University of Applied Sciences and Arts of Southern Switzerland
Department of Business Economics, Health and Social Care

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Originally in German, translated into English

Local changes in skin characteristics during and after a topical application of a warming or cooling product - a randomized, controlled, clinical trial

Clinical Trial Protocol

Short title	Local changes in skin characteristics during and after a topical application of a warming or cooling product
Study Type:	Observational clinical study of category A topical products
Study Categorisation:	Clinical observational study with category A medical device in accordance with the Swiss Ordinance on Clinical Trials in Human Research (ClinO: Art. 20)
Study Registration:	-
Study Identifier:	-
Sponsor:	**University of Applied Sciences** **Department of Business Economics, Health and Social Care** **Physiotherapy Graubünden** Weststrasse 8 7302 Landquart +41 81 300 01 70
Investigator:	***Contact / Director of Studies*** **Dr. Clijsen Ron**, PhD University of Applied Sciences and Arts Southern Switzerland Physiotherapy Graubünden Weststrasse 8, 7302 Landquart +41 81 300 01 75 ron.clijsen@supsi.ch
Investigational Product:	Over-the-counter, topical, warming or cooling ointments or creams and gels
Protocol Version and Date:	Study protocol – Version 04-24.06.2019

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CONFIDENTIALITY

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SIGNATURE OF THE PERSON RESPONSIBLE FOR THE STUDY

Study number	-
Study Title	Local changes in skin characteristics during and after a topical application of a warming or cooling product - a randomized, controlled, clinical trial.

Sponsor:

I have reviewed this study protocol, version 04-24.06.2019, and confirm that the study complies with the World Medical Association Declaration of Helsinki, ICH-GCP Guidelines, the ISO 14155 standard (where applicable), as well as the locally applicable Swiss Ordinance on Clinical Trials KlinV.

University of Applied Sciences Southern Switzerland, Department of Business Economics, Health and Social Care, Physiotherapy Graubünden

Sponsor (Thim van der Laan AG)

Thim van der Laan jr.

Landquart, 24.06.2019

Place/Date Signature

Investigator:

I have reviewed this study protocol, version 04-24.06.2019, and confirm that the study complies with the World Medical Association Declaration of Helsinki, ICH-GCP Guidelines, the ISO 14155 standard (where applicable), as well as the locally applicable Swiss Ordinance on Clinical Trials KlinV.

University of Applied Sciences Southern Switzerland, Department of Business Economics, Health and Social Care, Physiotherapy Graubünden

Investigator

Dr. Ron Clijsen

Landquart, 24.06.2019

Place/Date Signature

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Study Synopsis

Sponsor / Sponsor-Investigator	**Sponsor** **Thim van der Laan AG** **Thim van der Laan jr.** Weststrasse 8 / CH-7302 Landquart **Investigator** **University of Applied Sciences** **Department of Business Economics, Health and Social Care** Physiotherapy Graubünden Attn: Dr. Ron Clijsen Weststrasse 8 CH-7302 Landquart
Study Title:	Local changes in skin characteristics during and after a topical application of a warming or cooling product - a randomized, controlled, clinical trial.
Short Title / Study ID:	Local changes in skin characteristics during and after a topical application of a warming or cooling product
Protocol Version and Date:	Version 04 from 24.06.2019
Trial registration:	Cantonal Ethics Committee Zurich
Study category and Rationale	Observational study of category A according to KlinV (Art. 20)
Clinical Phase:	-
Background and Rationale:	In the field of sports medicine and physiotherapy, but also on a private basis, warming or cooling topical products are used. The indications include acute and chronic complaints of the musculoskeletal system[1]. Widely used and frequently described in the literature, topical products containing diclofenac as a nonsteroidal anti-inflammatory drug (NSAID) for pain relief[2,3]. The application forms vary from gels to patches. However, the evidence of effectiveness is low[2,4,5,6,7]. Lasanen et al. came to a similar conclusion in 2015, who were unable to observe any significant effect of menthol concentration on skin cooling[8]. A large number of these over-the-counter products are presented and advertised in daily advertising on television (including Flexor Tissugel, Voltaren Emulgel, Perskindol Cool Patch-N.).

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Objective(s):	The aim of this study is to investigate the local changes in skin characteristics during and after warming or cooling topical product applications without drug additives such as diclofenac, ibuprofen, etc. using non-invasive methods. The area of application includes the lumbar back.

Outcome(s):	Primary results in the application area during application and over the course of up to one hour of post-application in 10-minute intervals (time 0min, 10min, 20min, 30min, 40min, 50min, 60min):
	- Perfusion of skin microcirculation (Laser Speckle Contrast Imager, High Power Laser Doppler), (ultrasound X-flow (baseline only and 60min post-application))
	- Erythema formation (chromameter)
	  o of the skin
	  o of the superficial muscles
	- Surface skin temperature (i-button, infrared thermometer, thermal imaging camera)
	  o of the skin
	- Oxygen Saturation (Near-Infrared Spectroscopy)
	  o of the superficial muscles
	- Subjective parameters
	  o Perceived temperature (-4 very cold to +4 very hot)
	  o Thermal comfort (0 pleasant to 4 extremely uncomfortable)
	
	Secondary results within a 5cm radius of the application area during application and in the course of up to one hour of post-application in 10-minute intervals (time 0min, 10min, 20min, 30min, 40min, 50min, 60min):
	- Perfusion of skin microcirculation (Laser Speckle Contrast Imager, Ultrasound X-flow, High Power Laser Doppler)
	
	- Erythema formation (chromameter)
	  o of the skin
	  o of the superficial muscles
	- Surface skin temperature (i-button, infrared thermometer, thermal imaging camera)
	  o of the skin
	- Oxygen Saturation (Near-Infrared Spectroscopy)
	  o of the superficial muscles
	- Subjective parameters
	  o Perceived temperature (-4 very cold to +4 very hot)
	  o Thermal comfort (0 pleasant to 4 extremely uncomfortable)

Study design:	Randomized, controlled, clinical trial

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Inclusion / Exclusion criteria:	Margin criteria: - Adults aged 18 to 40 years - No surgical interventions on the musculoskeletal apparatus in the area of the trunk (neck C7 to pelvis, sacrum and hip joints) - Injuries to the trunk that occurred more than a year ago and do not cause any symptoms (pain at rest or during exertion, swelling, redness, restriction of movement of the adjacent joints) - Closed skin and scar conditions **Exclusion criteria:** - Age over 40 years - Surgical interventions on the musculoskeletal apparatus in the area of the trunk (neck C7 to pelvis, sacrum and hip joints) - Current injuries of any kind (skin abrasions, burns, sprains, muscle or tendon strains, bruises, fractures) in the area of the trunk that are still symptomatic - Scars in the lumbar back area - Fear of application - Regular intake of medication (including self-purchased medication), with the exception of anticonception drugs - Metal implants in the torso area - Known allergy to a possible ingredient of the products (wintergreen oil, menthol, alcohol) - Lack of epicritical and protopathic skin discrimination in the lumbar dorsal area (Th10-L5) (pointed-blunt, warm-cold, sense of vibration at the lateral malleoli) - Renal failure - Bronchial asthma - Pregnancy / breastfeeding - Diabetes mellitus type 1 or 2 - Polyneuropathies

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Preparation	Subject recruitment The subject information and declaration of consent are submitted. Questions may be asked. If the subject agrees with the information, he or she will be summoned to the first day of contact. This includes the explanations on site, the signature of the declaration of consent, the completion of the health questionnaire and the screening test. This includes a skin discrimination test both epicritically and protopathically (warm-cold, pointed-blunt, sense of vibration) of the lumbar back area paravertebral on both sides. If the test is passed, a possible skin intolerance to the products to be applied is ruled out. For this purpose, a small product sample is applied to the volar forearm and the reaction is waited for during 10 minutes of post-application. If excessive redness and/or itching, pain, uticalia occurs, the subject will be excluded from the study. The pregnancy test must be negative (women only). If all tests are passed, an appointment is made for the intervention. The subject must follow the following rules: do not apply body lotion to the back, do not consume any meal or drinks (coffee / tea / alcohol – water allowed) 2 hours before the appointment[9]. Test Subject Preparation Measurement Day The test subject lies topless in a prone position on a treatment table, women in bras. First, the lumbar back area is rubbed on both sides with distilled water (room temperature) and a soft cotton cloth with light pressure. This is followed by the 20-minute room acclimatization phase in the same storage[10]. The room temperature is kept as constant as possible (deviation of +/-2°C), the window blinds and windows are closed, and the ceiling lighting is minimal.

Measurements and procedures:	After the 20-minute acclimatization phase, the application area is drawn (skin-friendly pen), the template (recess 10cm x 10cm) is applied and the baseline measurements (a-e) are performed. After the baseline measurement, the product is applied (3g)[8]. The product is applied until it can no longer be distributed. The research employee wears a glove. This is followed by the measurements (a-d) at 0min, 10min, 20min, 30min, 40min, 50min, 60min post-application. a) Perfusion of skin microcirculation The perfusion of the skin microcirculation is performed using the Laser Speckle Contrast Imager (moorFLPI 2, moor instruments, www.moor.co.uk), the High Power Laser Doppler (moorVMS-LDF1-HP, moor instruments, www.moor.co.uk) and the ultrasound X-Flow (esaote MyLabClassicC, Maastricht, Netherlands, www.esaote.com). Since the contact gel, which is required for the ultrasound X-Flow measurement, could interfere with the product application, or could interfere with the subjective temperature perception of the subject, the ultrasound measurement is only measured at the time of baseline and 60min post-application. This was after questioning the subjective parameters. *b) Erythema formation* Erythema formation is visualized using the chromameter (www.konicaminolta.eu). The chromameter measures the light reflection and absorption of the skin. *c) Skin surface temperature* The surface temperature of the skin is measured using an infrared thermometer (Voltcraft InfraRed Thermometer, IR 800-20D) and the i-buttons. The iButton system consists of self-adhesive sensors that wirelessly transmit skin temperature information to a computer (www.ibuttonlink.com). In addition, a thermal imaging camera (www.csem.ch) records the skin surface temperature. *d) Oxygen saturation of the superficial muscles* The oxygen saturation of the superficial muscles is determined using the near-infrared measurement method (moorVMS-NIRS, moor instruments, www.moor.co.uk) The measurement is non-invasive and painless. The sensors are placed on the corresponding muscles. *e) Subjective Perception Parameters* The test subjects indicate their subjective temperature perception on a scale of 9 points from -4 (very cold) to +4 (very hot). They then rate the thermal comfort on a 5-point scale between 0 (pleasant) and 4 (extremely unpleasant)[11]. **Further processing of the data** Windows uses Excel for data pooling and the graphical representation of the end data® .

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Study Product / Intervention:	Over-the-counter, topical ointments/creams/gels with a warming or cooling effect
Control Intervention (if applicable):	The mutual paravertebral area of the lumbar back, which does not receive any application, acts as a control.
Number of Participants with Rationale:	We limit the number of subjects to N = 45 per warming or cooling product. A total of N = 90 subjects will be recruited. As part of a planned sub-analysis, an additional N = 15 subjects will be recruited. Thus, the total number of subjects increases to N = 105. Previous studies on topical diclofenac applications have tested groups of up to 200 subjects[4,6,7]. Roth et al. 2004 limited themselves to N = 80 subjects[12]. Lasanen et al. 2016 tested N = 10 subjects, they used a gel without drug ingredients[8].

Study Duration:	March 2017-December 2020
Study Schedule:	March 2017: effective start of measurements December 2020: planned end of measurements
Investigator(s):	Examiner - Dr. Ron Clijsen1,2 - Dr. Michael Villiger1,2 - Erich Hohenauer, Drs, MSc1,2 - Rahel Stoop, MSc2 1University College Physiotherapy "Thim van der Laan", Weststrasse 8, 7302 Landquart 2University of Applied Sciences and Arts Southern Switzerland, Department of Business Economics, Health and Social Care, Physiotherapy Graubünden, Weststrasse 8, 7302 Landquart ***Contact / Director of Studies*** **Dr. Clijsen Ron**, PhD University of Applied Sciences and Arts Southern Switzerland Department of Business Economics, Health and Social Care Physiotherapy Graubünden Weststrasse 8, 7302 Landquart +41 81 300 01 75 ron.clijsen@supsi.ch

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Study Centre(s):	Single Centre Study: University of Applied Sciences and Arts Southern Switzerland Physiotherapy Graubünden Weststrasse 8 7302 Landquart
Statistical Considerations:	Local changes in skin characteristics during and after a topical application of a warming or cooling product - a randomized, controlled, clinical trial. Repeated measures analysis of variance (MANOVA) 2 factors: - Topical application (warming versus control / cooling versus control) - Time (baseline, time 0min, 10min, 20min, 30min, 40min, 50min, 60min post-application) The significance level is set at $P < 0.05$, and the statistical data analysis is carried out with SPSS V. 23.
GCP Statement:	This study will be conducted in compliance with the protocol presented here, the current version of the Declaration of Helsinki, the ICH-GCP, ISO EN 14155 (where applicable), and the Swiss Human Research Ordinance HFV.

Overview of the study

The use and application of topical products for local pain relief in chronic or acute musculoskeletal apparatus complaints are widespread. Advertising propagates corresponding products from various pharmaceutical manufacturers with pain-relieving and circulation-promoting long-term effects. The products used in this study (ointments, creams, gels) are all commercially available without a prescription. Science is extensively concerned with the field of application and effectiveness of topical NSAID products on chronic pain in osteoarthritis[2,3]. Topical products have the advantage over oral medications of bypassing the gastrointestinal tract and thus avoiding possible side effects[1]. The application forms vary from sprays to gels to plasters. Derry et al. 2016 describe in their review that topical NSAID products achieve significant pain relief in subjects with osteoarthritis compared to placebo treatment[2]. The authors found no significance for other chronic pain conditions. Matthews et al. 2011 showed that topical applications with a hyperaemic effect (ingredient salicylate) were not successful in acute injuries and therefore recommended topical NSAID products for chronic pain conditions[5]. Several studies with different forms of application have been able to achieve pain relief through the use of topical NSAIDs[4,6,12,13].

Lasanen et al. 2016 tested different menthol concentrations of a cooling gel for skin cooling and concluded that all tested concentrations cooled the skin up to an hour of post-application, but the effect appeared to be independent of the concentration. Furthermore, the surrounding skin area did not cool significantly[8].

Aim of the study

The aim of our study is to investigate local changes in skin characteristics during and after a topical application of an over-the-counter, warming or cooling product without medicinal ingredients using non-invasive methods. Products with arnica or wallwort are excluded so as not to influence the subjective sensation of the subject. Products containing menthol, alcohol derivatives and wintergreen oil are included. The objective parameters are the perfusion of the microcirculation of the skin, erythema formation, skin surface temperature, oxygen saturation of the superficial muscles and the subjective temperature perception of the subject. The parameters are collected as a baseline before the application of the product, then directly in the postal application at 0 min, then in 10-minute intervals up to one hour of postal application. Thus, 8 measurement moments take place. The aim is to record the local changes in skin characteristics during and after a topical application and to recognize the effects of the products. The current state of scientific knowledge requires further studies with topical products without medicinal ingredients in order to substantiate or refute the effects already established.

Our preliminary study results of the effects of the warming products showed that one of the three tested products led to more significant changes in the measured skin parameters compared to the remaining two products. However, none of the three products had an effect on deeper tissue. However, this aspect is of great importance within rehabilitation and physiotherapy with regard to wound healing, regeneration and muscle tone. In the meantime, we have two more sensitive measuring instruments at our disposal, which can record the perfusion of the skin microcirculation up to the capillary bed and the oxygen saturation of the tissue up to a maximum depth of 30 mm. As part of a sub-analysis, we therefore plan to recruit additional N = 15 subjects to repeat the measurements with these more sensitive measuring instruments. The warming product with the greatest effect (shown above) serves as an intervention product.

Abbreviations

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CEC	Competent Ethics Committee
GCP	Good Clinical Practice
Ho	Zero hypothesis
H1	Alternative hypothesis
KlinV	Ordinance on Clinical Trials in Human Research

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Study Schedule

The completion of the measurement series is planned for October 2019, and the completion of the entire project for December 2020.

The sub-analysis is scheduled to be carried out from September to the end of October 2019. The data analysis will be carried out in November and December 2019. In 2020, the articles will be prepared and submitted for publication. The completion of the entire project (KEK, ZH ID 2016-01541) remains scheduled for the end of December 2020 as originally planned.

Table 1: Schedule

	January-February	March	April-June	July-October	November-December
2017		Subject information, screening, planning of measurements for warming products	Data collection	Data collection	Data collection
2018	Data processing	Data processing	Statistics	Statistics	Article Writing
2019	Subject information, screening, planning of measurements for cooling products	Data collection	Data collection	Data collection	Statistics
2020	Article Writing	Article Writing	Publication	Publication	Completion of the entire project

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1 STUDIEN-ADMINISTRATION

1.1 Sponsor

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1.3 Examiner

Investigator

Dr. Ron Clijsen1,2,3 *(PhD, GCP Module I – III & GCP Basic Course, Advanced Course Sponsor-Investigator)*

Selection of subjects, obtaining consent to study participation, study administration, implementation of the Measurements – collecting data, analyzing data, interpreting data, writing a report

University of Applied Sciences and Arts Southern Switzerland

Department of Business Economics, Health and Social Care

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Other examiners

Carlina Deflorin, MSc PT1 *(GCP Module I-III & GCP Basic Course)*

Data analysis, interpretation of results

Drs.Rahel Stoop1 *(GCP Module I-III & GCP Basic Course)*

Selection of subjects, obtaining consent to study participation, study administration, carrying out measurements – collecting data, assisting in data analysis, interpreting data, writing the report

1University of Applied Sciences and Arts Southern Switzerland, Department of Business Economics, Health and Social Care, Weststrasse 8, 7302 Landquart

Other employees

none

1.4 Statistician

Dr. Erich Hohenauer

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Research Assistant University of Applied Sciences and Arts Southern Switzerland
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1.5 Laboratory Manager (Investigator)

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1.6 Monitoring of the study

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1.7 Privacy

All data obtained from study participants will be coded and not passed on to other people. Personal data and personal details are stored in paper form in a locked filing cabinet. The head of the research laboratory and at the same time the head of the study has access here, and the administration of the documents also falls within his area of responsibility.

All digital data is encrypted and encoded. No conclusions can be drawn about individuals. The digital data is stored on internal computers, archived and not released to outsiders.

Employees involved in data processing have no insight into the personal data and the coding of it.

1.8 Other committees or institutes involved

The study is being conducted in the research laboratory at the University of Applied Sciences and Arts Southern Switzerland, Physiotherapy Graubünden, Weststrasse 8, 7302 Landquart, Switzerland.

The test products and measuring equipment are all located in this room and therefore all measurements can be carried out at the same location. The room offers enough space.

At present, no further studies with this arrangement are taking place in this experimental laboratory. Another study is currently taking place at our institute (NCT 02847663). However, the measurements of these two studies do not take place at the same time and do not hinder or influence each other. Thus, the utilization of the infrastructure is not excessive and therefore justifiable.

No other institutes and committees are involved in this study or in the approval or monitoring of the study.

2 ETHNIC & REGULATORY ASPECTS

2.1 Study Registration

The implementation of the present study is the responsibility of the Cantonal Ethics Committee Zurich. An application for admission is submitted. Any further conditions of the responsible ethics committee must be implemented in the study protocol.

When the study protocol is submitted to the Cantonal Ethics Committee in Zurich, the study is also registered with the Swiss Coordination Office for Research on Human Subjects. In addition, the study is registered in a WHO-recognized primary registry (clinicaltrials.gov ID: NCT03016221).

2.2 Categorization of the study

The study is categorized as a clinical trial with intervention products of risk category A (ClinO, Art. 20). The subjects are given over-the-counter topical products, warming products based on wintergreen oil, cooling products based on menthol and/or alcohol. Neither tissue samples nor other invasive methods are performed. Measurements are carried out with CE-certified equipment according to their instructions for use.

2.3 Competent Ethics Committee (CEC)

Human research in the Canton of Graubünden falls under the remit of the Cantonal Ethics Commission Zurich. Changes to the study protocol are not permitted without the prior consent of the CEC, except for the immediate elimination of obvious hazards to the participants. According to chap. 2.10 to the CEC.

An early termination or interruption of the study must be reported to the CEC within 15 days, and the regular end within 90 days. The final report must be submitted within one year of the end of the programme. Corrections are to be reported in accordance with Chapter 2.10.

2.4 Competent Authorities (CA)

The present study falls under the remit of the Cantonal Ethics Committee Zurich. Obligations and deadlines can be found in the previous point.

2.5 Ethical Leadership of the Study

The study will be conducted in accordance with this protocol and the current version of the Helsinki Declaration, the ICH-GCP, the European Medical Device Directive 93/42/EEC and the ISO standard 14155 and ISO 14971 (where applicable), as well as the Swiss Human Research Ordinance and thus Swiss law.

The CEC receives an annual report and is informed about the course of studies.

2.6 Conflict

There is no financial conflict of interest on the part of the sponsor/investigator, nor is there a corresponding relationship of dependency.

2.7 Patient information and informed consent

The examiners will explain to each participant individually the nature of the study, its content, intent and objective. This includes the protocol flow, approximate time duration, possible risks and benefits. The participant is informed that participation is voluntary and can be withdrawn from the study at any time, without personal consequences of any kind. The participant will be informed about data protection, the handling of personal data and their access.

Each participant receives written subject information and the declaration of consent with the detailed study description and all necessary information to be able to decide whether to participate in the study. The participant will also be given sufficient time to read this written information and to ask questions to the responsible examiners.

The subject information and the informed consent form are submitted to the CEC, where they must be reviewed and approved.

The signed declaration of consent must be submitted before the start of the study process. The participant should read them before signing and check their contents. The responsible examiner then also signs the declaration of consent. Finally, the participant receives a copy of the declaration of consent. The signed declaration of consent is kept in the original as a study document in a locked filing cabinet.

2.8 Confidentiality & Privacy

The examiners ensure that the privacy of the participants is maintained. In particular, data protection and confidentiality are guaranteed, and no personal data is presented or published. The signed declaration of consent, as well as the completed questionnaire with the other personal details, are kept in the original as a study document in a locked filing cabinet.

The digital data is encrypted and treated confidentially, and access to the personal data is denied to third parties. The digital data collected is stored solely on the institute's own computers and is not passed on to any external persons or transferred to other computers.

Direct access to the personal data is allowed only to the head of the research laboratory (study leader), as well as authorized persons of the CEC.

2.9 Early termination of the study

The sponsor or principal investigator may discontinue the study early if/if

- ethical concerns
- insufficient number of subjects
- the safety of the participants cannot be guaranteed
- Findings from clinical practice make it pointless to continue the study
- early evidence or harm of the experimental intervention has been proven

2.10 Adjustments to the protocol

Adjustments and changes to the current study are only permissible after review by the CEC.

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Short-term changes to the protocol prior to an audit by the CEC may be made to ensure the rights and safety of participants. However, such adjustments must be documented and reported to the CEC as soon as possible.

Significant changes are only permissible after a review of the CEC. Any other changes must be notified to the CEC as soon as possible and listed in the annual report.

3 BACKGROUND AND RATIONALE

3.1 Background and justification

The use and application of topical products for local pain relief in chronic or acute musculoskeletal apparatus complaints are widespread. The advertising propagates corresponding products from various pharmaceutical manufacturers with pain-relieving and circulation-promoting effects. The products used here are available without a prescription in online shipping or in stores. The field of application and the information on the application are contained in the insert. The application forms vary from sprays to gels to plasters. Science is extensively concerned with the field of application and effectiveness of topical NSAID products on chronic pain in osteoarthritis[2,3]. Topical products have the advantage over oral medications of bypassing the gastrointestinal tract and thus avoiding possible side effects[1]. Derry et al. 2016 describe in their review that topical NSAIDs achieve significant pain relief compared to placebo treatment in subjects with osteoarthritis[2]. The authors found no significance for other chronic pain conditions. Matthews et al. 2011 showed that topical applications with a hyperemic effect (ingredient salicylates) were not successful in acute injuries and therefore recommended topical NSAID products for chronic pain conditions[5]. Several studies with different forms of application have been able to achieve pain relief through the use of topical NSAIDs [4,6,12,13].

Lasanen et al. 2016 tested different menthol concentrations of a cooling gel for skin cooling and concluded that all tested concentrations cooled the skin up to an hour of post-application, but the effect appeared to be independent of the concentration. Furthermore, the surrounding skin area did not cool significantly[8].

Aim of the study

The aim of our study is to investigate local changes in skin characteristics during and after a topical application of a warming or cooling product without medicinal ingredients using non-invasive methods. Products with arnica or wallwort are excluded so as not to influence the subjective sensation of the subject. Products containing wintergreen oil, menthol or alcohol derivatives are included. The objective parameters are the perfusion of the microcirculation of the skin, the formation of erythema, the skin surface temperature, the oxygen saturation of the superficial muscles and the subjective perception of the subject. The parameters are collected as a baseline before the application of the product, then directly in the postal application at 0 min, then in 10-minute intervals up to one hour of postal application. Thus, 8 measurement moments take place. The aim is to record the local changes in skin characteristics during and after a topical application and to recognize the effects of the products. The current state of scientific knowledge requires further studies with topical products without medicinal ingredients in order to substantiate or refute the effects already established.

3.2 Medical product and indication

Topical ointments/creams/gels with a warming or cooling effect are used as over-the-counter products. The indication area of the warming ointments includes acute or chronic complaints of the musculoskeletal musculoskeletal system in closed wound or skin conditions (including rheumatic pain, muscle bruises, muscle cramps). The indication for a cooling product is a reduction in swelling after acute injuries or pain (e.g. joint sprains).

3.3 Preclinical evidence

Xu et al. 2014 showed in their clinical study that laser speckle imaging can be used to visualize a change

in skin blood flow after the application of a warming ointment[14]. Lasanen et al. 2016 reported that the cooling effect of the skin is independent of the menthol concentration in the applied gel, and that the surrounding tissue does not experience significant cooling[8].

3.4 Current clinical evidence

According to the authors' knowledge, there are currently hardly any clinical studies that investigate the effects of topical application of a warming or cooling product without an active pharmaceutical ingredient. The majority of existing studies are limited to topical products with the ingredient diclofenac.

3.5 Medical product: method of application in the study

The product to be applied is applied to the skin in an exactly measured amount (3g) on a given area (10cm x 10cm) on a lumbar paravertebral side of the skin. The procedure is carried out in a standardized way, by the same person.

3.6 Peers

Topical application versus no application

The test subject receives the product to be applied paravertebrally on one side, while the other side acts as a control. All test subjects are measured under the same environmental factors, the products to be applied are applied in the same way, quantity and technique.

Randomization

Randomization takes place with regard to the application side and the product to be applied. The application is paravertebral one-sided, the opposite side acts as a control. The allocation is made by drawing a lot.

The data obtained in this way is pooled accordingly after the application.

3.7 Risk / Benefits

Possible risks when using topical substances on the skin are spontaneously occurring skin redness with and without itching. If you are intolerant to an existing ingredient, an allergic reaction can occur. Furthermore, the participants can feel a feeling of warmth or cold in the application area. Subjects who may be at risk are recorded by the screening process and are not included in the study. Participants do not derive direct benefits from participating in the study. More information on securing the test subjects can be found in chap. 8.1.1.Justification

for the choice of population

This series of studies will be conducted with healthy adults, following on from previous studies[8,9]. The physiological responses of the tissue to topical applications are assumed to be probable in this population of subjects.

Inclusion Criteria

- Adults aged 18 to 40 years
- No surgical interventions on the musculoskeletal apparatus in the area of the trunk
- Injuries to the trunk that occurred more than a year ago and do not cause any symptoms (pain at rest or during exertion, swelling, redness, restriction of movement of the adjacent joints)
- Closed skin and scar conditions

Exclusion criteria

- Age over 40 years
- Surgical interventions on the musculoskeletal apparatus in the area of the trunk
- Current injuries of any kind (skin abrasions, burns, sprains, muscle or tendon strains, bruises, fractures) in the area of the trunk that are still symptomatic
- Injuries to the trunk that were not more than a year ago and/or still cause symptoms
- Scars in the lumbar back area
- Fear of application
- Regular intake of medication (including self-purchased medication), with the exception of anticonception drugs
- Metal implants in the area of the trunk (neck C7 to pelvis, sacrum and hip)
- Known allergies to the ingredients of the topical application (wintergreen oil, menthol, alcohol)
- Lack of skin ability to discriminate in the lumbar area epicritically and protopathically (pointed-blunt, warm-cold, sense of vibration)
- Renal failure
- Bronchial asthma
- Pregnancy / breastfeeding
- Diabetes mellitus type 1 or 2
- Polyneuropathies

The test subjects are comprehensively informed about the course of the study and possible risks before they are accepted to participate in the study. You will also receive the information in written form and have the opportunity to ask questions if anything is unclear. The declaration of consent explains to them what their rights and obligations are when participating. In addition, they are informed that they may withdraw from participation at any time without giving reasons, without incurring any disadvantages as a result. To clarify possible as yet unknown intolerances to an ingredient of the topical application, the product is tested on a small isolated skin area on the volar forearm, away from the actual application area to avoid interference. If there are positive signs of intolerance (including excessive redness,

urticaria, itching, local swelling), the subject will be excluded from the study for safety reasons.

4 STUDY OBJECTIVES

4.1 General objectives

The general objectives of the study are to investigate the local changes in skin characteristics in the application area during and after a topical application of a warming and cooling product without a drug ingredient. In addition, the changes in the skin characteristics in the adjacent area of the application area are observed. The data provide information on the mode of action and the radius of action of the topical applications. All measurement methods are non-invasive, as is the application.

4.2 Primary objectives

To investigate the local changes in the skin characteristics in the application area during and after a topical application of a warming and cooling product without a medicinal ingredient.

Objective parameters:

- Perfusion of skin microcirculation (perfusion flow rates in arbitrary units)
- Erythema formation (a* parameters in arbitrary units)
- Skin surface temperature (°C)
- Oxygen saturation of the superficial muscles (%)

Subjective parameters:

- Information on local temperature perception and thermal comfort (9-point scale or 5-point scale)

4.3 Secondary Objectives

To investigate the local changes in skin characteristics in the surrounding tissue during and after a topical application of a warming and cooling product without a medicinal ingredient.

Objective parameters:

- Perfusion of skin microcirculation (perfusion flow rates in arbitrary units)
- Erythema formation (a* parameters in arbitrary units)
- Skin surface temperature (°C)
- Oxygen saturation of the superficial muscles (%)

Subjective parameters:

- Information on temperature perception and thermal comfort in the surrounding tissue

4.4 Other safety aspects (long-term)

Apart from the possible directly occurring skin intolerance reactions, which were not recognizable in the screening test, to an ingredient of the topical applications and the feeling of heat or cold, no long-term risks are to be expected.

5 STUDENT OUTCOMES

5.1 Primary outcomes

Perfusion of skin microcirculation

The perfusion of the skin microcirculation is visualized using the Laser Speckle Contrast Imager and the X-Flow ultrasound.

Laser Speckle Contrast Imager:

The "moorFLPI-2 Full-Field Laser Perfusion Imager" measures blood flow measured in flow rates (arbitrary units) of the skin's microcirculation. The laser is intended for clinical and physiological research. The fabric is illuminated with a divergent infrared laser beam. The laser measures down to a depth of 1mm, so it mainly detects the superficial blood flow, speed and concentration of red blood cells.

Ultrasound X-Flow:

The electronic MyLabClass C ultrasound device measures blood flow using the Doppler principle.

In the sub-analysis, the High Power Laser Doppler Monitor (moorVMS-LDF1-HP, moor instruments, www.moor.co.uk) is also used.

High Power Laser Doppler Monitor

The High Power Laser Doppler Monitor records the perfusion of the skin microcirculation up to the vascular capillary bed. The measurement method is non-invasive and is based on the laser Doppler principle. The sensors are placed on the skin area to be measured, which detect the perfusion of the skin microcirculation (blood flow, speed and concentration of red blood cells) within a few seconds.

Erythema formation

The erythema formation is visualized by means of the chromameter.

Chromameter:

The "Chromameter CR 300" from the manufacturer Konica Minolta performs tri-stimulus colorimetry. In this way, it measures the reflection and absorption of the fired light flashes in the tissue. By measuring the a* parameters, the extent of erythema can be quantitatively recorded.

Skin surface temperature

The surface temperature of the skin is measured by means of an infrared thermometer and the i-buttons. In addition, a thermal imaging camera records the skin surface temperature.

Infrared thermometer:

The "Voltcraft Infrared Thermometer IR 800-20D" measures the infrared energy emitted by a body.

i-Buttons:

The sensors are glued to the skin, measure and store the skin temperature. The i-buttons are then read out with software developed for this purpose (www.ibuttonlink.com).

Thermal imaging camera:

The thermal imaging camera from Flir measures the surface temperature of the body using an infrared camera (www.flir.com).

Oxygen saturation of the superficial muscles

The oxygen saturation of the superficial muscles is determined in the sub-analysis using near-infrared spectroscopy.

Near-Infrared Spectroscopy moorVMS-NIRS:

Near-infrared spectroscopy makes it possible to record the absolute concentration of oxygenated and deoxygenated hemoglobin in human tissue down to a depth of 30 mm. Thus, the oxygenation of subcutaneous tissue structures (e.g. muscles) can be measured non-invasively. In contrast to the Moxy (Muscle Oxygen Monitor), the NIRS provides more stable readings in less time, which on the one hand guarantees more precise readings and on the other hand only touches (and disturbs) the skin area to be measured for a short time.

Subjective Perception Parameters

The test subjects indicate their subjective temperature perception on a 9-point scale from -4 (very cold) to +4 (very hot). They then rate the thermal comfort between 0 (pleasant) and 4 (extremely unpleasant) on a 5-point scale.

5.2 Secondary outcomes

As secondary results, the effects on the tissue area immediately adjacent to the area of application are examined analogous to point 5.1.

5.3 Security considerations

No further results are recorded that would serve safety.

Discontinuation of the experiment is the responsibility of the examiner with regard to the subject's subjective feelings and expressions.

If a test subject does not feel well during the application according to his or her subjective assessments, he or she can discontinue the experiment and withdraw participation in the study without any disadvantages. Distilled water and wipes are available within easy reach to wipe the product, as well as cold packs to alleviate possible skin irritation.

6 STUDIENDESIGN

Study design and justification

Randomized, controlled, clinical trial

This is a category A intervention study (ClinO, Art. 20), in which a tested and over-the-counter product is tested on healthy volunteers. The group size is N = 90.

For the planned continuation of the study within the framework of the sub-analysis described above, the recruitment of further N = 15 is planned. Thus, the total group size of the entire project increases to N = 105.

6.1 Method for minimizing influencing factors

6.1.1 Randomization

The area of application is randomized, right-sided or left-sided paravertebral lumbar. In addition, the assignment to the group "warming ointment" or group "cooling ointment" is hidden and randomized. The randomization procedure is carried out by lottery.

6.1.2 Blinding

Blinding of the subjects is possible with regard to the topical application of warming versus cooling, but not with regard to the control area, which remains blanco.

It is not possible to blind the applicator, but it is possible to blind the assessor of the primary and secondary results.

In addition, the blinding of the statistician can be guaranteed, who has no access to the personal data of the test persons and is not present during the data collection.

6.1.3 Other Methods

No other methods are used.

6.2 Procedure for unblinding (code break)

There is no provision for the statistician to be blinded.

6.3 Procedure for unblinding (code break)

Blinding the investigators and/or study participants is only permitted if an unforeseen incident or medical problems occur during or after the completion of study participation in a subject, which may be attributable to participation in the study.

In the event of incidents (AEs) that occur during or shortly after thermal application (within the first 24 hours) and can potentially be attributed to the application of the topical product, the principal investigator may, at his or her discretion, immediately waive the blinding of the study participant and the investigators present in order to ensure adequate treatment of the study participant.

In the case of incidents (AE) that occur more than 24 hours after the application of the topical product, clarification with a physician is mandatory and a medical certificate is required for the removal of blindness. Data may then also be passed on to the attending physician with the consent of the study

participant concerned. This approach is justified because with the topical products used here, no life-threatening incidents are to be expected after the intervention due to these applications.

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7 STUDENT POPULATION

7.1 Inclusion Criteria

Inclusion Criteria

- Adults aged 18 to 40 years
- No surgical interventions on the musculoskeletal apparatus in the area of the trunk
- Injuries to the trunk that occurred more than a year ago and do not cause any symptoms (pain at rest or during exertion, swelling, redness, restriction of movement of the adjacent joints)
- Closed skin and scar conditions

Exclusion criteria

- Age over 40 years
- Surgical interventions on the musculoskeletal apparatus in the area of the trunk
- Current injuries of any kind (skin abrasions, burns, sprains, muscle or tendon strains, bruises, fractures) in the area of the trunk that are still symptomatic
- Injuries to the trunk that were not more than a year ago and/or still cause symptoms
- Scars in the lumbar back area
- Fear of application
- Regular intake of medication (including self-purchased medication), with the exception of anticonception drugs
- Metal implants in the area of the trunk (neck C7 to pelvis, sacrum and hip joints)
- Known allergies to the ingredients of the topical application (wintergreen oil, menthol, alcohol)
- Lack of skin discrimination capacity lumbar epicritically and protopathic (pointed-blunt, warm-cold, sense of vibration)
- Renal failure
- Bronchial asthma
- Pregnancy / breastfeeding
- Diabetes mellitus type 1 or 2
- Polyneuropathies

7.2 Recruitment and Screening

Recruitment

It is advertised on the website (homepage & Facebook) of the "Thim van der Laan" University College Physiotherapy. In addition, information posters will be hung up in the school building. The exact texts have been prepared according to the checklist of the Cantonal Ethics Commission Zurich.

As advertisements (text visible):

- Homepage of the Thim van der Laan Physio School: www.physioschule.ch
- Facebook page of the Thim van der Laan School of Physiotherapy: https://www.facebook.com/physioschule

Screening

During the first contact, the potential participants are informed about the course and risks of the study, as well as the conditions for and the amount of compensation explained. A checklist for contacting them by telephone serves as a basis.

During the first telephone contact, a questionnaire is filled out by the study management to determine the suitability as a study participant.

Advertisements and health questionnaires for the first contact can be found in the supplement.

7.3 Group assignment

The group allocation (warming product, cooling product) is concealed by means of a lot in a sealed envelope, which is drawn under the supervision of the study leader. The product to be applied and the side of the application area are noted on this lot. The examiner determines the examination condition and only passes on the subject number to the assessor. At the end of the entire data collection, the auditor pools the data sets according to the application.

7.4 Discontinuation of study participation

If a participant withdraws from the study, the lot of the allocation is returned to the pot in a new envelope and a new participant is sought.

All data collected to date will be evaluated as far as possible and included in the data analysis (in accordance with Art. 9 ClinO). After evaluation, the data is irreversibly anonymized.

The conditions for the termination of the experiment were described in chap. 5.4.

There is no disadvantage for the participants if they discontinue their participation in the study.

8 STUDY INTERVENTION

8.1 Medical Device ID

8.1.1 Intervention product

The intervention products are topical ointments/creams/gels available without a prescription with a warming or cooling effect. The warming products are based on wintergreen oil, the cooling products on menthol and/or alcohol base. Eight different products are included. Of these, three products are said to have a warming effect (Axanova hot gel, Perskindol Dolo Gel, Dolor-X Hot Gel), three products to have a cooling effect and then a warming effect (Axanova activ gel, Perskindol Classic Gel, Dolor-X Classic Gel) and two products to have a cooling effect (Perskindol Cool Cooling Gel, Dolor-X Cool Gel).

In the context of the sub-analysis, the product Axanova hot gel serves as an intervention product.

Securing the test subjects

Only subjects who have completed the health questionnaire without risk factors, successfully passed the product testing without skin intolerance and the screening with regard to skin discrimination will be admitted to the study. In this way, at-risk test subjects are detected at an early stage and are not recruited for the study.

8.1.2 Control intervention

The control area that remains blanco is measured according to the same protocol.

8.1.3 Packaging, labeling and use

The products are purchased fresh and are within the expiration date. The opening date is noted on the tube.

8.1.4 Storage

The storage of the product is carried out in accordance with the package leaflet.

8.2 Administration of the experiment

Since no prescription drugs or invasive methods are used, the experiment is not discussed further in chapters 8.2-8.4 and only chapter 9 is referred to.

8.2.1 Experimental intervention

The intervention consists of a topical application of either a warming product or a cooling product. The area of application is in the lumbar back area, paravertebral on one side on an area of 10cm x 10cm.

8.2.2 Control intervention

The control intervention does not consist of any application, the selected skin area remains blanco. The lumbar paravertebral opposite side of the intervention site is taken as a control skin area.

8.3 Dosage, application modification

Exactly the same amount of product is used per subject, 3g. The product is stored at room temperature, weighed and then applied to the application surface with a glove and spread until it can no longer be spread further.

8.4 Adherence to the study intervention

The test subjects are neither motivated nor unnecessarily distracted by the examiners or the study director with conversations. Communication is kept to a minimum, only study-related discussions are held in order not to influence the physiological effects and to ensure homogeneity.

8.5 Follow-up treatment of eliminated participants

Data already collected from eliminated participants will be destroyed and will not be included in the data analysis of the study.

There is no disadvantage for the participants if they discontinue their participation in the study and no further interventions are necessary for follow-up treatment.

If study participation was discontinued due to an excessive skin reaction occurring during study participation, this will be recorded and reported to the sponsor investigator (head of the research laboratory), study leader and supervisor of the study. If medical care is necessary, the report is forwarded to the business liability insurance of Thim van der Laan AG (Basler Versicherung) in order to ensure the appropriate follow-up treatment.

8.6 Preventive measurements

The questionnaire asks about the intake of medication, injuries and operations, as well as known relevant diseases and allergies. In addition, a skin discrimination test is carried out in the area of application. Pregnant women or nursing mothers are not allowed to participate in the study. The test subjects must present a negative pregnancy test (provided free of charge by us). The test result is noted on the health questionnaire. Only then are the screening tests (skin discrimination test, product compatibility) carried out.

8.7 Accompaniments

No further side effects are expected from study participation.

8.8 Liability

The experiments take place exclusively in the research laboratory of the "Thim van der Laan" University College Physiotherapy in Landquart. This means that there is no transport of the products, equipment or test persons used. There is therefore no liability for transport.

8.9 Return of the medical device

Only as many over-the-counter topical applications are purchased as are needed. A return is neither necessary nor provided for.

9 STUDY STRUCTURE & EVALUATION

9.1 Schedule Study Protocol

1. ***Contact by e-mail, then by phone by the director of studies***
   a. Rough explanation of the study
   b. Announcement of the inclusion and exclusion criteria, corresponding examination of the suitability of the test persons
   c. If interested and suitable, delivery of further documents (see point 2)
2. ***Subject information, declaration of consent***
   a. Clarify possible questions
   b. If the subject agrees, make an appointment for screening tests
3. ***On-site explanations plus screening tests (pregnancy test (for women only), skin discrimination test, product skin compatibility), 1st day of contact***
   a. Time required 30min
   b. If the test person is suitable and consented, sign the declaration of consent and make an appointment for the actual measurement
4. ***Measurement day on site, 2nd contact day***
   a. 30min (cleansing of the skin in the application area and 20-minute room acclimatization, marking of the application area and adjustment of the measuring equipment)
   b. Executing the test protocol (see Intervention)

Intervention

-	Baseline measurement:	1min
-	Application of topical product: 1min	
-	Follow-up measurement time 0min:	1min
-	Follow-up measurement time 10min:	1min
-	Follow-up measurement time 20min:	1min
-	Follow-up measurement time 30min:	1min
-	Follow-up measurement time 40min:	1min
-	Follow-up measurement time 50min:	1min
-	Follow-up measurement time 60min:	1min
	Total Time Expenditure Intervention:	approx. 100 min

The total time required for both contact days together results in a duration of 130 minutes per test subject.

9.1.1 Measurement of primary and secondary results

Measurements of perfusion of skin microcirculation, erythema formation, skin surface temperature, oxygen saturation of the muscles and recording of subjective temperature perception can be performed within one minute.

9.1.2 Measurement of primary results

The primary measurements refer to the area of application, lumbar back area, right-sided or left-sided paravertebral depending on randomization.

Perfusion of skin microcirculation

The perfusion of the skin microcirculation is measured using the Laser Speckle Contrast Imager and the X-Flow ultrasound.

Erythema formation

The erythema formation is visualized by means of the chromameter.

Skin surface temperature

The surface temperature of the skin is measured by means of an infrared thermometer and the i-buttons. In addition, a thermal imaging camera records the skin surface temperature.

Oxygen saturation of the superficial muscles

The oxygen saturation of the superficial muscles is determined using the Moxy (Muscle Oxygen Sensor).

Subjective Perception Parameters

The test subjects indicate their subjective temperature perception on a 9-point scale from -4 (very cold) to +4 (very hot). They then rate the thermal comfort on a 5-point scale between 0 (pleasant) and 4 (extremely uncomfortable).

9.1.3 Measurement of secondary results

The measurement of the secondary results concerns the tissue directly surrounding the application area. The measurement method remains identical.

9.1.4 Collection of further results

No further results will be collected.

9.1.5 Collection of safety parameters

Apart from the health questionnaire (including pregnancy test for female subjects), the ability to discriminate against the skin and a skin compatibility test (product application in a small area on the volar forearm), no safety parameters are collected.

9.1.5.1 Unfavorable events

In the event of an allergic reaction, the experiment is stopped immediately.

9.1.5.2 Laboratory parameters

-

9.1.5.3 Vital signs

-

9.1.6 Collection of data in case of early termination of studies

For the participants, there is no disadvantage in the event of an (arbitrary) discontinuation of study participation and no further interventions are necessary for follow-up treatment. The data collected to date will be evaluated as far as possible and included in the data analysis (in accordance with Art. 9 ClinO).

However, if study participation was discontinued due to an excessive skin reaction occurring during study participation, this will be recorded and reported to the sponsor investigator (head of the research laboratory), study management and supervisor of the study. In the event of necessary medical treatment, the report is sent to the business liability insurance of Thim van der Laan AG (Basler Versicherung).

The following are recorded:

- Date and time of the incident
- Course of the incident
- Persons involved & witnesses
- Study ID (specified by the CEC)
- Personal data of the person concerned (if not previously recorded)

9.2 Procedure at each visit of the test subjects

9.2.1 Single measurement

The project involves multiple visits. After contacting them by telephone and announcing the inclusion and exclusion criteria, the subject information and the declaration of consent are submitted for inspection and reading. If the subject agrees with the study conditions and criteria, he or she registers to make an appointment for the 1st contact day. The 1st contact day includes, in the order described, the; Explanations on site, signing the declaration of consent, filling out the health questionnaire, carrying out the screening tests (including pregnancy test for female subjects). If the subsequent screening tests have been passed, an appointment is made for the actual measurement day (2nd contact day).

9.2.2 Multiple visits

1. On-site explanation and screening tests, 1st contact day

The subjects will be comprehensively informed about the process and possible risks before they are confirmed to participate in the study. You will also receive the information in written form and have the opportunity to ask questions. In the declaration of consent, they are explained what their rights and obligations are when participating and that they may withdraw from participation at any time without giving reasons, without incurring any disadvantages as a result. More detailed information can be found in chapter 2.7. In addition, a screening is carried out during the first contact in order to check the skin's ability to discriminate and to detect skin intolerances to an ingredient of the topical products to be applied at an early stage. An initial selection process of suitable test persons takes place.

2. Measurement, 2nd contact day

2.1 Preparation of the subject

The test subject lies with his upper body undressed for the men, women in a bra in a prone position on a treatment table. The lumbar back area is washed with distilled water (room temperature) and a soft cotton cloth to remove possible skin and fat residues. An alcohol solution is deliberately avoided so as not to influence the temperature perception of the test subjects. This is followed by a 20-minute room acclimatization to prepare the test subject for the measurements. The area of application (10cm x 10cm, paravertebral lumbar, randomized triggered) is drawn and the measuring apparatus is adjusted. This is followed by the baseline measurement.

2.2 Application

The topical product to be applied is then applied to the skin. Exactly 3g of product is used for this purpose.

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The amount of product is evenly distributed in the application area with a glove until it can no longer be spread.

2.3 Follow-up measurement

After the application of the topical product, the first follow-up measurement is taken directly at time 0min, followed by further follow-up measurements every 10 minutes (time 10min post-application, 20min, 30min, 40min, 50min, 60min).

2.4 Conclusion and compensation

After the last follow-up measurement at 60 minutes, the experiment is over for the test subject. He/she will receive the amount due to him/her according to the advertisement.

The lump sum is 50.-CHF.

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10 SAFETY

Clinical trial with a medical device in the risk category Cat. ***A*** KlinV (Art. 20)

The subjects are given topical products available over the counter with a warming effect or cooling effect locally. No other medication is dispensed. Nor are tissue samples taken or invasive (measurement) methods used.

No further security aspects are expected.

10.1 Drug study

The products used are available without a prescription, the warming substances are based on wintergreen oil, the cooling ones on menthol and/or alcohol.

10.1.1 Definition and assessment of (serious) adverse events and other safety related events

-

10.1.2 Reporting of serious adverse events (SAE) and other safety related events

-

10.1.3 Follow up of (Serious) Adverse Events

-

10.2 Medical Device Category C studies

-

10.2.1 Definition and Assessment of (Serious) Adverse Events and other safety related events

-

10.2.2 Reporting of (Serious) Adverse Events and other safety related events

-

10.2.3 Follow up of (Serious) Adverse Events

-

10.3 Medical Device Category A studies

This study is a category A clinical observational study in accordance with the Swiss Ordinance on Clinical Trials in Human Research (ClinO, Art. 20).

It is a study with 40 subjects. The study focuses on basic findings. The monitoring for quality assurance is carried out by Prof. Dr. Peter Clarys.

10.3.1 Definition and recording of safety-relevant events

An adverse event (ADVERSE EVENT) AE) is any unfortunate medical occurrence in a study subject who is exposed to a single application of a topical product (as listed in Chapter 8.1.1) that is not necessarily causally related to the study process. An AE can therefore be any adverse and unintended sign, symptom, or temporal illness with the use of an intervention product (according to Chapter 8.1.1), either or in relation to the medical intervention product (according to Chapter 8.1.1). The package leaflets

of the products used here describe possible side effects. These include skin itching, redness, burning as occasional side effects, eczematous skin lesions as rare and pronounced hypersensitivity reactions as very rare side effects.

According to swissethics.ch, a serious adverse event (SAE) is classified as any unfortunate medical occurrence that results in death, is life-threatening, requires or prolongs hospitalization of the subject, results in a persistent or significant disability/inability, or is a congenital anomaly/birth defect. In our study, SAE is not expected due to the possible side effects described in the product package inserts and/or product patient information.

The topical products used in this study are applied according to their package leaflet (not on mucous membranes, open, bleeding wounds / not near the eyes / not in case of hypersensitivity to one ingredient / not in subjects with bronchial asthma / not in subjects with renal insufficiency / not in children, pregnant women, during breastfeeding / do not cover with bandage or compress / do not cover several preparations at the same time on the same skin area). The contraindications and precautions described in the respective package leaflets are taken into account in the health questionnaire and the screening test. Thus, possible vulnerable subjects are recorded before the actual product application and excluded from the study. In addition, the one-time product application is below the recommended dosage according to the package inserts (massage briefly several times a day (max. five times) in a thin layer without pressure / rub in a sufficient amount on desired parts of the body).

If the application of the topical product leads to a side effect described above, this is classified as a safety-relevant event by the study leader. For the affected study participant, the study is completed at this time, and the data already collected will be processed as described in chapters 7.4 and 9.1.6.

The subject-specific demographic data collection sheet (page 4) records:

- Date and time of the incident
- Course of the incident
- Persons involved & witnesses
- Study ID (specified by the CEC)
- Personal data of the person concerned (if not previously recorded)

10.3.2 Reporting of Safety related events

In accordance with Art. 37, Art. 42, Art. 43

10.3.3 Notification of a security-relevant event

A safety-related event is logged and immediately reported to the sponsor investigator (head of the research laboratory), study management and supervisor of the study.

The CEC will be informed as soon as possible and appropriate changes will be made to the protocol of the study. Further explanations can be found in chapter 2.10. Safety and protective measures must be reported to the responsible CEC within two days.

The report continues to the business liability insurance (Basler Versicherung) of Thim van der Laan AG in Landquart.

11 STATISTICAL METHODS

11.1 Hypotheses & Factors

*Local change in skin characteristics during and after a topical application of a **warming** product*

Perfusion of skin microcirculation

H0 The perfusion of the skin microcirculation does not change significantly during and after the topical application of a warming product to the collateral side.

H1 The perfusion of the skin microcirculation changes significantly during and after the topical application of a warming product to the collateral side.

Erythema formation

H0 Erythema formation does not change significantly during and after topical application of a warming product to the collateral side.

H1 Erythema formation changes significantly during and after topical application of a warming product to the collateral side.

Skin surface temperature

H0 The skin surface temperature does not change significantly during and after the topical application of a warming product to the collateral side.

H1 The skin surface temperature changes significantly during and after the topical application of a warming product compared to the collateral side.

Oxygen saturation of the superficial muscles

H0 The oxygen saturation of the superficial muscles does not change significantly during and after the topical application of a warming product to the collateral side.

H1 The oxygen saturation of the superficial muscles changes significantly during and after the topical application of a warming product to the collateral side.

Subjective temperature perceptions

H0 The subjective temperature perception does not change significantly during and after the topical application of a warming product to the collateral side.

H1 The subjective temperature perception changes significantly during and after the topical application of a warming product compared to the collateral side.

*Local change in skin characteristics during and after a topical application of a **cooling** product*

Perfusion of skin microcirculation

H0 The perfusion of the skin microcirculation does not change significantly during and after the topical application of a cooling product to the collateral side.

H1 The perfusion of the skin microcirculation changes significantly during and after the topical application of a cooling product to the collateral side.

Erythema formation

H0 Erythema formation does not change significantly during and after topical application of a cooling product to the collateral side.

H1 Erythema formation changes significantly during and after topical application of a cooling product to the collateral side.

Skin surface temperature

H0 Skin surface temperature does not change significantly during and after topical application of a cooling product to the collateral side.

H1 The skin surface temperature changes significantly during and after the topical application of a cooling product with respect to the collateral side.

Oxygen saturation of the superficial muscles

H0 The oxygen saturation of the superficial muscles does not change significantly during and after the topical application of a cooling product to the collateral side.

H1 The oxygen saturation of the superficial muscles changes significantly during and after the topical application of a cooling product to the collateral side.

Subjective temperature perceptions

H0 The subjective temperature perception does not change significantly during and after the topical application of a cooling product to the collateral side.

H1 The subjective temperature perception changes significantly during and after the topical application of a cooling product compared to the collateral side.

A 2-factor analysis is carried out.

Factor 1:Intervention (warming product versus control / cooling product versus control)

Factor 2:Time (baseline, 0min, 10min, 20min, 30min, 40min, 50min, 60min postal application)

11.2 Sample size

The sample size in the literature varies greatly. The planned number of 105 subjects is within the wide range and is expedient, time-wise and financially feasible for the study.

11.3 Criteria for the statistical use of data in the case of incomplete data sets

Only data from subjects who have completed the entire protocol will be included in the study. This ensures that all data has been collected under the same conditions and thus remains homogeneous and comparable.

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11.4 Scheduled analyses

11.4.1 Datasets and Data Population

Only complete data sets will be included in the study. Data that contains only part of the protocol is not included in the analysis. No new test subject is being sought to replace the missing data.

11.4.2 Primary Analysis

The statistical data analysis will be carried out by Dr. Michael Villiger after completion of the data collection of the entire project.

Repeated measures analysis of variance (MANOVA)

2 factors:

Factor 1: Intervention (warming product versus control / cooling product versus control)

Factor 2: Time (baseline, 0min, 10min, 20min, 30min, 40min, 50min, 60min postal application)

The significance level is set at $P < 0.05$, and the statistical data analysis is carried out with SPSS V. 23.

11.4.3 Secondary Analysis

Nonexistent.

11.4.4 Interim analyses

The data is processed after the project ends. No additional interim analyses are planned.

11.4.5 Security analyses

No security analyses are provided.

11.4.6 Deviations

Deviations from the planned statistical analysis are recorded and justified and reported to the CEC in the annual report.

11.5 Drop-outs and missing data

If a test subject does not complete the experiment, any data that has already been collected is destroyed and is not included in the final data analysis.

12 QUALITY ASSURANCE AND CONTROL

12.1 Data Archiving

12.1.1 Forms

Data protection and confidentiality are guaranteed and no personal data is presented or published. The signed declaration of consent, as well as the completed questionnaire with the other personal data and demographic and medical personal data are stored in the original as a study document in a locked filing cabinet. Only the head of the study (head of the research laboratory of the University of Applied Sciences and Arts Southern Switzerland, Physiotherapy Graubünden) has access (key possession) to this cabinet. The encryption of the identity of the test persons is not digitally recorded, i.e. surname, first name and date of birth are not digitally recorded in any way.

Direct access to the personal data will continue to be allowed only to authorized persons of the CEC.

12.1.2 Specification of forms

The data collected in writing is recorded in the form listed in the enclosures and is marked as study data. They are therefore subject to data protection and are stored in accordance with the information described in chapter 12.1.1.

12.1.3 Archiving of data

The data collected will be kept for 10 years. Data protection will continue to be guaranteed.

12.2 Data management

12.2.1 Data Management System

The raw data of the perfusion of the skin microcirculation (Laser Speckle Contrast Imager, Ultrasound X-Flow) are processed with the software "moorFLPI-2 full-field laser Perfusion Imager V1.1" and "esaote MyLab". The erythema formation is measured with the chromameter and read by the display device and transferred by hand to the raw data sheet. The skin surface temperature is also read from the digital display of the infrared thermometer and transferred by hand to the raw data sheet. The i-buttons are read out with the i-Button MMT software. The data from the thermal imaging camera is processed with the "Flir Research IR max" software. The oxygen saturation values of the muscles are stored on a PC by the software provided for this purpose by the company Swinco (PeriPedal v2.4.8). The subjective perceptual parameters with regard to temperature perception are asked orally and the answers are transferred by hand to the raw data sheet.

12.2.2 Data security and backup

The digital data (laser speckle contrast imager, ultrasound, chromameter, i-button, thermal imaging camera, Moxy) will be anonymized and treated confidentially, access to the personal data will not be allowed to third parties. The digital data collected is stored solely on the institute's own computers and is not passed on to any external persons or transferred to other computers. Access to the computers of the research laboratory at the "Thim van der Laan" University College Physiotherapy is only granted to the principal investigator and the investigators (listed in Chapter 1), as well as persons authorized by the CEC.

12.2.3 Analysis and archiving

After collection, the digital data is encrypted and stored on another external hard drive for further backup. This is stored in a locked filing cabinet to ensure data protection.

12.2.4 Validation of electronic data

Immediately after data collection, the quality of the data is checked and verified with the help of the visual representation.

12.3 Monitoring

The data collected can be viewed by authorised persons at any time (see Chapter 12.2.2)

The study is to be monitored by the following person:

Prof. Dr. Peter Clarys

Vrije Universiteit Brussels
Faculty of Physical Therapy
Pleinlaan 2, 1050 Brussels
peter.clarys@vub.ac.be

12.4 Audits and inspections

A report on the current status of the study is given orally to the study supervisor (Prof. Dr. Peter Clarys) on a monthly basis. This also includes demonstrating and presenting results and statistical analyses.

An annual report on the course of the study will be submitted to the CEC. Authorized persons of the CEC can view the data forms as well as the digital data on the institute's own computers at any time.

Data protection is guaranteed at all times.

12.5 Confidentiality and data protection

The examiners ensure that the privacy of the participant is guaranteed. In particular, data protection and confidentiality are guaranteed and no personal data is presented or published. The signed declaration of consent, as well as the completed questionnaire with the other personal details, are kept in the original as a study document in a locked filing cabinet.

The digital data will be anonymized and treated confidentially, and access to the personal data will not be allowed to third parties. The digital data collected is stored solely on the institute's own computers and is not passed on to any external persons or transferred to other computers.

Direct access to the personal data is only allowed to authorized persons of the CEC.

12.6 Retention of biological material and health-related data

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13 PUBLICATION AND DISCLOSURE OF DATA

The examiners ensure that the privacy of the participant is maintained. In particular, the data protection and confidentiality of the data are guaranteed and no personal data is presented or published nor passed on to outsiders and unauthorized persons.

14 FUNDING AND SUPPORT

14.1 Financing

The study is funded by the University of Applied Sciences and Arts Southern Switzerland, Physiotherapy Graubünden. The auditors are employed by this institute and are remunerated for their work on this study in accordance with their employment contracts. No further support is needed.

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15 INSURANCE

There is a public liability insurance policy with Baloise Insurance for the Thim van der Laan University College Physiotherapy in Landquart, where the study is being conducted.

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17 APPENDIX

1. Subject information, informed consent and demographic data (health questionnaire)
2. Recruitment of test persons (advertisements)
3. Data Collection Questionnaire Measurements (Screening Test and Measurement Data Sheet)
4. Protocol Synopsis
5. Employee
6. CVs of all examiners