UNIVERSITY OF GOTHENBURG

THE SAHLGRENSKA ACADEMY

# Treatment of Lion´s Mane jellyfish stings-<br>hot water immersion versus topical corticosteroids

Degree Project in Medicine

Anna Nordesjö

Programme in Medicine

Gothenburg, Sweden 2016

Supervisor: Kai Knudsen

Department of Anesthesia and Intensive Care Medicine

# CONTENTS

## ABSTRACT

In Sweden, contact with the Lion's Mane jellyfish *Cyanea capillata* is not uncommon during the summer months, with subsequent local symptoms such as pain and itching, which may persist for several hours.

Several remedies for jellyfish stings, such as urine, vinegar and baking soda are described in numerous websites and in the literature, most of them citing limited or no scientific evidence. Hot-water immersion is a popular treatment for many marine stings and has recently been found to reduce local pain following stings from certain species of jellyfish. Topical corticosteroids are recommended as symptomatic treatment for jellyfish stings by the Swedish Poisons Information Centre (Giftinformationscentralen), but the effect has not yet been researched.

The objective of this study is to evaluate treatment with cortisone cream compared to hot water immersion (HWI) for reducing local symptoms such as pain and itching. The study was carried out as a clinical trial including 20 healthy human test subjects who were exposed to the tentacles of *Cyanea capillata* on each foot and then treated with HWI on one foot and a topical corticosteroid on the other. The results suggest that HWI is slightly more effective for treating acute pain and itch than cortisone up to 6 h after treatment with p-values $<0.05$, and after 24 hours there was basically no remaining symptoms.

This study increases the evidence for HWI treatment, which is a safe and accessible method and should therefore be further communicated to the public.

The second part of this study was a laboratory trial and investigated whether various substances recommended for treatment of local symptoms did fire the nematocysts, jellyfish stinging cells. The results suggest that vinegar does cause the nematocysts to fire and should therefore not be used for treatment of stings from this particular species.

## INTRODUCTION

During the months of summer in Scandinavia, common leisure activities take place in and around the sea, thus exposing people to the risk of jellyfish stings. The most common stinging jellyfish in Scandinavian waters is the Lions' Mane jellyfish, *Cyanea capillata*. The less common blue jellyfish *Cyanea lamarckii* is also capable of painful stings.

There is apparent confusion and many myths among the public about treatment of jellyfish stings, and there is no clear consensus among researchers. This stems from a lack of randomized clinical trials, and the difficulty of generalizing results due to great variability in nematocyst construction between species, toxin composition, biological activity and potency (1).

The need for distinct and effective treatment of symptoms following jellyfish stings is, needless to say, most important concerning jellyfish capable of causing severe or deadly reactions.

In the colder waters of the North, Atlantic and west Baltic seas there are few species of dangerous cnidarians (1), but the stings from *Cyanea capillata*, though mildly toxic in comparison (2) are common and may result in pain which can persist for hours or days. Sometimes damage can be extensive. For example, in 2010, one giant Lions Mane jellyfish stung 150 people at the beach in New Hampshire(3). Safe, effective and easily available treatment is desirable, especially for children.

# BACKGROUND

## Jellyfish

Jellyfish descend from one of Earth's oldest multi-cellular life forms. Research suggests that they may have existed for about 550-700 million years (4). What is commonly called jellyfish is the medusa form of marine invertebrates in the phylum Cnidaria, which is divided in subphylum Medusozoa, and Anthozoa (sea anemones and corals). The phylum Subphylum Medusozoa contains classes Scyphozoa (true jellyfish) Cubozoa (box jellyfish) and Hydrozoa. Cnidarians are characterized by specialized stinging cells, cnidocysts. One kind of cnidocyst is called nematocysts (5).

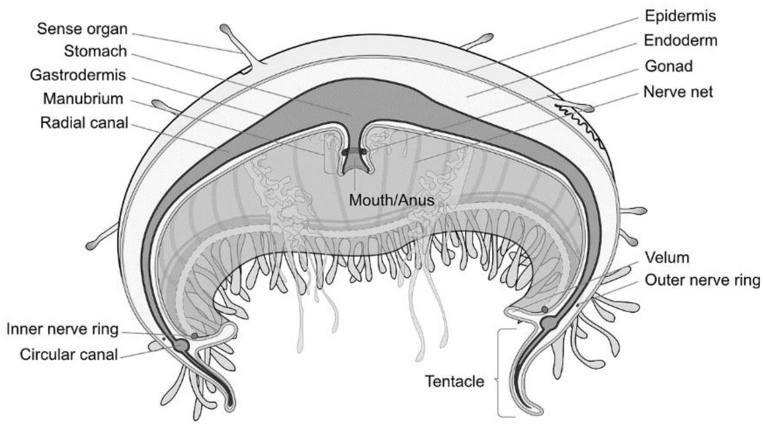


**Figure 1: Jellyfish anatomy**

### Anatomy

The cnidarian body consists of two cell layers, the epidermis and the gastrodermis separated by mesoglea, a gelatinous layer consisting mainly of water. Together these layers form an umbrella- or bell-like structure enclosing a gastrointestinal cavity. From the margin of the bell, there are whorls of tentacles used primarily for capturing prey and defence (6). Movement is facilitated by contraction of coronal muscles which forces a water jet from the bell, causing the medusa to move forward (7). Adult scyphozoans are carnivores who feed on crustaceans, some species of small fish and other jellies. Upon contact with the tentacles or manubrium, the prey is injected with venom from the nematocysts and is paralyzed or wounded. Cnidarians does not have lungs or breathing organs. Circulation of water and diffusion over the cell layers facilitates gas exchange.

### Nematocysts

The stinging cells, nematocysts, are clustered in batteries along the tentacles and around the bell and mouth in some species. The number of nematocysts per tentacle differs from a few thousand to several billion, depending on species (8). The nematocysts contain encapsulated highly coiled barbed tubules, which fire after mechanical or chemical stimulation. Following triggering, the tubule is fired within 700 ns, at high velocity (18.6 m/s) (9). Upon firing, the barbed tubule penetrates the epidermis and upper dermis and venom is injected through the tubule (8). Chemical stimulation might be more important than mechanical according to a study by Heeger et al. 1992 (10) where application of sunscreen to human skin before tentacle contact was seen to decrease the discharge of nematocysts from *Cyanea capillata*.

# Jellyfish in Scandinavian waters

**Figure 2: Lion's mane jellyfish, Swedish west coast. Photographer: Carl Johan Brengesjö**

## Lion's Mane jellyfish, Cyanea capillata

The jellyfish investigated in this study, *Cyanea capillata,* is a pelagic jellyfish, common in the North and parts of the Baltic Sea. It can be found all around the world, in waters of Australia, Japan and North America. In Australian waters the bell can grow up to 1 m in diameter, and up to two meters in colder waters (1, 11). The largest documented specimen had tentacles measuring 36.5 m, which is longer than the biggest blue whale (12). However, most Lion's Mane jellyfish found are smaller in size.

Lion's Mane jellyfish belongs to the class scyphozoa and holds a bell ranging from light yellow to orange or reddish brown, colours which have given it the name Lion's Mane. The bell has eight lobes and 70-150 tentacles hanging from it. From underneath the bell, the tube-like manubrium hangs down and connects the mouth opening with the gastrointestinal cavity.

The venom from *Cyanea capillata* has cytotoxic, cardiotoxic, hemolytic, neurotoxic and phospholipase A activities (5). Two kinds of toxins from the venom have been isolated. The first isolated toxin, CcTX-1, was found to be cytotoxic to human hepatocyte cells and the second, a neurotoxin, CcNT was purified based on toxicity to mouse neuroblastoma and was found to be neurotoxic (5). Unfractionated venom was toxic to cells from rainbow trout, mouse neuroblastoma, human hepatocytes and rat renal tubular epithelial cells shown in *in vitro* and *in vivo* tests (5).

There is abundant evidence from in vitro and in vivo studies that venom from different cnidarians are heat labile and are therefore inactivated through immersion of the affected area in water above 45 degrees. So far, no studies have investigated the heat lability of the toxins from *Cyanea capillata* (13).

## Moon jelly, Aurelia aurita

The common jellyfish *Aurelia aurita* is widely studied. It can be found all over the world, in the Indian ocean, Pacific ocean and Atlantic ocean (14). It has a translucent bell-shaped body, visible gonads, and can grow up to 40 cm in diameter. The vast majority of *Aurelia aurita* are innocuous to humans, but there is cases where *Aurelia aurita* stings have caused harm to humans (15), as stinging led to dermatological lesions and itching.

## Blue hair jelly, Cyanea lamarckii

*Cyanea lamarckii* shows great similarities with the same genus medusa *Cyanea capillata* mentioned above, and they are sometimes difficult to distinguish. However, *Cyanea lamarckii* typically has a more blueish bell colour, although colours may vary (16). Its stinging capacity and venom composition have been less studied than *Cyanea capillata*, but it should also be considered a potential toxic organism according to Helmholz et al. 2007 (17).

# Dangerous stinging jellyfish around the world

## Physalia species

The Physalia genus does not belong to the class Scyphozoa (true jellyfish) but Hydrozoa. Colonies of siphonohores, working together as one individual, form the Physalia species. A blueish-purplish gas-filled bladder, the pneumatophore, makes the creature float on the surface. It also functions as a sail, catching the wind for transportation. From underneath one or many tentacles emerge. There are two major Physalia species, The results from the laboratory test correspond to earlier studies (18) and indicates that vinegar should not be used as treatment for *Cyanea capillata* as acetic acid causes nematocysts to fire. The interesting findings that mixing Solu-Cortef® and vinegar caused precipitation can possibly be of importance since it seemed to destroy the tentacles. However, it is not known what happens to the nematocysts in this reaction. It is unclear which substances was involved in the chemical reaction since Solu-Cortef® contains other components than only hydrocortisone, as benzyl alcohol and sodium.

and *Physalia utriculus*. *Physalia physalis* has a pneumatophore sized 2-25 cm and multiple tentacles. *Physalia utriculus* becomes up to 2 cm but only has one main tentacle. Both are capable of painful stinging, but only *Physalia physalis* causes systemic symptoms such as headache, vomiting, abdominal pain and collapsing, although such symptoms are quite uncommon (11, 19). Local symptoms include sharp instant pain and red wheals resembling a linear “string of beads” appear. In most cases the symptoms disappear in 24 hours. Physalia have a worldwide distribution, but are more frequently found in warm and temperate waters. They are responsible for estimated 10 000 stings per year in eastern Australia (11).

## Cubozoans

*Chironex fleckeri* is considered the deadliest jellyfish to humans, and inhabits waters of northern Australia and Southeast Asia (9). Translucent, box-shaped, with over 2 m long tentacles, it can weigh up to 6 kg and causes extremely painful stings. Until 1994, at least 63 people died from stinging from *Chironex fleckeri*, many of them children, by circulatory and respiratory effects (11). Severity of stings is related to size of jellyfish and extent of tentacle contact. Most stings from small specimen can cause painful local lesions, resembling whip marks. In severe cases lesions can become necrotic and ulcerative a few days later. Systemic reactions include headache, nausea, fever, vomiting, muscle spasm, respiratory distress and renal failure. Death can occur either due to drowning following muscular spasms, or respiratory and cardiac arrest following spreading of venom in the circulatory system (1). *Chironex fleckeri* antivenom is the only jellyfish antivenom manufactured worldwide. It consists of immunoglobulins from serum of sheep that have been hyperimmunised with *Chironex fleckeri* venom (11).

## The Irukandji syndrome

This syndrome is primarily caused by the jellyfish *Carukia barnesi*. It is a tiny box jellyfish, so small that it’s difficult to see with the naked eye. The bell is 2x2.5 cm and the tentacles can be up to 35 cm long. A single tentacle descends from each of the four corners of the bell. Initially, mild to moderate pain follows a sting (20). After 20-30 minutes, systemic reactions with muscle cramps and severe generalized pain in abdomen, chest, back and limbs. Other symptoms are nausea, vomiting, excessive sweating and shaking, followed by pyrexia, tachyarrhythmia and hypertension. Cases with severe toxicity may lead to cardiogenic shock and pulmonary edema or cerebrovascular events (1). Hypertension due to catecholamine release has been demonstrated in animal models, but not yet in humans. For moderate envenomations, pain relief is the most important feature, and in more severe cases also treatment of hypertension. Although vinegar has been shown to deactivate nematocyst release in other box jellyfish as *Chironex fleckeri*, it has not been clearly shown to work for *Carukia barnesi* (20).

# Symptoms

Symptoms from jellyfish stings are species-dependent and vary from mild local reactions such as pain, itching and blistering of skin to severe systemic reactions and in some cases death. Severity of the symptoms depends on many factors, including jellyfish species, length of nematocyst tubuli, composition and potency of toxins, and size of the stung area. The size and vulnerability of the stung person also affects symptoms, and children are more sensitive than adults.

Symptoms from *Cyanea capillata* are typically local reactions with mild to moderate pain and itching and occasionally dermatological symptoms as redness and rashes. No human deaths have been associated with stinging from this species. Although systemic reactions such as nausea, sweating, muscle cramps and impaired consciousness are described in the literature (5, 11), search in the medical databases PubMed and Scopus did not retrieve any results related to case reports.

Eye injuries after contact with *Cyanea capillata* are described, with symptoms such as pain, swelling, conjunctival injection and vision loss. Usually these symptoms disappear in 24-48 hours, but may in some cases require narcotic analgesia (21).

# Treatment

## First aid

First aid after jellyfish stings aims to relieve local symptoms and prevent further nematocyst discharge as well as anticipation and prevention of possible systemic symptoms. Since venom composition and sting severity varies significantly among species, species-specific treatment is desirable for effective symptom relief.

For prevention, avoiding jellyfish contact is essential. This can be achieved by wearing protective clothes such as full-body lycra (1), using stinger-nets, or avoiding swimming in seawater when large amounts of jellyfish are present.

If contact with a jellyfish should occur, it is useful to observe characteristics of the jelly, such as colour and size to be able to give species-specific treatment (1).

Following a sting, it is helpful to remove remaining tentacles without causing nematocysts to discharge by rinsing with salt water (1, 8). Freshwater could change the osmotic pressure and instead facilitate discharge of additional nematocysts, possibly worsening the symptoms (8).

## Vinegar

Diluted acetic acid (vinegar, 4-6%) is a recommended treatment for stings from several tropical jellyfish. It has been shown to inhibit nematocyst discharge in cubozoans as *Alatina alata*, *Caruka barnesi* (causing Irukandji syndrome) and *Carybdea alata*, and also reduce pain following stings from *Pelagia noctiluca* (1, 22). In contrast it has been shown to cause further nematocyst discharge in *Cyanea capillata, Physalia physalis* and *Chironex fleckeri* (1, 18).

## Urine

There is a widespread old myth that urine is an effective treatment for jellyfish stings which was made even more popular after a certain episode of the TV-series Friends in 1997. This myth was described and discarded as early as in 1987 (23).

Despite the popularity of this cure there is no evidence that urine has any effect on local symptoms. Instead urine may increase nematocyst discharge and thus increase symptoms such as pain, swelling and itching (22).

## Hot water immersion

Hot water immersion is a popular and scientifically proven treatment for various marine stings, traditionally reserved for penetrating fish stings (24). It has been used for treatment of weever fish stings as far back as the 18th century. It is also a recommended treatment for echinoderms (sea stars, sea urchins) and also freshwater and marine fishes (13). Recent research suggests that HWI is also effective for relieving pain after certain cnidarian stings (13, 24). A review article from 2016 by Wilcox et al. (13) states that “hot-water immersion is a safe and effective method for reducing pain from cnidarian envenomations", and also that no cases or studies have been found that report worsened symptoms following HWI.

The proposed mechanism for pain relief by HWI treatment is through inactivation of venom components. However, some researchers have postulated that the mechanism of pain relief at these temperatures are instead facilitated by physiological mechanisms such as increased blood flow and that the temperature for toxin inactivation are much higher (above 60°C). (13).

# RESEARCH QUESTION

The objective of the clinical trial was to evaluate treatment after Lion's mane jellyfish stings.

**Is there any difference in effectiveness for relieving local symptoms following Lion's mane jellyfish stings, such as pain and itching between cortisone cream and hot water immersion?**

Topical corticosteroids are used to reduce inflammation and relieve itching for several dermatological conditions, and they are recommended as symptomatic treatment for jellyfish stings by the Swedish Poisons Information Centre (25). So far no studies have been carried out evaluating the effect of topical corticosteroids for cnidarian stings.

A laboratory experiment was also conducted.

**Does any of the tested substances used for treatment of jellyfish stings visibly discharge nematocysts?**

The substances tested were: Vinegar (apple cider- and red wine vinegar), diluted acetic acid (ättika), chlorine, cortisone injection solution (Solu-Cortef®), lidocaine, baking soda mixed with freshwater, freshwater and urine.

# CLINICAL TRIAL

## Material and methods

20 healthy test subjects, 11 men and 9 women between 22-38 years old, were recruited using social media. Exclusion criteria were: Severe illness, pregnancy, earlier severe reaction to marine envenomation. Informed consent was obtained by filling out a form (see Appendix A).

The trial took place in the harbor at Saltholmen, Gothenburg, during two days at the end of august 2016. Each day, six *Cyanea capillata* were collected at the coast of Särö, south of Gothenburg. They were identified based on their characteristic red-brown color and eight-lobed bell. The specimen used ranged in bell sizes from approximately 15-30 cm in diameter. The jellyfish were collected either by using a net, by scooping them up in a bucket, or by lifting them up by the bell using gloves and placing them in a bucket filled with seawater. We attempted to collect the jellyfish as gently as possible to avoid premature firing of the nematocysts.

Depending on size, one or two jellyfish were placed in each bucket.

While conducting the trial the test subjects immersed both feet in a bucket containing one to two jellyfish. Once they felt a painful or itching sensation on each foot they removed the feet from the bucket and also removed any remaining tentacles from the skin. The test subjects were instructed to try to get as similar exposure at both feet as possible by extending the exposure time for the foot with least stinging sensation.

30 minutes after exposure to the tentacles, the test subjects graded the sensation of pain and itch on the Numeric Rating Scale (0-10) for each foot on a questionnaire (see Appendix B). Immediately after, the left foot was immersed in hot water, at a temperature between 40-45°C, which is considered safe. A topical steroid (Dermovat®, group IV) was applied generously on the right foot in all areas where the

test subject felt any stinging sensations. The hot water immersion continued for 30 minutes. To maintain the adequate temperature (>40°C but not painful) the test subjects themselves regulated the temperature by telling when hot water refill was needed and the temperature was measured with a pool thermometer to make sure it was within the intended range.

Pain and itch were then graded immediately after the treatment, 30 minutes later, 6 hours and 24 hours later.

## Statistical methods

For calculating the statistical significance of differences between pain- and itch-scores following treatment at certain time points for every individual, the Wilcoxon signed-rank test was used, using SPSS software. Since normality in the data could not be assumed to be due to the small sample size, and since data was not in a continuous scale, the equivalent Wilcoxon signed rank-test was used.

## Results

The test subjects only experienced minor pain and itching, and no one expressed any major discomfort during the experiment.

The results showed that 30 minutes after exposure of jellyfish tentacles and immediately before treatment, the median pain-score was 2 for the foot to be treated with HWI and 2 for the foot to be treated with cortisone. The median itch score for the same time was 3 for HWI and 3 for cortisone.

At 30 minutes after treatment start, the median pain-score was 1 for HWI and 1.5 for cortisone ($p = 0.009$) and the median itch score was 1 for HWI and 2 for cortisone ($p = 0.021$).

At 1 hour after treatment start, the median pain-score was 1 for HWI and 1 for cortisone ($p = 0.035$) and the median itch score was 1 for HWI and 2 for cortisone ($p = 0.032$).

At 6 hours after treatment start the median pain-score was 0 for HWI and 0.5 for cortisone ($p = 0.031$) and the median itch score was 0 for HWI and 1 for cortisone ($p = 0.039$).

At 24 hours after treatment start the median pain-score was 0 for both HWI and cortisone. The median itch score was 0 for both HWI and cortisone. At this time, only one test subject graded the pain-score to 1, no one else had any symptoms left.

One person did not feel any pain or itching sensation whatsoever even though both feet and hands were exposed to different jellyfish for several minutes.

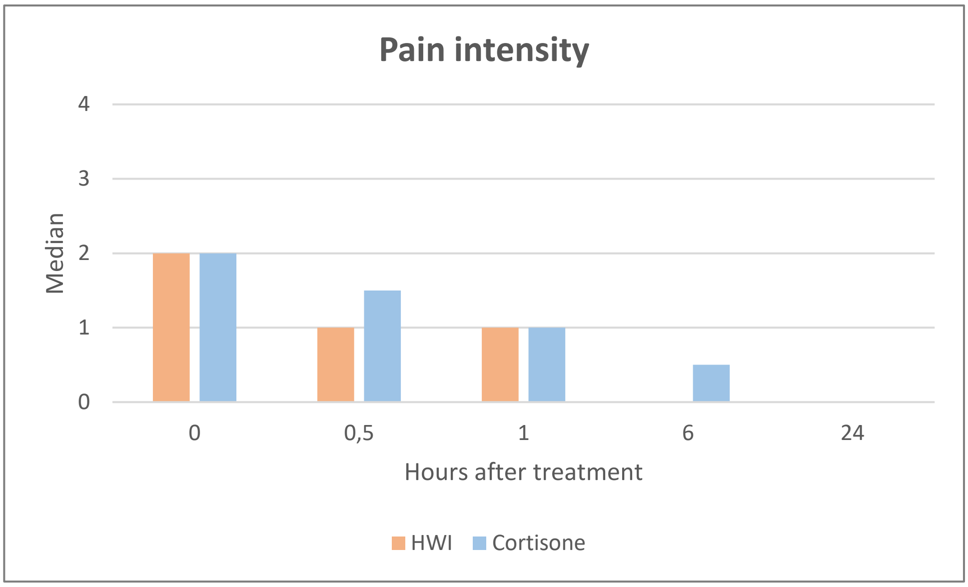


**Figure 3: Pain intensity. Significantly lower median pain intensity for HWI-treated limb at 0.5 and 6 hours after treatment.**

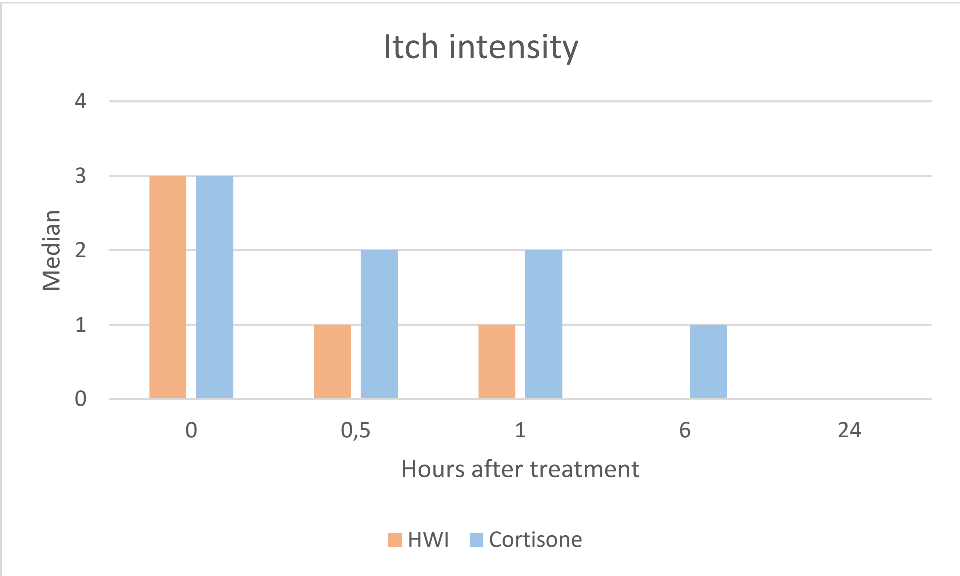


**Figure 4: Itch intensity. Significantly lower median itch intensity for HWI-treated limb at 0.5, 1 and 6 hours after treatment.**

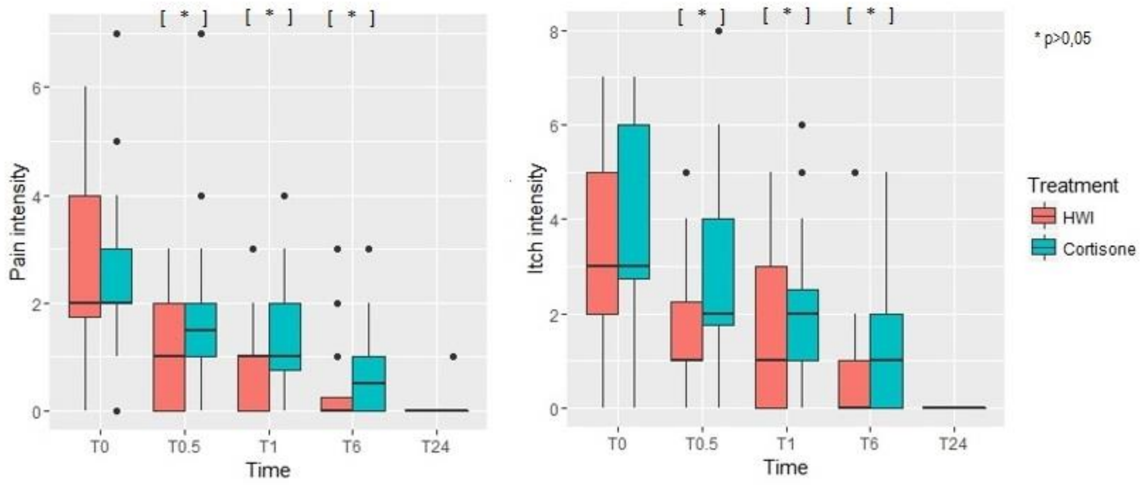


**Figure 5: Statistical method: Wilcoxon signed rank test. Boxplots showing pain and itch intensity. The line represents the median value. (The upper and lower "hinges" correspond to the 25th and 75th percentiles.)**

# LABORATORY TEST

## Material and methods

One *Cyanea capillata* jellyfish was identified as mentioned above and collected from the coast south of Gothenburg the same day as the experiments. It was transported to the lab in a sealed bucket filled with seawater. In the lab, tentacles were removed using a scissor and tweezer and put in a petri dish. Using a light microscope, tentacles were examined and photographed before and after various substances were added to investigate whether they caused the nematocysts to discharge or not. The tested substances were chosen among common treatments for pain or nematocyst inactivation: Vinegar, chlorine, cortisone injection solution (Solu-Cortef®), lidocaine, baking soda mixed with freshwater, freshwater and urine.

## Results

The only tested solutions that visibly caused the tentacles to fire were household vinegar (Ättika, 24 % acetic acid. Figure 6, image 2) and red wine vinegar (7,1% acetic acid. Figure 6, image 4). Apple cider vinegar (5% acetic acid) did not visibly fire the nematocysts. Freshwater and urine caused the tentacles to contract. We also observed that adding vinegar to Solu-Cortef® caused precipitation which destroyed the tentacles (Figure 8, image 19).

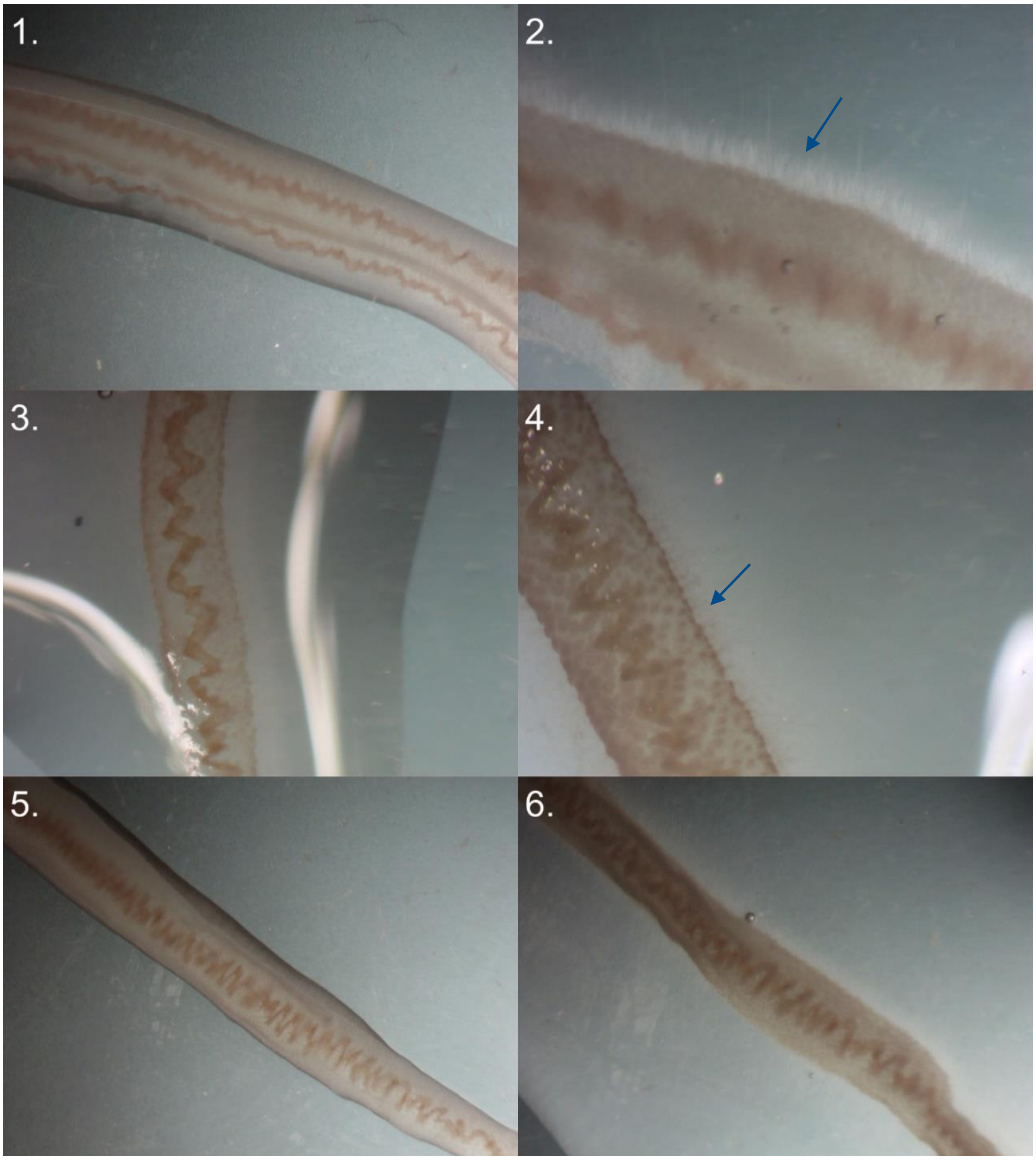


**Figure 6: Tentacles from C. Capillata before and after addition of substances.**
**1. Before household vinegar.**
**2. After household vinegar. Arrow showing fired nematocysts.**
**3. Before red wine vinegar.**
**4. After red wine vinegar. Arrow showing fired nematocysts.**
**5. Before apple cider vinegar.**
**6. After apple cider vinegar.**

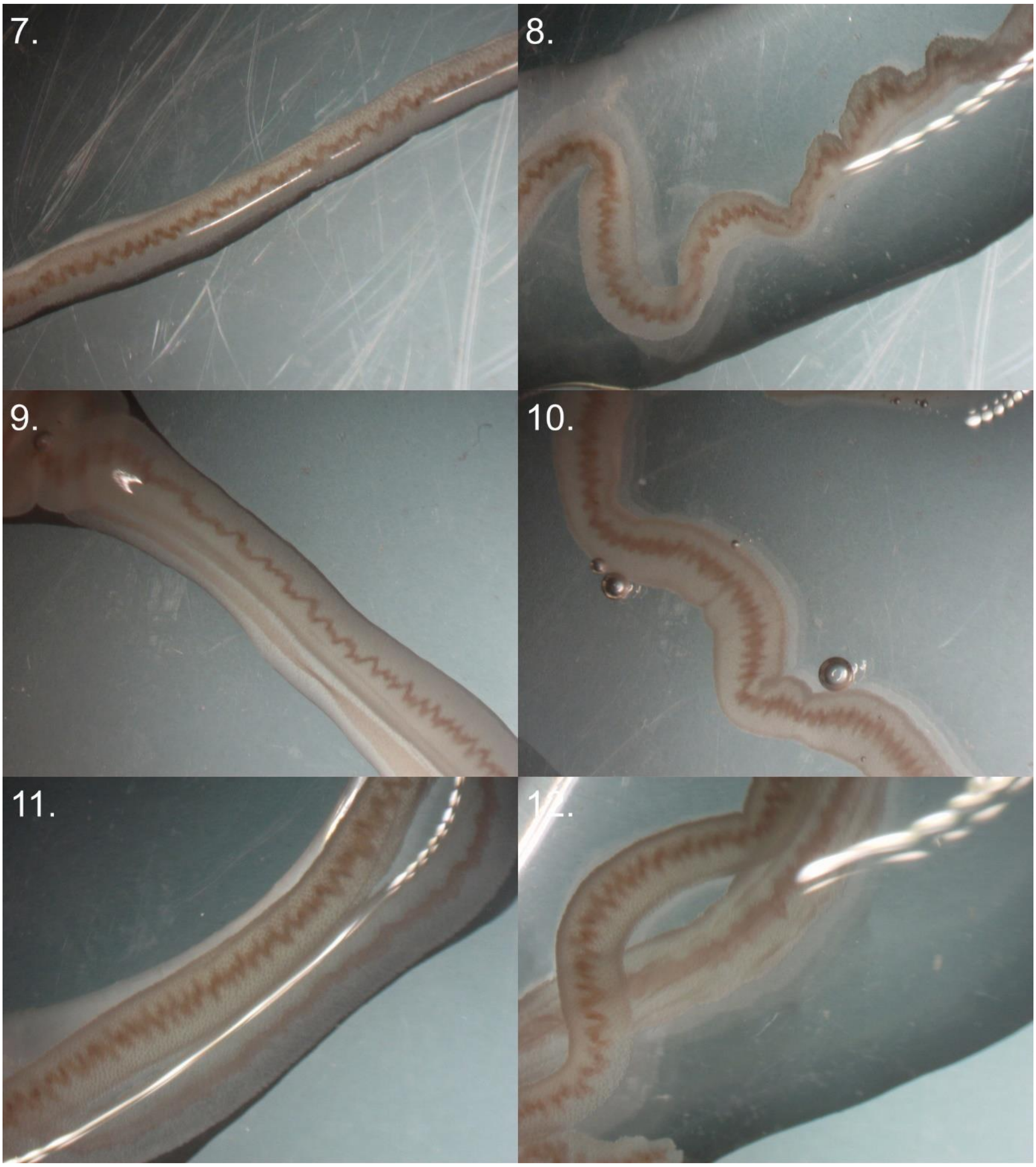


**Figure 7: Tentacles from C. Capillata before and after addition of substances.**
**7. Before freshwater.**
**8. After freshwater.**
**9. Before urine.**
**10. After urine.**
**11. Before lidocaine.**
**12. After lidocaine.**

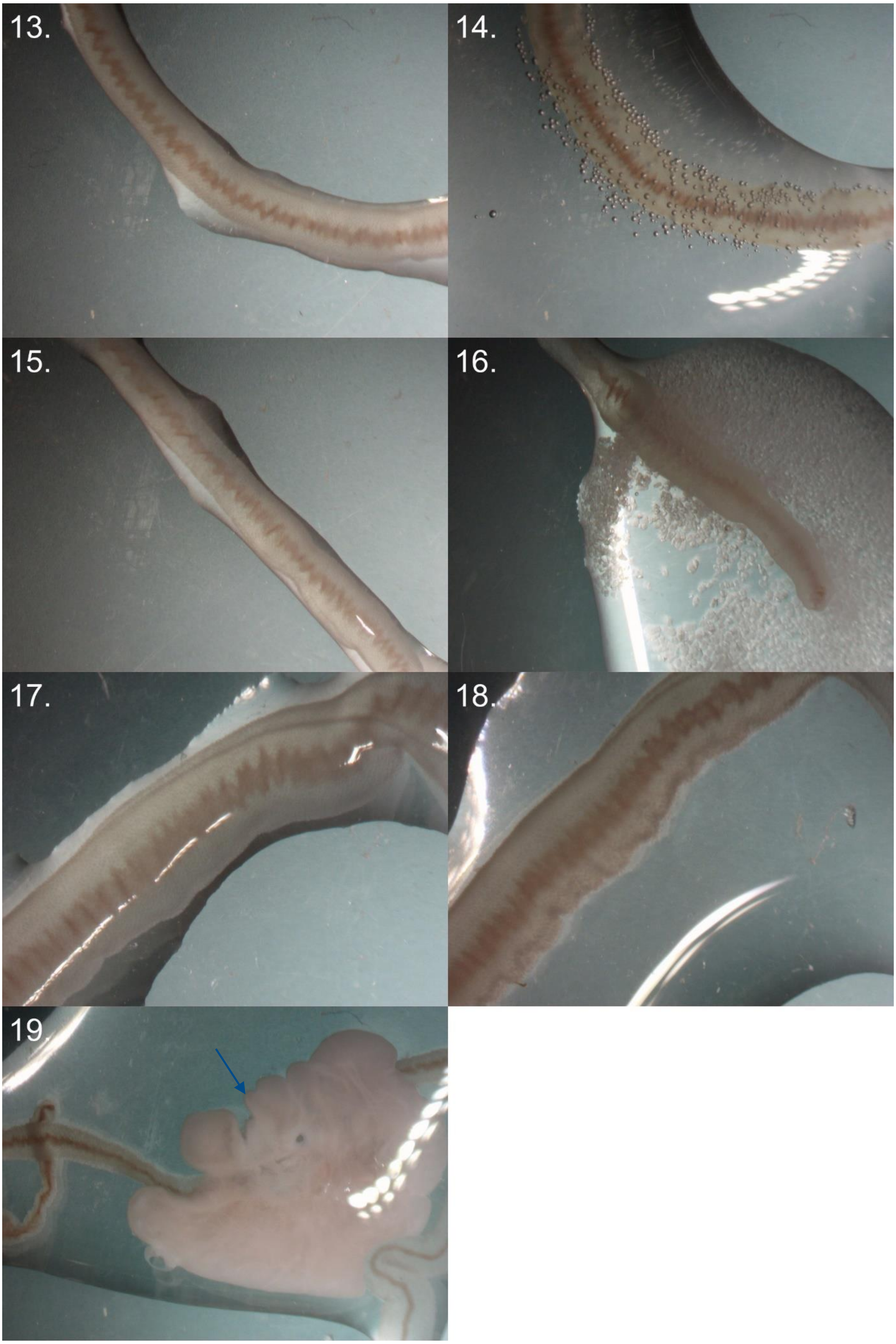
13.
14.
15.
16.
17.
18.
19.

**Figure 8: Figure 7: Tentacles from C.Capillata before and after addition of substances.**
**13. Before chlorine (undiluted).**
**14. After chlorine (undiluted).**
**15. Before baking soda (mixed with freshwater).**
**16. After baking soda (mixed with freshwater.**
**17. Before Solu-Cortef®.**
**18. After Solu-Cortef®.**
**19. After Solu-Cortef® and vinegar. Arrow showing precipitation.**

## ETHICS

This experimental trial was conducted on healthy adults following obtained informed consent. To minimize the risks of severe reactions following tentacle exposure the exclusion criteria were any serious illness, pregnancy or previous severe reaction after contact with marine animals. Exposure to *Cyanea capillata* is common at the Swedish west coast in summertime, with typically mild symptoms following stings. It is extremely unlikely that stinging of *Cyanea capillata* should cause any severe or general symptoms.

The Regional Ethical Review Boards does not consider student work, and therefore this project was not considered for ethic approval. Nevertheless, ethical considerations have been made according to the declaration of Helsinki. In p. 16, it is stated that "Medical research involving human subjects may only be conducted if the importance of the objective outweighs the risks and burdens to the research subjects" (26).

Jellyfish are invertebrates with a simple nervous system and does not acquire approval from the Swedish Board of Agriculture for use in experiments (27).

The corticosteroid cream used (Dermovat®) is a prescription pharmaceutical that is widely used in both primary and specialized care for treatment of various inflammatory dermatological conditions. Adverse effects from this cutaneous pharmaceutical product from a single application on intact skin on healthy adults are highly unlikely. The corticosteroid cream was supplied by anesthesiologist and supervisor Kai Knudsen.

The trial was supervised by anesthesiologist Kai Knudsen and the test subjects were informed that they could withdraw from the trial at any time. However, no one wished to withdraw. The test subjects were compensated with 500 SEK per person.

## DISCUSSION WITH CONCLUSIONS AND IMPLICATIONS

The results of the experimental study suggest that HWI is a more efficient treatment for acute pain and itch than cortisone up to 6h after treatment (fig. 5). The efficacy of hot water treatment agrees with earlier results where many review articles have reported pain relief from several jellyfish species(13, 19, 24)

The results from the laboratory trial show nematocyst discharge after addition of acetic acid (24%) and vinegar (acetic acid, 5%). This correspond to earlier studies where vinegar has been found to cause nematocyst discharge in *Physalia physalis*, *Chrysaora quinquecirrha* and *Cyanea capillata*(18) and indicates that vinegar should not be used as treatment for *Cyanea capillata* as acetic acid causes nematocysts to fire.

Lidocaine has been found to inhibit further discharge of nematocysts, supposedly by effects on calcium ion channels by changing the osmotic pressure in *Physalia physalis*, *Chrysaora quinquecirrha* and *Pelagia noctiluca* (18, 28). No discharge of nematocysts after addition of lidocaine was observed in our study. However, there were no further attempts to induce discharge after adding the substance.

Treatment with topical steroids has not been mentioned in RCT:s. A few case reports has shown positive outcome for local symptoms after contact with Cnidarians (29-31)

The interesting findings that mixing Solu-Cortef® and vinegar caused precipitation can possibly be of importance since it seemed to destroy the tentacles. However, it is not known what happens to the nematocysts in this reaction. It is unclear which substances was involved in the chemical reaction since Solu-Cortef® contains other components than only hydrocortisone, as benzyl alcohol and sodium.

One strength of the clinical trial was that the test subjects acted as their own control group since they obtained both treatments, different on each foot. This made comparing the treatments easier.

One limitation of the study is the difficulty involved in comparing the stinging sensations for the test subjects using a subjective measuring scale such as the NRS (scale of 0-10). A possible improvement would be to use the VAS scale, where the test subjects get to indicate a position along a line where one end is the worst possible sensation (pain or itch) and the other end is no unpleasant sensation at all. This would be a more sensitive methodd. It was also unclear to some of the test subjects what a 10 on the scale would correspond to. Was it the worst imaginable pain supposedly caused by a jellyfish or the worst pain imaginable at all? This should be further clarified in a follow-up study.

Keeping the adequate temperature in the HWI containers was challenging as the experiment was conducted outdoors, exposed to weather conditions, in addition to the containers were uninsulated. The weather differed during the two days the experiment was conducted. The first day offered sun, it was fairly windy and the temperature was 20°C. On the second day it was cloudy and rained lightly, it was not so windy and the temperature was 15°C. The weather conditions made it difficult to quickly correct for decreasing water temperatures. In a study conducted by Lau et al. 2011, different containers were tested with respect to insulation capacity, and it was found that thermal insulators (coolboxes) were able to maintain water temperature for 30 minutes (32). Due to budget limitations the use of thermal insulators was not possible for this study.

To increase the certainty of the results in a possible follow-up study, the use of a control group would be valuable. For instance, a control group which instead of cortisone cream could be treated with a lotion with similar consistency but no active substance.

Blinding in this study was hard, due to the nature of the HWI treatment. If a control group with placebo lotion was used, this treatment could be blinded and randomized.

## Recommendations

Use of hot water treatment for local symptoms following *Cyanea capillata* envenomation is a topical, relatively easily accessible, safe treatment with no adverse effects if precaution is taken to avoid scalding. People who could benefit from information about this are parents of children with risk of being stung, as well as divers, snorkelers and health centres on the Swedish West Coast. Improved information about this treatment at for instance Swedish health websites could reduce discomfort following jellyfish stings and help to further extinguish existing myths about various treatments, such as urine and vinegar, although vinegar is an appropriate treatment for other kinds of jellyfish stings as seen above.

In Sweden the recommended tap water temperature is above 50°C to prevent the growth of the bacteria *Legionella pneumophila* causing pneumonia in water pipes (33). Thus, tap water is more than hot enough and can easily be used for HWI as the recommendations are to use as warm water as the person can tolerate but not above 45°C (1).

Further research is needed to determine suitable temperature and time for the most effective HWI treatment. Further research about the mechanism of action for pain relief is also of interest.

# POPULÄRVETENSKAPLIG SAMMANFATTNING PÅ SVENSKA

## Behandling av manetsting på Västkusten- varmvattenbehandling vs kortisonkräm

Under sommarmånaderna i Sverige är havsbad, dykning och surfing uppskattade fritidsaktiviteter. Det är då inte ovanligt att man kommer i kontakt med brännmaneter, vilket kan leda till obehagliga hudirritationer samt klåda och smärta. Den vanligaste brännmaneten i svenska vatten är röd brännmanet, *Cynaea capillata*, men det finns också flera andra arter.

På den röda brännmanetens tentakler finns nässelceller, så kallade nematocyster, som består av en giftinnehållande kapsel och ett ihoprullat rör. Vid mekanisk eller kemisk stimulans skjuts röret ut med hög hastighet och penetrerar målobjektet, varpå giftet utsöndras i huden på den stungna personen.

Flera olika huskurer mot manetsting finns beskrivna, såsom användning av vinäger, urin och bakpulver, de flesta med liten eller ingen vetenskaplig förankring. Vinäger har visats vara effektiv som behandling efter kontakt med tropiska kubmaneter men har i vissa studier visats avfyra ytterligare nematocyster hos andra arter, däribland den svenska röda brännmaneten.

Denna studie har jämfört behandling med kortisonkräm och med varmvatten efter kontakt med röd brännmanet. 20 försökspersoner exponerades för tentakler från röd brännmanet på vardera underben. 20 minuter efter exponering sänktes det ena benet ned i 40-45-gradigt vatten och på det andra applicerades kortisonkräm (grupp IV). Försökspersonerna fick därefter gradera smärtan och klådan på en skala mellan 0-10 efter 0, 30, 60 minuter samt efter 6 och 24 timmar efter behandlingen.

Resultaten visade att varmvatten var en något mer effektiv behandling än kortisonkräm mot smärta och klåda upp till 6 timmar, men efter 24 timmar var det inte någon skillnad mellan de två behandlingarna.

En laboratoriestudie har också utförts där det har undersökts i mikroskop om vissa olika substanser får nematocysterna att fyras av. Det observerades att koncentrerad ättika och vinäger fick nematocysterna att avfyras. Sötvatten och urin gjorde det inte, men fick tentaklerna att dra ihop sig.

Dessa resultat indikerar att nedsänkning av den påverkade kroppsdelen i varmvatten, vilket är en säker och lättillgänglig metod, kan vara en effektiv behandling mot smärta och klåda efter kontakt med röd brännmanet i svenska vatten. Ättika och vinäger bör däremot inte användas då de istället kan få fler nematocyster att avfyras vilket kan leda till ökat obehag.

# ACKNOWLEDGEMENT

I would like to thank the following people for their help and for making it possible for me to carry out this study and write my report.

All the test subjects for participation in the study.

Roger Lindberg at Göteborgsregionens Fritidshamnar AB for kindly letting us use their premises at Saltholmen when conducting the clinical trial.

Eva Jennische at the Institute of Biomedicine at the University of Gothenburg for generously letting us use her laboratory and microscope when conducting the laboratory trial.

Olle Nordesjö for valuable help with proofreading, ideas and construction of statistical charts.

Carl Johan Brengesjö for letting me use his pictures of Lion’s mane jellyfish.

Kai Knudsen, my supervisor, for idea, help and support with the project.

## REFERENCES


1. Lakkis NA, Maalouf GJ, Mahmassani DM. Jellyfish Stings: A Practical Approach. Wilderness & environmental medicine. 2015;26(3):422-9.

2. Wang B, Zhang L, Zheng J, Wang Q, Wang T, Lu J, et al. Multiple organ dysfunction: A delayed envenomation syndrome caused by tentacle extract from the jellyfish Cyanea capillata. Toxicon : official journal of the International Society on Toxinology. 2013;61:54-61.

3. Zezima K. Death Does Not Deter Jellyfish Sting. The New York Times. 2010 23/6.

4. Hamilton G. The secret lives of jellyfish. Nature. 2016;531:432-4.

5. Badre S. Bioactive toxins from stinging jellyfish. Toxicon : official journal of the International Society on Toxinology. 2014;91:114-25.

6. Arai MN. A Functional Biology of Scyphozoa. London, UK: Chapman & Hall; 1996.

7. Ruppert F, Barnes Invertebrate zoology a functional evolutionary approach. 7 ed. London: Thomson Brooks/Cole; 2004.

8. Montgomery L, Seys J, Mees J. To Pee, or Not to Pee: A Review on Envenomation and Treatment in European Jellyfish Species. Marine drugs. 2016;14(7).

9. Tibballs J, Yanagihara AA, Turner HC, Winkel K. Immunological and toxinological responses to jellyfish stings. Inflammation & allergy drug targets. 2011;10(5):438-46.

10. Heeger T, Möller H, Mrowietz U. Protection of human skin against jellyfish (Cyanea capillata) stings. Marine Biology. 1992;113(4):669-78.

11. Tibballs J. Australian venomous jellyfish, envenomation syndromes, toxins and therapy. Toxicon : official journal of the International Society on Toxinology. 2006;48(7):830-59.

12. Rafferty JP. Lion's mane jellyfish: Encyclopaedica Britannica; 2016 [cited 2016-09-12. Available from: http://academic.eb.com.ezproxy.ub.gu.se/levels/collegiate/article/574216.

13. Wilcox CL, Yanagihara AA. Heated Debates: Hot-Water Immersion or Ice Packs as First Aid for Cnidarian Envenomations? Toxins (Basel). 2016;8(4):97.

14. R.Rodriguez. Aurelia aurita Animal Diversity Web: University of Michigan; 1999 [cited 2016-10-05. Available from: http://animaldiversity.org/accounts/aurelia_aurita/.

15. Simmons BJ, Griffith RD, Falto-Aizpurua LA, Nouri K. Moon jellyfish stings. JAMA dermatology. 2015;151(4):454-6.

16. Holst S, Laakmann S. Morphological and molecular discrimination of two closely related jellyfish species, Cyanea capillata and C. lamarckii (Cnidaria, Scyphozoa), from the northeast Atlantic. J Plankton Res. 2014;36(1):48-63.

17. Helmholz H, Ruhnau C, Schutt C, Prange A. Comparative study on the cell toxicity and enzymatic activity of two northern scyphozoan species Cyanea capillata (L.) and Cyanea lamarckii (Peron & Leslieur). Toxicon : official journal of the International Society on Toxinology. 2007;50(1):53-64.

18. Birsa LM, Verity PG, Lee RF. Evaluation of the effects of various chemicals on discharge of and pain caused by jellyfish nematocysts. Comparative biochemistry and physiology Toxicology & pharmacology : CBP. 2010;151(4):426-30.

19. Cegolon L, Heymann WC, Lange JH, Mastrangelo G. Jellyfish stings and their management: a review. Marine drugs. 2013;11(2):523-50.

20. Tibballs J, Li R, Tibballs HA, Gershwin L-A, Winkel KD. Australian carybdeid jellyfish causing “Irukandji syndrome”. Toxicon : official journal of the International Society on Toxinology. 2012;59(6):617-25.

21. Winkel KD, Hawdon GM, Ashby K, Ozanne-Smith J. Eye injury after jellyfish sting in temperate Australia. Wilderness & environmental medicine. 2002;13(3):203-5.

22. Yanagihara AA, Wilcox C, King R, Hurwitz K, Castelfranco AM. Experimental Assays to Assess the Efficacy of Vinegar and Other Topical First-Aid Approaches on Cubozoan (Alatina alata) Tentacle Firing and Venom Toxicity. Toxins (Basel). 2016;8(1).

23. Halstead BW. Clinics in Dermatology1987 1987/07/01. 8-13 p.

24. Atkinson PR, Boyle A, Hartin D, McAuley D. Is hot water immersion an effective treatment for marine envenomation? Emergency medicine journal : EMJ. 2006;23(7):503-8.

25. Giftinformationscentralen. Manet 2016 [cited 2016-09-26 ]. Available from: https://giftinformation.se/djurregister/manet/#.

26. Association WM. WMA Declaration of Helsinki - Ethical Principles for Medical Research Involving Human Subjects [cited 2017-01-02 ]. Available from: http://www.wma.net/en/30publications/10policies/b3/.

27. Djurförsöksetiska utredningen. Etisk prövning av djurförsök: delbetänkande (SOU 2002:86) Stockholm: Fritzes offentliga publikationer. Hämtad från: http://www.regeringen.se/rattsdokument/statens-offentliga-utredningar/2002/01/sou-200286/.

28. Morabito R, Marino A, Dossena S, La Spada G. Nematocyst discharge in Pelagia noctiluca (Cnidaria, Scyphozoa) oral arms can be affected by lidocaine, ethanol, ammonia and acetic acid. Toxicon : official journal of the International Society on Toxinology. 2014;83:52-8.

29. Veraldi S, Carrera C. Delayed cutaneous reaction to jellyfish. International journal of dermatology. 2000;39(1):28-9.

30. Silfen R, Vilan A, Wohl I, Leviav A. Mediterranean jellyfish (Rhopilema nomadica) sting. Burns. 2003;29(8):868-70.

31. Tezcan ÖD, Sarp S. An unusual marine envenomation following a rope contact: A report on nine cases of dermatitis caused by Pennaria disticha. Toxicon : official journal of the International Society on Toxinology. 2013;61:125-8.

32. KK Lau CC, ML Tse, FL Lau. Hot water immersion therapy with a thermal isolator in patient with marine envenomation. Hong Kong Journal of Emergency Medicine. 2011;18(4):204-9.

33. Boverket. Hushållning med kallt och varmt tappvatten. Individuell mätning och temperaturstyrning 2002 [cited 2013-10-13 ]. Available from: http://www.boverket.se/globalassets/publikationer/dokument/2002/hushallning_med_kallt_och_varmt_tappvatten.pdf.

34. DeClerck MP, Bailey Y, Craig D, Lin M, Auerbach LJ, Linney O, et al. Efficacy of topical treatments for Chrysaora chinensis species: A human model in comparison with an in vitro model. Wilderness Environ Med. 2016;27(1):25-38.

# APPENDIX A

# INFORMATION TILL FÖRSÖKSPERSONER I MANETSTUDIE

## Bakgrund och syfte

Under sommaren i Sverige är en vanlig fritidssyssla havsbad och olika vattenaktiviteter. Det är då inte ovanligt att man kommer i kontakt med brännmaneter, vilket kan leda till obehagliga brännskadeliknande hudirritationer. Flera olika huskurer mot manetsting finns beskrivna på otaliga websidor på Internet, såsom vinäger, urin, bakpulver, de flesta med liten eller ingen vetenskaplig förankring. Vissa studier har visat god effekt av behandling med varmvatten och på giftinformationscentralens hemsida rekommenderas lokala kortisonkrämer som behandling mot smärta och klåda. Syftet med denna studie är att jämföra smärta, klåda och hudreaktion efter behandling med lokal kortisonkräm med behandling med varmvatten.

## Förfrågan om deltagande

Du tillfrågas om deltagande eftersom du har anmält intresse för studien via Facebook.

## Hur går studien till?

Försöken kommer utföras på plats i Göteborgs skärgård där brännmaneter är vanligt förekommande under sommar och höst. Försökspersonerna kommer exponeras för brännmanettrådar på båda underben. 30 minuter efter exposition kommer ena benet sänkas ned i 45-gradigt vatten och det andra smörjas in med kortisonkräm. De exponerade områdena kommer eventuellt fotograferas för att kunna jämföra den dermatologiska reaktionen. En gradering av smärta/klåda kommer ske efter 30 min, 60 min och efter ett dygn.

## Vilka är riskerna?

Vanliga hudreaktioner efter kontakt med brännmaneter är nässelutslag med smärta och klåda. Inga bieffekter av varmvattenbehandling har rapporterats från tidigare studier.

## Finns det några fördelar?

Ekonomisk ersättning för deltagande i projektet, 500 SEK. Utbetalning kan dröja men ska göras under hösten.

## Hantering av data och sekretess

Dina personuppgifter och resultat kommer att behandlas så att inte obehöriga kan ta del av dem. Inga personuppgifter kommer publiceras.

## Hur får jag information om studiens resultat?

Studiens resultat kommer att redovisas med en posterpresentation 16 januari 2017 för termin 10 på läkarprogrammets på Göteborgs Universitet som är öppen för allmänheten.

## Frivillighet

Deltagande i forskningsprojekt är helt frivilligt och du har rätt att avbryta försöket när som helst utan att behöva motivera varför.

## Försäkring

Ingen extra försäkring kommer att tecknas för deltagare i studien.

## Ansvariga

**Anna Nordesjö**

Läkarstudent Göteborgs Universitet

a.nordesjo@gmail.com

0736857987

**Kai Knudsen**

Överläkare i anestesi, Sahlgrenska Universitetssjukhuset

031-342 8115

kai.knudsen@aniv.gu.se

## SAMTYCKE - MANETSTUDIE

Jag har fått information om studien, fått möjlighet att ställa frågor, fått dem besvarade och samtycker till deltagande i studie.

Datum: __(34)(33)(32)(31)(31)(30)(30)(30)(30)(30)(30)(30)(30)________________

Försökspersonens namnteckning: ______________________

Namnförtydligande: _________________________________

## APPENDIX B

# Manetstudie 27-28 augusti 2016

Försöksperson nr ____________________

Namn ____________________

Ålder ____________________

Kön ____________________

Swishnummer alt. bankkontonummer för ersättning ____________________

Har du någon allvarlig sjukdom?

Ja ☐ Nej ☐

Tar du några regelbundna mediciner?

Ja ☐ Nej ☐

Om ja, vilka? ____________________

Är du gravid?

Ja ☐ Nej ☐

Har du tidigare reagerat kraftigt vid kontakt med marina djur, t.ex. maneter?

Ja ☐ Nej ☐

Behandlingen pågår i 30 minuter. Därefter behöver du inte stanna på platsen men ta med dig formuläret hem och fyll i under nästa dygn. Gradera med ett heltal mellan 0-10 där 0 är ingen smärta/klåda och 10 värsta tänkbara smärta/klåda på området som exponerats för manettrådar på höger respektive vänster underben.

1. Omedelbart innan behandling.

    **Höger ben:**

    Smärta (0-10) ____________________

    Klåda (0-10) ____________________

    **Vänster ben:**

    Smärta (0-10) ____________________

    Klåda (0-10) ____________________

2. 30 minuter efter påbörjad behandling:

    **Höger ben:**

    Smärta (0-10) ____________________

    Klåda (0-10) ____________________

    **Vänster ben:**

    Smärta (0-10) ____________________

    Klåda (0-10) ____________________

3. 60 minuter efter påbörjad behandling:

    **Höger ben:**

    Smärta (0-10) ____________________

    Klåda (0-10) ____________________

    **Vänster ben:**

    Smärta (0-10) ____________________

    Klåda (0-10) ____________________

4. 24 timmar efter påbörjad behandling:

    **Höger ben:**

    Smärta (0-10) ____________________

    Klåda (0-10) ____________________

    **Vänster ben:**

    Smärta (0-10) ____________________

    Klåda (0-10) ____________________

När du är klar med att fylla i formuläret 24 timmar efter behandlingen är jag tacksam om du lämnar in det ifyllda formuläret till mig, antingen genom att lämna direkt till mig eller genom att fota och skicka på sms, mail eller via facebook.

Tack för ditt deltagande!

Anna