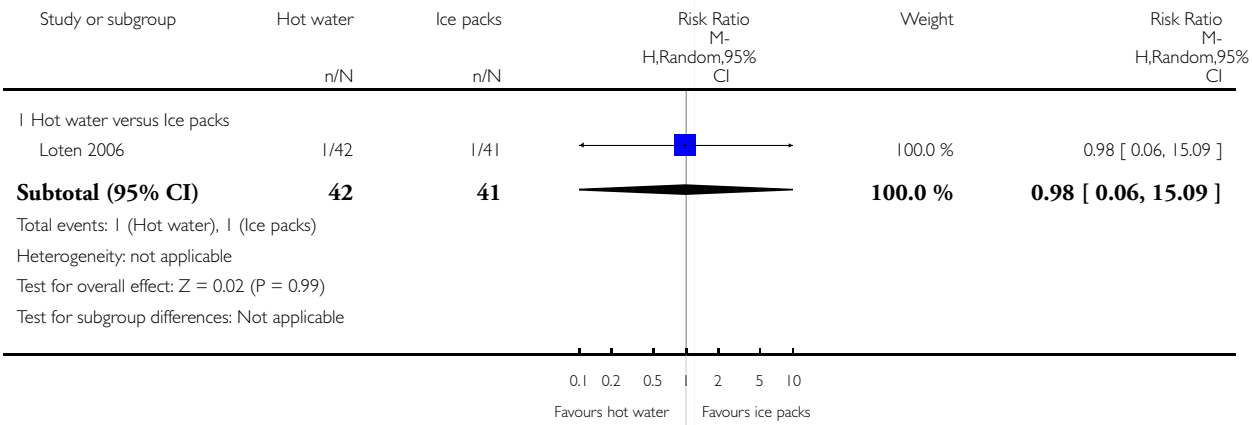


Analysis 2.5. Comparison 2 Dermatological signs, Outcome 5 Bullous reaction 24 hours or later.

Review: Interventions for the symptoms and signs resulting from jellyfish stings

Comparison: 2 Dermatological signs

Outcome: 5 Bullous reaction 24 hours or later



ADDITIONAL TABLES

Table 1. Summary of findings

Population: adults stung by *Physalia* species
Setting: Australian beach
Intervention: hot water
Comparison: ice packs

Outcome	Probable outcome with intervention	Probable outcome with comparator	Number needed to benefit	Number of participants and events	Quality of the evidence	Comments
≥ 50% reduction in pain (10 minutes) (VAS scale)	531 in 1,000	319 in 1,000	4.7 (2.5 to 54.4)	96 participants 41 events	Low	Data from a single trial at high risk of bias
≥ 50% reduction in pain (20 minutes) (VAS scale)	867 in 1,000	326 in 1,000	1.8 (1.4 to 2.7)	88 participants 53 events	Low	Data from a single trial at high risk of bias
Itchiness	429 in 1,000	415 in 1,000	71.8 (not significant)	83 participants 35 events	Low	Data from a single trial at high risk of bias
Red mark or minor rash	429 in 1,000	415 in 1,000	71.8 (not significant)	83 participants 35 events	Low	Data from a single trial at high risk of bias
Wheal reaction	190 in 1,000	268 in 1,000	12.9 (not significant)	83 participants 19 events	Low	Data from a single trial at high risk of bias
Bullous reaction	24 in 1,000	24 in 1,000	1,722 (not significant)	83 participants 2 events	Low	Data from a single trial at high risk of bias

Population: adult volunteers stung by *Carybdea alata* (Hawaiian box jellyfish)
Setting: laboratory setting
Intervention: hot water
Comparison: Adolph's meat tenderizer or vinegar

Table 1. Summary of findings (*Continued*)

Outcome	Probable outcome with intervention	Probable outcome with comparator	Number needed to benefit	Number of participants and events	Quality of the evidence	Comments
Visibly worse skin appearance	200 in 1,000	640 in 1,000	2.3 (1.5 to 5.1)	50 participants 21 events	Low	Data from a single trial at high risk of bias

Based on advice from the Cochrane Pain, Palliative & Supportive Care Review Group (http://papas.cochrane.org/sites/papas.cochrane.org/files/uploads/V%20-%20PaPaS%20Summary%20of%20Findings%20document.pdf).

APPENDICES

Appendix 1. CENTRAL (via *The Cochrane Library*) search strategy

Date	Issue 9, 2013
Search strategy	#1 jellyfish* #2 jelly near/6 fish* #3 medusa* #4 MeSH descriptor Cubozoa, this term only #5 MeSH descriptor Hydrozoa, this term only #6 MeSH descriptor Scyphozoa, this term only #7 MeSH descriptor Cnidarian Venoms, this term only #8 (#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7)

Appendix 2. MEDLINE (via Ovid SP) search strategy

Date	1948-October 2013
Search strategy	#1 jellyfish*.mp. #2 (jelly adj6 fish*).mp. #3 medusa*.mp. #4 cubozoa/ or hydrozoa/ or scyphozoa/ #5 cnidarian venoms/ #6 1 or 2 or 3 or 4 or 5 #7 randomized controlled trial.pt.

(*Continued*)

	#8 controlled clinical trial.pt. #9 randomized.ab. #10 placebo.ab. #11 drug therapy.fs. #12 therapy.fs. #13 randomly.ab. #14 trial.ab. #15 groups.ab. #16 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 #17 6 and 16 #18 exp animals/ not humans.sh. #19 17 not 18

Appendix 3. EMBASE (via Ovid SP) search strategy

Date	1980-October 2013
Search strategy	#1 jellyfish/ #2 poisonous jellyfish/ #3 jellyfish*.mp. #4 (jelly adj6 fish*).mp. #5 medusa*.mp. #6 cubozoa/ #7 hydrozoa/ #8 coelenterate venom/ #9 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 #10 crossover procedure/ #11 double-blind procedure/ #12 randomized controlled trial/ #13 single-blind procedure/ #14 random*.mp. #15 factorial*.mp. #16 (crossover* or cross over* or cross-over*).mp. #17 placebo*.mp. #18 (double* adj blind*).mp. #19 (singl* adj blind*).mp. #20 assign*.mp. #21 allocat*.mp. #22 volunteer*.mp. #23 (dt or th).fs. #24 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 #25 9 and 24 #26 (exp Animal/ or Nonhuman/ or exp Animal Experiment/) not Human/ #27 25 not 26

Appendix 4. Web of Science (Thomson Reuters) search strategy

Date	1899-October 2013
Search strategy	Topic=(jellyfish* or cubozoa* or hydrozoa* or medusa* or jelly NEAR/6 fish* or scyphozoa* or cnidarian*) AND Topic = (sting* or poison* or venom*) AND Topic=(therap* or treatment* or relief*)

CONTRIBUTIONS OF AUTHORS

RGM: designing the protocol and instigating the review, running searches, selecting studies, extracting data, analysing results and writing the main review. RGM will be responsible for the update of the review.

LL: designing the protocol, running searches, selecting studies, extracting data, analysing results and writing the main review.

GI: designing the protocol, identifying studies, providing content area advice and writing the main review.

ACW: designing the protocol, providing methodological advice, identifying studies and writing the main review.

DECLARATIONS OF INTEREST

RGM: None known.

LL: None known.

GI: Is an author of one of the trials included in this review (Loten 2006). GI did not have any influence on its inclusion or analysis. No other interests known.

ACW: None known.

INDEX TERMS

Medical Subject Headings (MeSH)

*Cnidaria; Acetic Acid [therapeutic use]; Bites and Stings [complications; *therapy]; Cryotherapy [methods]; Cubozoa; Drug Combinations; Hot Temperature [therapeutic use]; Hydrozoa; Pain Management [*methods]; Papain [therapeutic use]; Randomized Controlled Trials as Topic; Sodium, Dietary [therapeutic use]

MeSH check words

Adult; Animals; Child; Humans