NOVA

University of Newcastle Research Online

nova.newcastle.edu.au

Isbister GK, Palmer DJ, Weir RL and Currie BJ. Hot water immersion v icepacks for treating the pain of Chironex fleckeri stings: a randomised controlled trial. Med J Aust 2017; 206 (6): 258-261.

Available from: <http://dx.doi.org/10.5694/mja16.00990>

© Copyright 2017. *The Medical Journal of Australia* - reproduced with permission.

Accessed from: <http://hdl.handle.net/1959.13/1352600>

A Randomized Controlled Trial of Hot Water (45°C) Immersion versus Ice Packs for the treatment of pain in *Chironex fleckeri* stings

Abstract

Objective: Major box jellyfish (*Chironex fleckeri*) stings cause severe pain. Hot water was shown to be effective for pain in blue bottle stings. We investigated the effectiveness of hot water immersion for pain in box jellyfish stings.

Design: Open-label randomised controlled trial comparing hot water immersion (45°C) to ice packs.

Setting: Tertiary hospital in northern Australia.

Participants: From 46 patients with painful box jellyfish stings, 42 were randomised.

Interventions: Patients were randomly allocated (1:1) to hot water immersion (45°C) or ice packs.

Main outcome measures: The primary outcome was clinically improved pain 30min post-treatment using the visual analogue scale (VAS). Secondary outcomes were cross-over to alternate treatment, opioid analgesia, emergency department length of stay (LOS) and delayed urticarial rashes.

Results: Of 42 patients (median age 19y; interquartile range[IQR];13-27y;26 males), 25 were allocated ice packs and 17 hot water immersion. Both groups had similar demographics and baseline VAS. 30min post-treatment 14/25 (56%) patients treated with

ice packs had clinically improved pain compared to 11/17 (65%) treated with hot water [absolute difference: 9%;95%CI: -22 to 39%;p=0.75). One patient treated with ice packs was crossed over. Two patients in each arm got intravenous opioid analgesia. Median emergency department LOS for ice pack patients was 1.6h (IQR:1 to 1.8h) compared to 2.1h (IQR:1.6 to 2.8h;p=0.07). Only seven patients were followed up; five developed delayed urticarial rashes.

Conclusion: Hot water immersion was no better than ice packs for treatment of acute pain in box jellyfish stings. Hot water immersion increased the LOS by about 30min.

(Key Words: envenoming, jellyfish, hot water, ice pack, sting, pain)

- The known: Hot water immersion has been shown to be effective for the pain of some jellyfish stings, including blue bottle stings.
- The new: Hot water immersion was no more effective than ice packs for the pain of major box jellyfish (*Chironex fleckeri*) stings in the emergency department.
- The implications: Current protocols recommending ice packs for pain in major box jellyfish stings should remain unchanged.

Introduction

There remains controversy over the appropriate treatment for the pain of jellyfish stings. Although hot water immersion has been shown to be an effective and safe treatment for blue bottle (*Physalia* spp.) stings,¹ there is less evidence for other types of jellyfish.² Hot water immersion has been used in some box jellyfish (Cubozoan) stings, including studies in Hawaii,³ but icepacks have remained the standard of care for treating pain following stings by the major box jellyfish *Chironex fleckeri*.^{4,5}

C. fleckeri stings remain a problem in northern Australia and large stings in children can result in severe and life-threatening envenoming. A more common problem in non-life threatening *C. fleckeri* stings is the pain, which in more severe cases may persist for several hours and require parenteral opioid analgesia.^{4,6} Current protocols in the Northern Territory recommend that after vinegar is applied and life-threatening effects are treated, pain should be treated with ice first, and if unresponsive then oral and finally parenteral analgesia, depending on the severity of the pain.^{4,6} To date, no study has investigated the effectiveness of hot water immersion for the treatment of the pain in *C. fleckeri* stings. If hot water immersion was effective for *C. fleckeri* stings it would allow much more rapid treatment of patients with stings and a reduction in the use of parenteral analgesia (which adds to emergency department length of stay).

Cubozoan venoms have been shown to be heat labile, and *C. fleckeri* venom is inactivated at temperatures above 43°C for short periods of time.⁷ It is therefore reasonable to postulate that hot water immersion will also be effective for *C. fleckeri* stings, similar to other jellyfish.^{1-3,8} The clinical trial of hot water immersion for blue bottle stings demonstrated

that the immersion technique was safe with no patients suffering burns or adverse effects because it did not expose patients to temperatures over 46°C. However, hot water immersion is unlikely to be effective in preventing further envenoming from undischarged nematocysts remaining on the skin after a *Chironex* sting. Vinegar is believed to be effective in inactivating these undischarged nematocysts and is currently always recommended prior to treatment with ice or hot water.

The aim of this study was to investigate the effectiveness of hot water immersion for the treatment of the pain from *C. fleckeri* stings in the emergency department.

Methods

Study Design

We undertook an open-label randomised controlled trial that compared hot water immersion at 45°C (active treatment) to ice packs (current standard therapy) for the pain of *C. fleckeri* stings in an emergency department in northern Australia. The study was approved by the Human Research Ethics Committee of the Northern Territory Department of Health and Community Services and Menzies School of Health Research. All patients gave written and informed consent for the study. The study was registered with the Australian and New Zealand Clinical Trials Registry, number ACTRN12605000007639.

Patients

Any patient presenting with a suspected *C. fleckeri* sting to Royal Darwin Hospital from September 2005 to October 2008 was eligible for the study. Patients were included if they had the sting within 4 hours and clinical findings were consistent with a *C. fleckeri* sting (typical local pain and linear red and raised lesions). Exclusion criteria were children less than 8 years of age because the primary tool for measuring pain, the visual analogue score (VAS) is not validated in this age group; severe envenoming requiring resuscitation or antivenom; any sting that is clinically consistent with Irukandji syndrome and not *C. fleckeri*; stings to the eyes; and baseline hypotension (blood pressure [BP] < 90mmHg).

Treatment Protocol

Patients were initially assessed and had vinegar applied to all stings sites if this was not already done. Patients meeting the inclusion criteria were then asked to be involved and

consented to the study or their parents/guardians consented. A baseline physical examination was done and they were asked to score their pain on a VAS. An electrocardiogram was done and an intravenous cannula inserted. Patients were then randomized to either receive hot water immersion or ice packs by opening sequentially numbered envelopes.

Treatment was randomised by computer in variable sized blocks of 4 or 6 (eg, AABB, ABAB, or ABABAB, AABBBAB...) from which a single piece of paper with either “Hot water immersion” or “Ice Packs” written on it was placed in sequentially numbered envelopes. Patients randomised to receive ice packs were placed in a normal acute bed and had ice packs applied to the sting sites. The ice packs were left on for 30 minutes (as much as could be tolerated by the patient) and then removed. Patients randomised to receive hot water immersion were moved to a bath in the emergency department. The bath was supplied by water that has passed through a thermostatic mixing valve set to exactly 45°C and filled with water. The stung area was then immersed in water. For smaller limb or distal stings a bucket was used instead, but was re-filled regularly to maintain the temperature. The patient was supervised at all times in this area. The hot water immersion continued for 30 min.

During the allocated treatment phase a VAS was done at 10, 20 and 30 min and blood pressure (BP) and heart rate (HR) measured at 30 min. After completion of the allocated treatment patients were given the option to cross-over to the other treatment if they had persistent pain. Otherwise they were observed for 30 min. VAS was done at 60 min. If pain persisted after 60 min then repeat treatment was offered for another 30 min. Patient observation and treatment was then continued as per the normal box jellyfish sting protocol.

On discharge from the emergency department (either home or to an inpatient unit) a final VAS was recorded. The time of discharge was recorded on the datasheet.

Data Collection

Demographic information, details of the sting (site, time, conditions, activity), other clinical effects (radiating pain, systemic effects), standard observations (HR, BP), any other treatments administered (analgesia) and length of stay (LOS) in the emergency department. The Northern Territory Jellyfish Sting Datasheet was used for most data collection, as previously documented,^{4,6} with an additional datasheet used to collect the VAS and other serial data.

Data Analysis

The primary outcome was a clinically significant reduction in pain severity 30 min after the allocated treatment commenced using the VAS. A clinically significant change was defined according to Bird and Dickson [the change in millimeters on the VAS is dependent on the baseline starting point and is 16 mm for an initial VAS in the range 0 – 33 mm, 33 mm for 34 – 67 mm and 48 mm for 67 – 100 mm].⁹ Secondary outcomes were the proportion crossing-over to the alternate treatment; need for repeat treatment for recurrent or ongoing pain; use of opioid analgesia; LOS in the emergency department; development of regional or radiating pain; frequency of systemic features of stings; proportion with papular urticaria on telephone follow up after 7 to 10 days.

The sample size calculation was based on a previous study of *Physalia* stings where the number of patients pain-free after hot water immersion increased from 33% to 80%.¹

Therefore to detect whether hot water immersion increases the proportion of patients pain free at 30 min from 33% to 80%, with a significance level (alpha) of 5% and a power of 80%, 20 patients were required to be recruited in each arm of the trial (ie. 40 patients in total). We intended to recruited 55 because some stings may not be confirmed *C. fleckeri* stings.^{4,6} Recruitment was ceased after 46 patients because funding was complete. One author (GKI) measured the VAS, extracted the data and checked outcomes while remaining blinded to each patient allocation. The analysis was then undertaken after the dataset was finalised.

Statistical analysis

Medians, ranges and interquartile ranges (IQR) were calculated for all continuous variables and 95% confidence intervals (CIs) for proportions. The primary outcome was by intention to treat with Fisher exact test. Secondary outcomes were analysed using the appropriate statistical tests for the data distribution. For all outcomes a p value of less than 0.05 was considered to indicate statistical significance. All statistical analyses were done with GraphPad Prism version 6.03 for Windows (GraphPad Software, San Diego California USA, www.graphpad.com).

Results

There were 46 patients recruited to the study but pain scores and treatment allocation were not recorded in four patients. Of 42 patients (median age 19y; IQR: 13-27y; 26 males), 25 were allocated to ice packs and 17 to hot water immersion (Figure 1). Twenty patients (48%) had distal limb stings and 14 (33%) developed systemic effects. Both groups had similar demographics, baseline VAS and systemic effects (Table 1). All patients were discharged from the emergency department and the pain had resolved in 40 of the 42. The median LOS in the emergency department was 1.8h (Range: 0.5 to 6h)

Primary Outcome

Thirty minutes after treatment commenced 14/25 (56%) of patients treated with ice packs had clinically improved pain compared to 11/17 (65%) treated with hot water immersion [absolute difference: 9%; 95%CI: -22 to 39%; $p=0.75$]. The percentage reduction in pain scores for individual patients comparing ice pack to hot water immersion is shown in Figure 2. There was no difference in the changes in absolute VAS over the 90 min period between each arm (Figure 3).

Secondary Outcomes

One patient in the ice pack arm was crossed over to hot water immersion. Two patients in each arm were given intravenous opioid analgesia. The median emergency department LOS for patients treated with ice packs was 1.6h (IQR: 1 to 1.8h) compared to 2.1h (IQR: 1.6 to 2.8h; $p=0.07$). No patients represented with recurrent pain. No patients developed

hypotension. Only seven patients were able to be followed up, and five of these developed delayed hypersensitivity rashes.

Discussion

The study found that hot water immersion was no better than ice packs in the treatment of acute pain from *C. fleckeri* stings. Over half of the patients had improvement in the pain after 30 min and almost all patients were discharged pain free. There were no severe stings consistent with severe envenoming being rare⁴ and the frequency of delayed hypersensitivity reactions was similar to previous studies in those followed up.⁶ The application of hot water extended the LOS in the emergency department by about 30 min, most likely due to the practicalities of administering this treatment. There was no difference between groups in the use of opioid analgesia, treatment of recurrent pain or systemic effects.

This finding that hot water was not more effective than ice packs was unexpected considering the highly beneficial effect of hot water immersion in blue bottle (*Physalia*) stings.¹ It suggests that in *C. fleckeri* stings both ice packs or hot water provide reasonable pain relief at 30 min. Interestingly, the improvement of between 56% ~~to and~~ 65% was intermediate to that of *Physalia*, better than ice packs for *Physalia* (33% at 20 min), but inferior to hot water (87%). There could be a number of reasons for this, including The differences between jellyfish suggest possible differences in the venoms in the effect of heat. It means We cannot assume that the effects of treatments for pain from stings by one jellyfish group can be applied to another jellyfish.

A more likely explanation for hot water and ice packs being equally effective is that treatment was delayed in this study because of the time required to reach the emergency department. In the study of *Physalia* stings treatment was administered on the beach, often

within minutes of the sting, when heat is more likely to be effective. The delay in treatment in the emergency department means that venom may have been absorbed and heat treatment ineffective. The treatment effect in our study is therefore more likely to be symptomatic in nature, rather than providing definitive treatment by inactivating venom. This is consistent with both hot water and ice packs being equally effective. A future pre-hospital study should investigate the use of hot water immersion.

Measurement of pain can be problematic and numerous scores have been developed. The visual analogue scale (VAS) is one of the most commonly used, including in previous studies of blue bottle stings¹ and red back spider bites.¹⁰ More recent studies have used the verbal numerical rating score because it is easier to administer (no requirement for paper)¹¹ and ~~it is now~~ used in clinical practice. Treatment of *C. fleckeri* stings should incorporate regular assessment of the pain with the verbal numerical score. Correction for the baseline pain score is controversial but allows for an easier comparison between patients with different severities of pain or different perceptions of pain severity. This approach has been used in three previous studies of painful envenoming syndromes.^{1,10,11} Figure 2 and figure 3 suggest that the responses to treatment were similar using both relative (Figure 2) and absolute VAS (Figure 3).

One limitation of this study is that the diagnosis of *C. fleckeri* envenoming was made clinically. Previous studies have shown that *C. fleckeri* is the dominant box-jellyfish in the Darwin harbour,^{4,6} with the only other recorded multi-tentacle stings being minor stings from the Darwin carybdeid (4-tentacled box jellyfish), *Gerongia rijkinae*.¹²

A further limitation of the study was the small size which was based on expecting a large treatment effect of hot water immersion compared to ice packs. A larger study would be required to show that hot water immersion had a smaller beneficial effect compared to ice packs. However, there did not appear to be any trends between groups ~~and overall~~with the majority of patients having~~d~~ good pain relief. —Studies of analgesia require a large treatment effect, so a larger study may show a statistically significant difference, which may not be regarded as clinically significant. Another limitation of the small sample size was the chance of an imbalance in the allocation of patients, which occurred in this study due to the block size and excluded patients.

In conclusion, ice packs are simpler, more practical and potentially safer than hot water immersion for the emergency department treatment of box jellyfish stings in tropical Australian ~~waters~~. With no major benefit of hot water immersion seen in this study and its use increasing the LOS, ice packs can be considered more appropriate and remain the recommended ~~first aid~~emergency department treatment for the pain of major box jellyfish stings after the use of vinegar.

Figure Legends:

Figure 1: CONSORT diagram showing all suspected *Chironex fleckeri* stings presenting to the emergency department, the number of patients randomized and the number with improved pain.

Figure 2: Scatter plot of the percentage change in the VAS from baseline to the 30 min VAS comparing ice packs to hot water immersion. The lines show the median and interquartile range. No significant difference between the median percentage change in VAS (76% versus 96%; $p=0.46$)

Figure 3: Box and whisker plots of the VAS for baseline, 30 min, 60 min and 90 min after treatment was commenced. Patients treated with ice packs are in blue and those treated with hot water immersion in red. The boxes are the 25th to 75th percentile and the whiskers are 5 to 95 percentiles.

Table 1: Comparison of the demographic features and clinical effects for patients allocated to hot water immersion versus ice packs.

	Ice	%	Hot	%
Sex (Male)	15	60%	11	65%
Age (y;median;IQR)	22 (15 - 30)		14 (9 - 23)	
Sting Site (Distal Limb)	11	44%	9	53%
Systemic Effects	9	36%	5	29%
GI Effects (Nausea/Vomiting)	5	20%	2	12%
Respiratory Effects (SOB)	2	8%	3	18%
Generalised Pain	2	8%	2	12%
Baseline VAS	50 (20 - 70)		49 (26 - 90)	

IQR – interquartile range; SOB – shortness of breath

References

1. Loten C, Stokes B, Worsley D, Seymour JE, Jiang S, Isbister GK. A randomised controlled trial of hot water (45 degrees C) immersion versus ice packs for pain relief in bluebottle stings. *Med J Aust* 2006; **184**(7): 329-33.
2. Li L, McGee RG, Isbister G, Webster AC. Interventions for the symptoms and signs resulting from jellyfish stings. *Cochrane Database Syst Rev* 2013; **12**: CD009688.
3. Thomas CS, Scott SA, Galanis DJ, Goto RS. Box jellyfish (*Carybdea alata*) in Waikiki: their influx cycle plus the analgesic effect of hot and cold packs on their stings to swimmers at the beach: a randomized, placebo-controlled, clinical trial. *Hawaii Medical Journal* 2001; **60**(4): 100-7.
4. Currie BJ, Jacups SP. Prospective study of *Chironex fleckeri* and other box jellyfish stings in the "Top End" of Australia's Northern Territory. *Medical Journal of Australia* 2005; **183**(11-12): 631-6.
5. Toxicology and Wilderness Medicine. 2 ed. Melbourne: Therapeutic Guidelines; 2012.
6. O'Reilly GM, Isbister GK, Lawrie PM, Treston GT, Currie BJ. Prospective study of jellyfish stings from tropical Australia, including the major box jellyfish *Chironex fleckeri*. *Medical Journal of Australia* 2001; **175**(11-12): 652-5.

7. Carrette TJ, Cullen P, Little M, Peiera PL, Seymour JE. Temperature effects on box jellyfish venom: a possible treatment for envenomed patients? *Medical Journal of Australia* 2002; **177**(11/12): 654-5.
8. Nomura JT, Sato RL, Ahern RM, Snow JL, Kuwaye TT, Yamamoto LG. A randomized paired comparison trial of cutaneous treatments for acute jellyfish (*Carybdea alata*) stings. *American Journal of Emergency Medicine* 2002; **20**(7): 624-6.
9. Bird SB, Dickson EW. Clinically significant changes in pain along the visual analog scale. *Annals of Emergency Medicine* 2001; **38**(6): 639-43.
10. Isbister GK, Brown SG, Miller M, et al. A randomised controlled trial of intramuscular vs. intravenous antivenom for latrodectism--the RAVE study. *QJM* 2008; **101**(7): 557-65.
11. Isbister GK, Page CB, Buckley NA, et al. Randomized controlled trial of intravenous antivenom versus placebo for latrodectism: the second Redback Antivenom Evaluation (RAVE-II) study. *Ann Emerg Med* 2014; **64**(6): 620-8 e2.
12. Gershwin L, Alderslade P. A new genus and species of box jellyfish (Cubozoa: Carybdeidae) from tropical Australian waters. *The Beagle, Records of the Museums and Art Galleries of the Northern Territory* 2005; **21**: 9.