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Research Article

Experimentally Evoked Itch Response to a Newly Developed Hand-Held Mobile Device Delivering Non-Noxious Heat, Cold, and Vibration: A Pilot Study in Healthy Humans

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Abstract

Introduction: Evidence demonstrates that cold or warm temperatures can modulate itch. Noxious heat has inhibited histamine-evoked itch in humans. A cold stimulus has also been shown to inhibit itch in human models. However, a combination of these modalities, in form of warm-cold stimulation on itch is less studied and has yielded conflicting outcome. For example, short term alternating temperature has been shown to enhance histamine-evoked itch. On the other hand, alternating temperatures delivered by a roller device could reduce lactic acid induced-itch in humans. This controversy in the literature stimulated our interest to further test the pattern of evoked itch modulation by temperature modality in humans. Since vibration has also been found with an itch relieving effect, we combined this modality and developed a hand-held mobile device that can deliver heat, cold, and vibration simultaneously or individually. We investigated patterns of itch modulation in healthy volunteers undergoing experimental human model of histamine-evoked itch in response to the newly developed device. We expected to identify different degrees of itch modulation and an optimal combination that can further be examined for alleviating itch in patients with pruritic conditions.

Methods: This study was approved by the North Jutland Region Committee on Health Research Ethics (N-20170071) and was conducted in accordance with the Declaration of Helsinki. Sixteen healthy volunteers (age range: 18-65 years) participated in the pilot phase of the study: 8 males (35.75 ± 10.74 (28-61 years)), and 8 females (38.0 ± 14.89 (24-62 years)). Skin prick test on the volar aspect of forearm was used to provoke histamine-induced itch in a quiet room with a temperature of 23-24°C. Following cleaning of the skin with a sterile disinfectant, a drop of 1.0% histamine dihydrochloride (Lofarma S.p.A., Milano, Italy) was placed and a lancet with 1 mm tip was used to prick the skin through the drop. Evoked itch intensity was rated by volunteers on a VAS scale of 0 (no itch) to 10 (the most intense itch). The newly constructed prototype of a mobile itch-modulating device was applied two times for each paradigm lasting for 30 seconds with a 150 sec inter-application interval. Paradigms of non-noxious heat, cold, heat-cold, with and without vibration were randomly applied in 4 sessions each lasting for one-hour, separated by a minimum of 24 hrs. Application arm (dominant vs. non-dominant) was also randomized. Data are presented as mean and standard deviation. ANOVA tests were performed for statistical analysis by IBM-SPSS and $p < 0.05$ was considered significant.

Results: All volunteers completed the study sessions and no safety issues were recorded or reported. Histamine-evoked itch intensity was diminished in response to the different applied paradigms. Combined thermal application paradigm (heat-cold) with vibration demonstrated the largest itch reduction effect. In general, including vibration yielded a greater reduction in itch intensity compared with no vibration for any given paradigm (heat alone, cold alone, heat-cold combination). Overall, first application of the device at the peak of the histamine-evoked itch intensity was more effective in itch reduction than the second application. Small sample size and large inter-individual variations affected the power of the statistical analysis. A larger cohort to substantiate findings of this study is warranted.

Discussion: This study demonstrated that histamine-evoked itch responded to the newly developed hand-held mobile device delivering non-noxious heat, cold, and vibration. Different application modes of the device (heat alone, cold alone, heat and cold combination, with and without vibration) yielded different magnitude and pattern of reduction on the evoked itch model. This pilot study showed that a combination of alternating thermal stimulation paired with vibration could produce the largest anti-pruritic effect. However, this needs to be confirmed in a larger sample size study.

Introduction

Itching (pruritus) is a symptom of dermatological disease, which may be defined as a cutaneous sensation provoking a desire to scratch or rub [1]. Atopic eczema and psoriasis are among the most commonly described conditions that accompany itch [2]. Besides skin diseases, itch can be a symptom of other health conditions, for example HIV, diabetes mellitus, systemic diseases, and renal diseases [3,4], and it is linked to both inflammatory and non-inflammatory diseases [5]. Itch can broadly be classified to acute or chronic itch, persisting less or more than 6 weeks, respectively [6]. Average prevalence of chronic itch has been estimated >16% of adults [2]. Elderly population is more likely to be affected by chronic itch [7]. However, studies have demonstrated conflicting results and due to a large range of variations, no significant difference can be found [2]. Quality of life in patients with pruritus is dramatically disturbed [8]. Chronic itch has not only been considered a burden to affected individuals, but also to health care systems around the globe [9]. Despite the chronic itch prevalence, and its consequences on quality of life of affected patients, current treatment strategies for pruritus are only partially effective and pose several side effects [10]. Lack of sufficient treatment strategies for chronic itch is mainly associated with insufficient knowledge about itch pathways and specific targets [11]. Considering personal, social, and economical aspects of chronic itch and its related complications, further investigation seems necessary in order to obtain better insights into mechanisms contributing to development of chronic itch and identification of novel targets that can assist in strategies or treatments for itch relief [12].

Thermal modulation of itch has been of interest as a non-pharmacological technique to subside itch. When the skin is stimulated by either innocuous cold, or noxious heat, the signaling pathway is different. The cold stimuli activate innocuous thermosensitive cold (COLD) cells [13]. The heat stimuli activate Heat, Pinch, Cold (HPC) cells, these cells are also sensitive to mechanical and cold stimuli [14]. This means that during innocuous cold stimulation, both COLD and HPC cells are activated. When the skin is exposed to noxious heat stimuli, only the HPC are activated. Collectively, based on the evidence in the literature [15-17] and according to Chuquilin et al. [18], it seems that heat increases itch whereas cooling relieves it and that the thermal stimuli need to be noxious to elicit the inhibitory effect on itch. Besides the possibility of tissue damage, noxious thermal stimulation gives rise to another concern. Murota et al. [19] found that both in patients with atopic dermatitis and in histamine-induced itch models in healthy individuals, itch was experienced after either noxious heat (>45°C) or noxious cold (<5°C) stimuli. This was related to a sensitization of the TRPV1 expressed in un-myelinated C-fibers. It is therefore of great importance to maintain temperatures within the required interval where no noxious stimuli occur.

Combining thermal bars with alternating temperatures creates a Thermal Grill (TG) that is known to provoke an illusion. TG creates a cold burning sensation despite the temperature of both the warm and cold parts of the grill to be innocuous [20]. The activity of the COLD and HPC cells has been tested in relation to TG. Findings present that with cold stimuli activation of both COLD and HPC are seen, but with warm stimuli, only HPC activation is evident [21]. This finding presents that simultaneous application of warm and cold causes an imbalance between firing of spinal HPC neurons and those only responsive to cold (COLD). In response to the TG, HPC activity increases disproportionately compared to COLD. Based on this and earlier studies [21,22], thermosensory disinhibition hypothesis was put forward to explain that HPC activity is centrally inhibited by COLD activity and that the illusion of TG leads to a disinhibition or unmasking of HPC-related percepts [21,22].

Besides the effect of thermal modulation on itch, vibration has long been described to relieve itch sensation [23]. Wall and Cronly-Dillon [23] described that the neural pathway associated with itch was overwritten with signals stemming from vibration. Melzack and Schechter [24] tested subjects with vibration applied on the site of itch, adjacent to the itch area, and the opposite arm and found that applying vibration directly to the site of itch had the largest and quickest effect. Therefore, it would be beneficial if thermal and vibration stimuli can be combined in one device, capable of delivering these stimuli simultaneously at itch area to potentially enhance the itch relief. Watanabe and Kajimoto [25] were first to develop a roller-type device capable of delivering thermal and vibration stimuli. They tested it on healthy subjects under experimental setting of the evoked itch by lactic acid 2.5% applied on cheek and found itch relief effects. BITE HELPER is a small pen-shape commercially available device that has been designed to neutralize itch and irritation following insect stings and bites from mosquitoes, flies, bees, wasps, and ants. This device only delivers heat and vibration for spot treatment. Considering limitations of TG roller device, and spot itch reliever, we decided to design and produce a prototype for a mobile, and easy to use device that is capable of producing different thermal and/or vibrational stimuli within innocuous and non-painful range. We considered 8 different combinations to find the most effective in relieving histamine-evoked itch in healthy adult males and females. We hypothesized that the different combinations of stimuli would result in different amount of itch relief and that at least one of the eight combinations would yield an optimal relief

Methods

Design

We aimed at designing a device that is capable of delivering both non-noxious thermal warm, thermal cold, and vibrational stimulation. The device also had to be mobile, battery powered,

rechargeable, simple to use, and most importantly safe. We developed several prototypes (Figure 1).

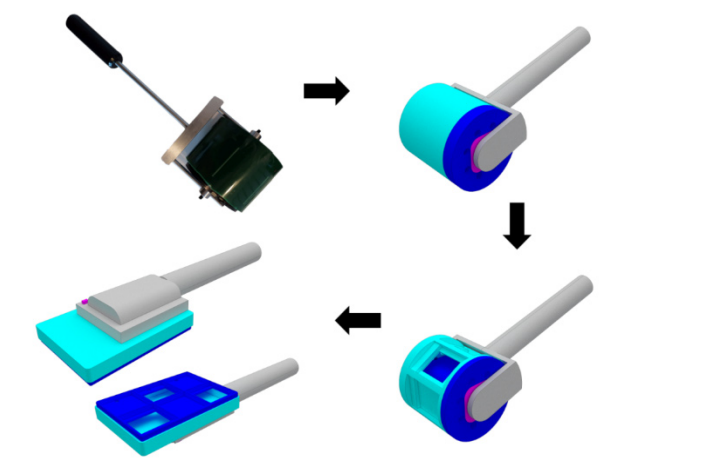


Figure 1: Prototypes of hand-held mobile device delivering non-noxious heat, cold, and vibration.

The final design (Figure 2) resembles a spatula, with a long handle to facilitate hard-to-reach areas on the body.

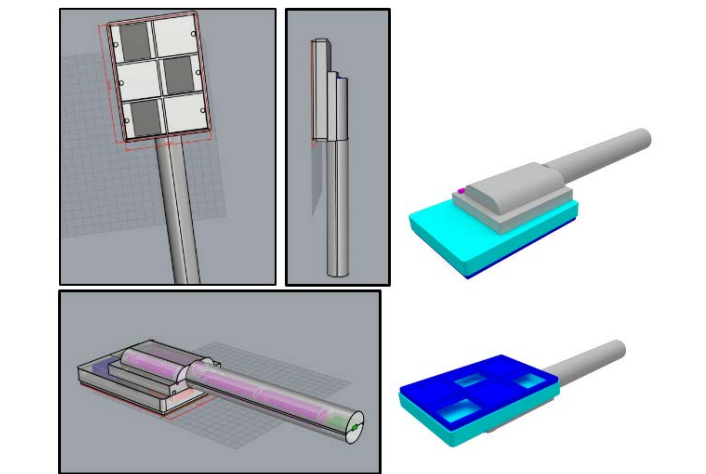


Figure 2: Final spatula prototype of hand-held mobile device delivering non-noxious heat, cold, and vibration. The main structure is made by a 3D print.

On the bottom of the final prototype, four equal and separate aluminum plates (47mm x 40mm) are arranged side by side in a checkboard layout (Figure 3A). These plates are capable of producing either a warm or cold stimulus. The thermal layout of the plates is set with switches inside the device (Figure 3B). On the top, two external switches are placed to either turn on/off the thermal stimulation or the vibration (Figure 3C). The charging port is placed at the end of the handle (Figure 3D).

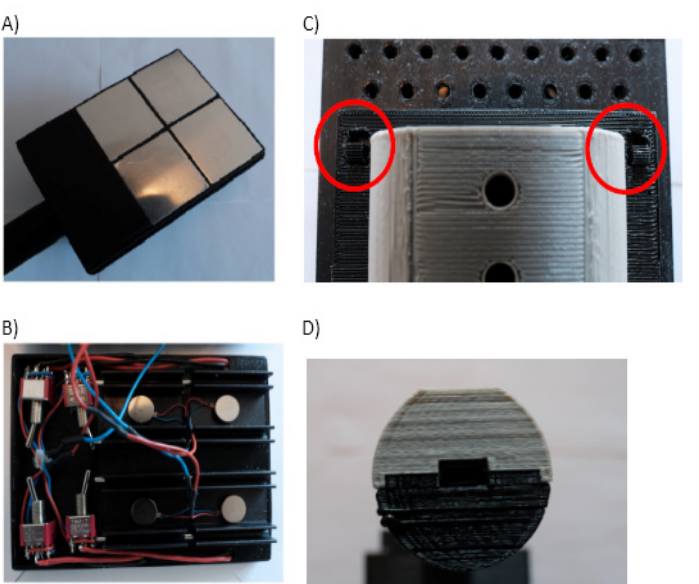


Figure 3 (A-D): A) Layout of the aluminum plates. B) Inside view shows the circular vibration units, and the switches to control the thermal configuration. The two switches to the left are set to warm, and the two to the right are set to cold. C) The two switches on top of the device (red circles). The left turns the vibration on/off, the right turns the temperature stimulation on/off, and both are in the “off” position in this picture. D) Charging port at the end of the handle.

Settings

The device was capable of producing four distinct temperature layouts. All warm, all cold, and two alternating, warm-cold. One alternating was the warm and cold panels arranged in a linear layout, and one where they were placed opposed to each other like the black and white squares in a check board. As most literature describes and tests the TG illusion as linear [20,21], the linear layout was chosen for this pilot study. The device was also provided with a vibration function, which could be turned on regardless of the thermal setting. The overview of the device setting can be seen in Table 1.

Temperature layout	Vibration off	Vibration on
Alternating temperature	Linear	Linear Vibration
Warm	Warm	Warm Vibration
Cold	Cold	Cold Vibration
Turned off/room temperature	Off	Off Vibration

Table 1: Overview of the eight settings applied with the final prototype of hand-held mobile device delivering non-noxious heat, cold, and vibration.

Pilot Test

Sixteen healthy participants, 8 males (35.75±10.74 (28-61

years)), and 8 females (38.0 ± 14.89 (24-62 years)), participated in this pilot test. Before each experiment, the participants were informed about the procedure, the risks involved in the different procedures, and planned stimuli. They were also informed that they were able to withdraw from the experiment at any time in accordance to the version 2013 of the Declaration of Helsinki [26]. This study was approved by the North Denmark Region Committee on Health Research Ethics (approval no.: N- 20170071). The pilot test was conducted in a randomized fashion for application of different settings (Table 1) and the tested arms (dominant, non-dominant).

In the middle of the chosen volar forearm, a standard skin prick test [27] was performed with one drop of 1% histamine dihydrochloride (LOT# 161214, Lofarma S.p.A., Milano, Italy) placed on the skin following cleaning with a sterile disinfectant. A lancet with 1 mm tip was used to prick the skin through the drop. Skin prick test was performed in a quiet room with temperature of 23-24°C. The test subjects were asked to score itch intensity every 30 seconds on a visual analogue scale (VAS 0-10), with 0 indicated no itch, and 10, the most intense itch. Two minutes after the prick test, the participants were asked to place the device, on top of the prick test site, for 30 seconds. During these 30 seconds, the subjects were asked to report their itch intensity every 15 seconds. When the device was removed, the test subjects were again asked to record the itch intensity every 30 seconds, for the next 2.5 minutes. The device was once more placed on the skin, on top of the prick test site, for 30 seconds. Again, the subjects rated their itch intensity every 15 seconds and after removal of the device, itch intensity was rated every 30 seconds for one minute. When the itch sensation was completely vanished, no earlier than 25 minutes after the first forearm, the process was repeated on the other forearm, with a different setting (chosen from Table 1). The newly constructed prototype of a mobile itch-modulating device was applied two times for each paradigm lasting for 30 seconds with a 150 sec inter-application interval. Paradigms of non-noxious heat, cold, heat-cold, with and without vibration were randomly applied in 4 sessions each lasting for one-hour, separated by a minimum of 24 hrs.

Statistical Analysis

Two sets of data were analyzed. First, the change in itch intensity under stimulation from the device. This was calculated by taking the average itch intensity just before, and right after the stimulation (at 90 seconds, and at 180 seconds, and also at 270 seconds, and at 360 seconds) and deducting the average itch intensity during stimulation (at 120, 135, and 150 seconds, and also at 300, 315, and 330 seconds). Also, the absolute change in

the VAS score was timed with percentage change (VAS%). This would ensure that participants with a high absolute change, but low percentage change would not outweigh participants with a small absolute change but large percentage change, and vice versa. These data would give insight to how effective the different settings performed when stimulating the itch area.

Second, the area under the VAS score curve (AUC) from 90 to 390 seconds was calculated. This would give insight to how the anti-pruritic effect of the settings would work both during and after stimulation. From these data sets (VAS score, change in VAS%, and AUC), it was tested if the different setting had equal starting point at 90 seconds, if any of the 8 settings (Table 1) differed from each other, and lastly if the 4 settings with vibration varied from the 4 settings without.

All data from the pilot test were checked for normal distribution by performing tests of normality (Shapiro-Wilk). One-way analysis of variance (ANOVA) followed by a Tukey post-hoc test was used when data were normally distributed to compare means of 16 independent groups with setting as a factor (Linear, Linear with vibration, Warm, Warm with vibration, Cold, Cold with vibration, Off, and Off with vibration). When the data were not normally distributed, The Kruskal-Wallis H test also called the one-way ANOVA on ranks was used. The data from the analyses are presented as mean \pm standard deviation (SD) and significance level was set at $p \leq 0.05$.

Results

All participants completed the pilot test and no safety issue was reported or recorded. All participants generated a flare response to the histamine application. Regarding the two off-settings, almost every participant reported a cold sensation. After the first and second stimulation by both warm settings, around half of the participants reported that it felt like the itch sensation had spread out from the site of the prick test to a larger area. A few participants described the vibration similar to scratching act.

Itch intensity

The primary outcome of this pilot study was to find out the effect of 8 settings delivered by the hand-held mobile device. Overall, all type of stimuli followed a similar pattern, meaning that all settings presented with a peak of effect on itch intensity 90 seconds after the histamine prick (when the itch was at its maximum). A remarkable itch relief was seen at this time point when the device was applied, and the effect was regardless of the setting (Figure 4).

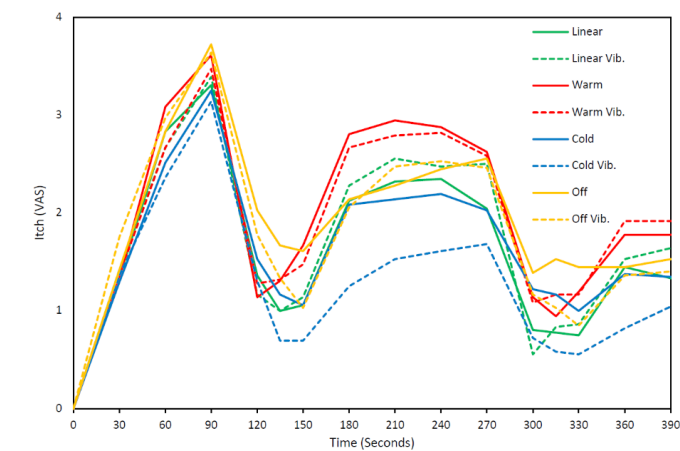


Figure 4: The pattern of average itch intensity (VAS: 0-10) recorded over time. Please note that the histamine was applied at time 0. From this, two sets of data were analyzed. First, the change in itch intensity under stimulation from the device. This was calculated by taking the average itch intensity just before, and right after the stimulation (at 90 seconds, and at 180 seconds, and also at 270 seconds, and at 360 seconds) and deducting the average itch intensity during stimulation (at 120, 135, and 150 seconds, and also at 300, 315, and 330 seconds).

One-way ANOVA results compared the itch intensity at 90 seconds to test if all settings had equal itch intensity before the first stimulation. All groups were normally distributed, and a Tukey post-hoc test - with settings as variable - was performed with confidence interval set at 95%. No significant difference was found (Table 2).

Setting	Mean (VAS)	S.D.
Linear	3.59	± 1.68
Linear Vib.	3.69	± 1.58
Warm	3.94	± 2.11
Warm Vib.	3.78	± 2.07
Cold	3.53	± 2.20
Cold Vib.	3.41	± 1.53
Off	4.06	± 1.84
Off Vib.	3.97	± 2.05

Table 2: Mean ± SD of the itch intensity (VAS) at 90 seconds. SD: standard deviation.

Itch Intensity Alterations

The average changes in itch intensity times the percent wise changes in itch intensity (Figure 5) were tested for normal distribution. Only two settings (linear and cold with vibration) were normally distributed (Table 3). The Off-setting showed the smallest change whereas the linear setting with vibration showed the largest. Six out of eight groups were not normally distributed. A

one-way nonparametric ANOVA was run to compare the average change with confidence interval set to 95%. In the comparison of Linear with vibration and Off, significant difference was found with a p-value of 0.048. The power was calculated and found as 81.2%.

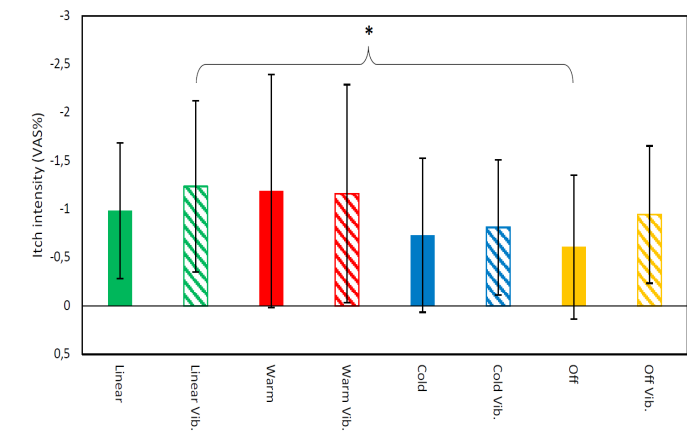


Figure 5: The average ± SD change in itch intensity times the percent wise change in itch intensity for the 8 settings. Clamp marks the two settings, which differed significantly. * P-value=0.048. SD: standard deviation.

Setting	Mean (VAS*%)	S.D.
Linear	-0.98	± 0.70
Linear Vib. *	-1.24	± 0.89
Warm *	-1.19	± 1.21
Warm Vib. *	-1.16	± 1.13
Cold *	-0.73	± 0.80
Cold Vib.	-0.81	± 0.70
Off *	-0.61	± 0.74
Off Vib. *	-0.95	± 0.71
*not normally distributed		

Table 3: Mean ± SD of the changes in itch intensity times the percent wise change for the 8 settings. SD: standard deviation

Area Under the Curve

The mean AUC from 90-390 seconds (Figure 6) was calculated for the 8 settings and tested for normal distribution. The AUC had the largest value in the warm setting with no vibration, whereas the cold setting with vibration showed the lowest value (Table 4). Seven out of 8 settings had normally distributed data. One-way ANOVA was run to compare the average AUC followed by a Tukey post-hoc test, with settings as variable, with confidence interval set to 95%. No comparisons yielded p-values ≤ 0.05. The power was calculated and found as 46.6%.

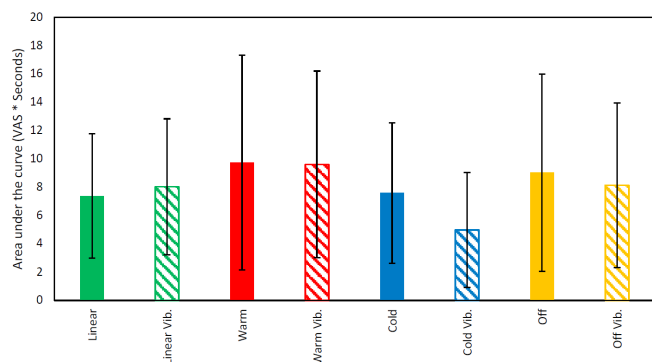


Figure 6: Mean \pm SD area under the curve for the 8 settings. SD: standard deviation.

Setting	Mean (AUC)	S.D.
Linear	7.39	\pm 4.39
Linear Vib.	8.03	\pm 4.80
Warm	9.75	\pm 7.59
Warm Vib.	9.61	\pm 6.59
Cold	7.59	\pm 4.96
Cold Vib. *	4.98	\pm 4.05
Off	9.03	\pm 6.97
Off Vib.	8.15	\pm 5.81

*not normally distributed

Table 4: Mean \pm SD of the area under the curve from 90 - 390 seconds. SD: standard deviation.

Vibration

In order to identify whether vibration was an important factor in reduction of itch, data from the change in itch intensity and the AUC were grouped to represent either vibration on or off. The data showed a larger change in itch intensity when vibration was on (Table 5). Two sample t-test was performed for both data sets of itch intensity and AUC, but none of those yielded any significant difference with p-values \leq 0.05. The power was 17% for the change in itch intensity, and 13% for the AUC.

VAS%			AUC		
Vibration	Mean	SD	Vibration	Mean	SD
Off	-0.88	\pm 0.90	Off	8.44	\pm 5.32
On	-1.04	\pm 0.88	On	7.69	\pm 4.62

Table 5: Comparison of vibration off vs. on. Left panel) mean \pm SD of the change in itch intensity times the percent wise change in itch intensity. Right panel) mean \pm SD of the area under the curve from 90 - 390 seconds. SD: standard deviation.

Discussion

The aim of this study was to design and test a mobile device with an antipruritic effect. The goal was to develop a prototype that can be easy to use and capable of producing a thermal and vibrational stimulation simultaneously. After developmental and production phase, the final prototype was tested to identify an optimum setting for antipruritic effect in an experimental model of itch in healthy humans. Findings showed the optimal setting for antipruritic effect to be linearly arranged alternating thermal stimulation paired with vibration. This setting showed the greatest drop in itch intensity under the condition of this pilot study. Larger studies are required to substantiate the findings. Below, design modifications for prototypes and the identification of optimal setting with the final prototype are discussed.

Design of Prototypes

The first prototype of a mobile thermal grill roller was made in the spring of 2017. Thermoelectric peltier elements (Thermonamic Electronics (Jiangxi) Corp., Ltd., China) of 40mm x 40mm were placed on the outside of a hexagon tube. The tube width was 44mm on each side, and the length was 58mm. Six thermoelectric elements were placed with alternating warm and cold side facing out. On the inside of the cooling elements a heat sink radiator was placed to conduct the excess heat from the surface (Figure 7).



Figure 7: A) Top view of aluminium hexagon tube with the thermoelectric elements attached on the outside, B) Side view, C) Inside view, note the three heat sink radiators.

Lids were cut from a Polyoxymethylene (POM) blank. Six holes were drilled in each POM lid to accommodate ventilation, and a ball bearing was fitted in the center. The bottom lid was fitted, and a cast was made around the contraption to create a round surface. The cast was made from Epoxy 091108-1M1 (Resin Design, LLC, MA 01801, USA) and set to dry overnight (Figure 8).

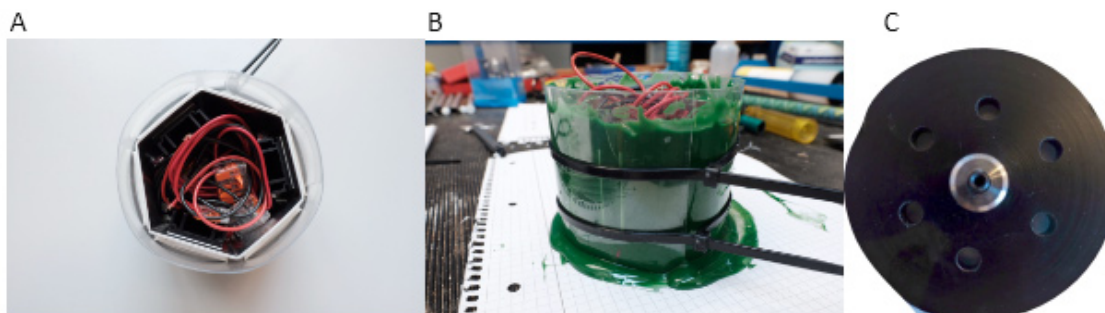


Figure 8: A) Top view without epoxy, B) Side view with epoxy, C) POM lid with six ventilation holes and a centred ball bearing.

When cast was set, excess epoxy was removed, and the top lid was fitted. Inside, a double AA battery holder was fitted in parallel circuit to the cold elements, and a double AAA battery holder was fitted in parallel circuit to the warm elements. An on/off switch was also fitted (Figure 9).

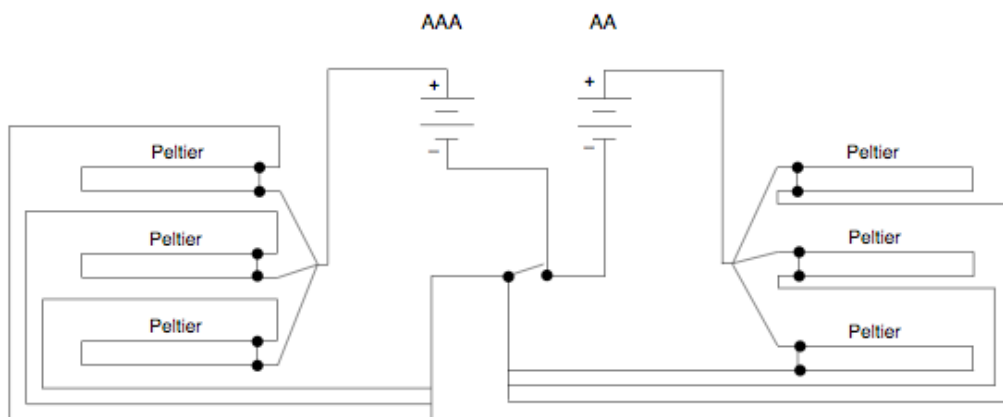


Figure 9: Schematic circuit of the thermal grill roller. The peltier circuit to the right (warm circuit) are the warm panels with 2 AAA batteries as power source. The peltier circuit to the left (cold circuit) are the cold panels with 2 AA batteries as power source.

A detachable handle was made from aluminum and POM, and resulted in the final roller (Figure 10).

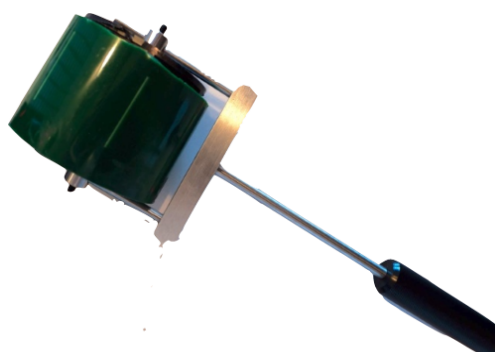


Figure 10: Alternating warm-cold roller prototype.

The surface temperature of the roller was tested three times. A preliminary test was performed without the epoxy cast and using a controlled power with fixed voltage and amps (1.6 volts and 1.4 amps for the three cold elements, and 1.6 volts and 1.3 amps for the warm elements). This was done to get an approximation of the current needed and monitored to investigate whether the peltier elements would overheat. Next test, was the test with the cast and a battery power source, but without the wires soldered and the

detachable fitted lid. This was done to test the set up with epoxy cast and batteries as power source. Finally, a test was performed with a full test run with epoxy cast, soldered wires, a switch, detachable lid and the attached handle. This test run was carried out for a longer timeframe to also test the capacity of the batteries. Before the tests new batteries were installed to ensure comparable and optimal conditions. Figure 11 shows the results.

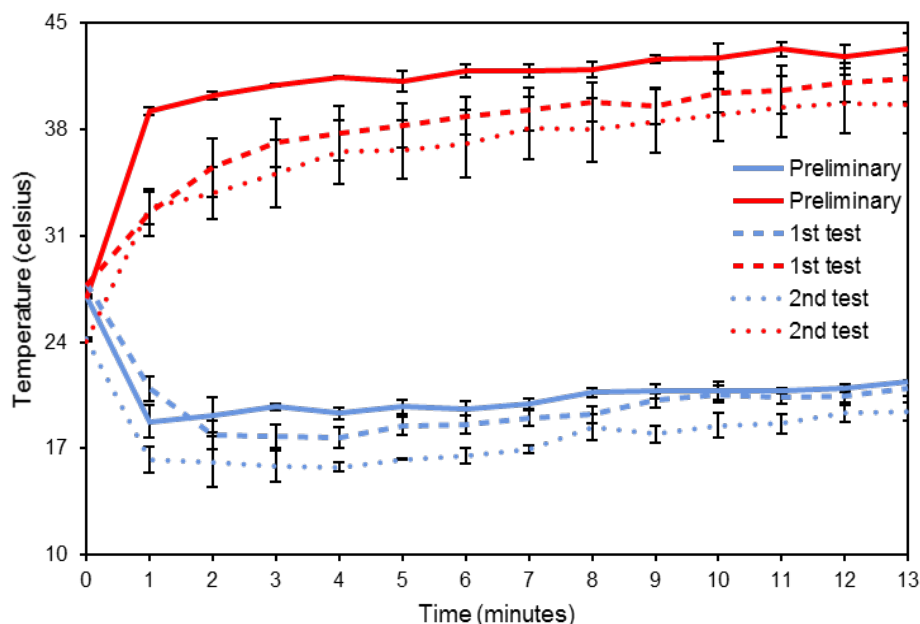


Figure 11: Average temperature \pm SD measurements from the preliminary, 1st, and 2nd tests. Red lines represent warm panels, and blue ones represent cold panels. The temperature (Celsius) at 0 minutes were 26.9 ± 0.09 , 27.83 ± 0.12 , and 24.13 ± 0.08 for preliminary, test 1 and test 2, respectively. SD: standard deviation

Major issues with this prototype consisted of battery life, non-rechargeable batteries, overheating of peltiers, and the fact that the roller was to be disassembled to be turned on/off.

The 2nd prototype of the roller was made at the beginning of autumn 2017. This time, the roller was constructed from a 3D model, using Rhinoceros 5.4 software (Robert McNeel & Associates, Seattle, WA, USA), printed using a Makerbot Replicator+ (Makerbot Industries, Brooklyn, NY, USA) (Figure 12). To improve some of the issues from the previous model, the 2nd prototype had 4 LG 3.6V, 2600mAh rechargeable lithium battery packs (LG Chem mobile energy division, Seoul, South Korea) installed. A 5V micro USB 1A Lithium Battery 18650 Charging Board Charger Module LED TP4056 (NedRo, Eindhoven, Netherlands), was used to charge the batteries. A switch was attached to the outside of the cylinder making it possible to turn the roller on/off without having to disassemble it

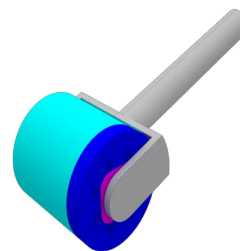


Figure 12: 3D rendering of the 2nd prototype. The main structure was made completely from a 3D print, and it consisted of 5 parts.

To both the warm and cold circuits, individual resistors were fitted to ensure that the correct amount of current was delivered

to the peltier elements. The peltier elements were fitted inside the cylinder, in the same arrangement as on the first prototype. Rectangular holes were made on the backside of the peltier elements facing the cold side out, to accommodate the cooling bridges to be fitted directly onto the warm surface. Holes were fitted in both ends of the cylinder to enable air flow and hopefully provide sufficient cooling. When testing the surface temperature of the roller, two major issues were noticed. First, the electronics overheated despite the cooling holes. The overheating was even greater compared to the first prototype. This was assigned to the newly fitted resistors. The resistors work by releasing the excess current from the batteries as heat. This created a great deal of heat

inside the cylinder overheating the peltier's after only 3-4 minutes. Second, as the second prototype was made entirely from the plastic compound used by the 3D printer, the temperature generated by the peltiers was not conducted through to the surface of the cylinder. Facing these issues, no further testing was made.

The 3rd prototype was also a 3D printed roller consisting of 5 parts. Design changes were made to create a more conducting surface. Holes were made in the surface of the cylinder, on for each peltier element, and six aluminum plates were cut to fit the holes (Figure 13). To fit flush with the cylinder, the plates had one curved side (Figure14). The plates were attached using heat conducting tape, to ensure thermal conduction from the peltier elements.

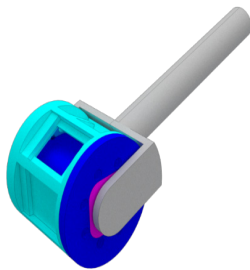


Figure 13: 3D rendering of the 3rd prototype. The main structure was still made from a plastic 3D print, and it consisted of 5 parts, but holes were added to the surface to accommodate curved aluminium plates to improve thermal conduction.

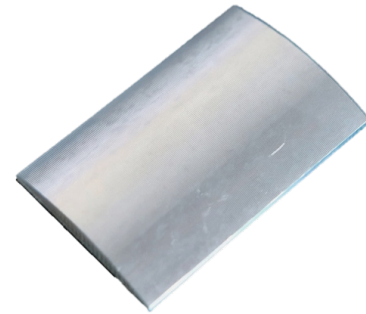


Figure 14: Curved aluminium plate, six were made for the 3rd prototype

The simple resistors were replaced with buck resistors. These regulate current through pulsation, as they turn the circuit on and off continually. As this would create an uneven current, a capacitor is fitted. The capacitor function by collecting the current released by the buck regulator, and releasing it at a steady pace, much like a water tank with a fosset attached. As the current is down regulated by essentially turning the batteries on and off instead of releasing the excess energy as thermal energy, less overheating should occur, and battery life should be increased.

This prototype was tested on the skin of few participants, but it failed to live up to the set criteria, of delivering warm and cold thermal stimulation simultaneously. This was due to the physical design, where the size of the aluminum plat and the diameter of

the cylinder did not allow for simultaneously stimulation of warm and cold. The major issue was that the roller type was not able to deliver alternating temperature of cold and heat at the same time of application to the skin.

Therefore, roller design was changed to a spatula like design (Figure 15) to ensure that both warm and cold stimulation could be delivered simultaneously. The 4th prototype, featured the same electronics as the 3rd. The peltiers were now placed in a checkerboard like arrangement, alternating warm and cold. Hole were made on the backside of the cold peltiers to make room for the cooling bridges, and a 2mm thick aluminum plate was taped to the outside of all six peltier elements.

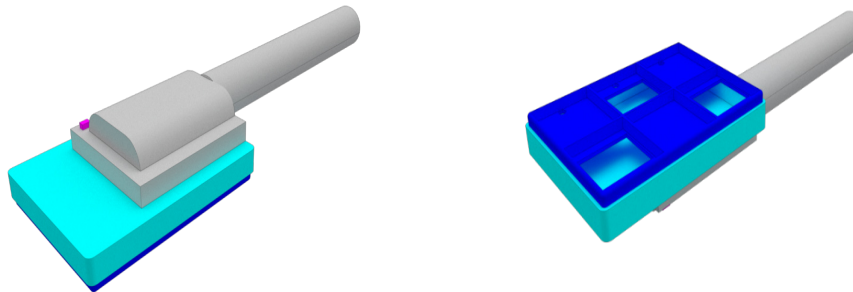


Figure 15: Top and bottom view of the 4th prototype. The main structure was still made from a 3D print, and it consisted of 4 parts. For this version the roller design was swapped for a spatula like design. The batteries were placed in the handle, the peltier elements on the bottom, the on/off switch (pink box) and charging port was still on the outside

This prototype was able to deliver both warm and cold thermal stimulation simultaneously. It would overheat, but this could be solved by increasing the thickness of the plate creating a larger internal space and putting 2mm diameter holes all over the design to accommodate ventilation. Two of the six peltier elements removed to make space for additional switches inside the final device to be able to have heat or cold alone as well. Finally, a vibration function was added to the final device to test if it can enhance the antipruritic effect.

Optimal Setting

The 8 different settings were tested to find pattern of anti-pruritic effect in response to each setting. By looking at the recorded itch intensity over time, it is clear that all settings generally followed a similar pattern. All settings produced a clear decrease in itch intensity during the 30 seconds stimulations at 120 and 300 seconds. The setting with both thermal stimulation and vibration turned off (Off), was then used as a baseline. Using this setting instead of just itch intensity without intervention from the device was chosen to isolate the thermal and vibrational stimulation from any physical stimulation interference from simply placing the device overlying the skin. In addition, there was a risk that some participants might have pressed the device against the test site on the skin, although it was instructed to just place it without pressing. By using “Off” setting as the baseline, difference between participants would become less influential. Following the data analysis, one setting (Linear with vibration) showed a significantly larger deduction in itch intensity from the baseline (Off), at $-1.24 \text{ VAS}\% \pm 0.89$ vs. $-0.61 \text{ VAS}\% \pm 0.74$, with a p-value of 0.048 and power of 81.2%. This suggests that the most likely the optimal setting is linear with vibration. This fits well with the results we obtained earlier with our non-mobile device where we found that alternating non-painful temperatures of warm and cold had the greatest effect of subsiding histamine-evoked itch. However, there is still a small chance of

18.8% (considering the study power) that the findings would be either false positive or false negative. Therefore, it is still possible that another setting would differ significantly from the baseline if the sample size would have been larger. This requires further investigation. Vibration is most likely an important element to be included in the optimal setting [23,24].

Measurement of AUC allowed us to gain insights into the itch experience during the entire experimental time. This would therefore help in identifying which settings would be capable of creating a lasting anti-pruritic effect. The power analysis showed a low power for this analysis, 46.6%, and no significant difference was found between the 8 settings. Increasing the sample size would therefore be of great interest to identify any difference between the settings. It was suspected to find difference between warm and cold settings [18] as they were visually differed in data plotting. In particular, cold with vibration looked to have a lasting anti-pruritic effect when comparing to the other settings.

Both warm settings were reported as spreading of itch sensation to surrounding areas. This is also visually noticeable by looking at data plots, where the itch intensity seems elevated compared with the other settings. It is known that elevation in skin and underlying muscle temperature leads to increased blood flow [28]. Considering this phenomenon, it seems plausible that the increased blood flow generated from warm thermal stimulation could have increased diffusion of the histamine into the surrounding tissue from the application point. However, the changes seen are not significant therefore, no conclusion can be made.

When only evaluating the effect of vibration, it was expected that this would have an anti-pruritic effect [23,24]. In this study, however, no difference was found when looking at both the VAS% and AUC data. This might be due to the low power of 17% and 13% for these two parameters, respectively. A larger sample size

would confirm or disprove the finding from this study.

When evaluating the anti-pruritic effect of the different settings it is important to consider what type of relief is the most desirable. In general, the two major wishes are being instant and long lasting, and a combination of these two, if possible, would be the optimal. Instant itch relief seems desirable but perhaps only for brief and recurrent itch periods. However, as described by Twycross, et al. [29], chronic itch originates from either a malfunctioning pruritic neuron or a pruritogen stimulating the nerve and it is long lasting. A lasting effect would be desirable for chronic conditions to allow patients benefit from anti-pruritic effect while not being forced to perform the stimuli frequently over time.

While the focus has been clinically on inhibiting itch, it would be of great interest to identify if the anti-pruritic stimulation not only affect the itch but also the underlying cause. Inflammation, plays a significant role in some of diseases causing secondary itch, for example psoriasis, and atopic eczema. Inhibiting inflammatory response leads to less scratching [30]. Interleukin-4 and -10 (IL-4 and IL-10), are cytokines involved in this response, and have a suppressing role to reverse the inflammatory response [31]. Elevation of level of these cytokines by cold thermal modulation, could not only produce a local direct anti-pruritic response, but potentially an inhibitory effect on the underlying mechanism promoting itch.

When studying the whole spectrum of itch, it might not be possible to identify only one optimal setting for the device, because different settings might yield different optimal anti-pruritic effect based on different types of itch. It also seems very important to test the device for different itch related diseases, as the specific underlying causes of the itch might also be influenced differently by the thermal and vibrational stimulation.

Limitations and Methodological Considerations

Even though the device was easy to use and mobile, and functioned sufficiently to carry out the pilot test, it still faced some limitations. This device runs on rechargeable batteries, which are charged using a 5V micro USB charger, identical to most current smart phones. Battery life was not tested, but in average, the device could run for maximum one hour. This limits the mobility indirectly as charging would be necessary. Having only two switches, one for thermal stimulation and one for vibration, it would seem easy to use. It is noted that if vibration is found to be turned on in the optimal setting, this could be linked to the same switch as the thermal stimulation, simplifying the device even further. In regard to the thermal stimulation, the device faced some limitations. This was due to overheating of the device and consequently, the peltier elements inside it. These would warm up the device regardless of the setting if the device left turned on for longer periods of time.

Overheating has been a problem throughout the design process, and has been faced by other researchers [25]. A fan attached to the top of the device would help; but, could also decrease the battery life.

As already mentioned, the Off was used as baseline to remove bias and isolate the thermal and vibration stimulation as factors. The pilot test was done in a room with a temperature of 23-24°C, whereas the surface temperature of the skin in the arms are just over 32°C under stable conditions [32]. This explains why this setting was reported, by the participants, as cold, and it can create a bias. For future research, it will be of interest to match the surface temperature of the device to the skin of the participant. This might be feasible by placing the device in an incubator set to 32°C before testing is initiated. Another point to consider is that this study has only tested histaminergic itch response in healthy participants; but, future studies should also focus on other modalities of itch in both models and real patients.

Conclusion

The study was successful in designing and producing a mobile, and easy to use prototype of an antipruritic device. The prototype device, however, needs some improvements, as it tends to overheat and is challenging to use it for long periods due to a limited battery life.

Findings from testing device on histamine-evoked itch in healthy humans showed that the optimal setting for antipruritic effect is linearly arranged alternating thermal stimulation paired with vibration stimulation. This setting showed the greatest drop in itch intensity. Small sample size, however calls for cautious conclusions. Further studies increasing the sample size, and testing other itch models in healthy humans would be of great interest to systematically test the optimal setting. Likewise, it would be of interest, to test the optimal setting in different diseases linked to chronic itch.

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Conflict of Interest

None.

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