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CLINICAL RESEARCH CENTER FOR HAIR AND SKIN SCIENCE

CONFIDENTIAL

Study Protocol

An exploratory randomized controlled study to evaluate the effect of a basic skin care product on the structural strength of the dermo-epidermal junction

Code: CRC-SP-A-31

Version 1.0, February 28, 2018

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1 Administrative Information

1.1 Title

An exploratory randomized controlled study to evaluate the effect of basic skin care products on the structural strength of the dermo-epidermal junction

1.2 Trial registration

Will be done at clinicaltrials.gov after positive approval by the Ethics Committee.

1.3 Protocol version

Version 1, February 28, 2018

1.4 Funding

This investigator-initiated study (IIS) is conducted and funded by the Clinical Research Center for Hair and Skin Science, Department of Dermatology and Allergy, Charité – Universitätsmedizin Berlin.

1.5 Roles and responsibilities

Project leader and Principal Investigator

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2 Introduction

2.1 Background and Rationale

The world population is growing, and the life expectancy has risen continuously in developed and developing countries. One consequence is an increase of age associated disabilities and diseases (Kuhlmey A, 2008). The process of aging involves numerous structural and functional changes also affecting the skin. The skin is often considered as the largest organ of the human body and it fulfills a variety of protective and regulatory functions. Compared to other organs, the skin is constantly exposed to harmful environmental influences. Besides intrinsic factors these external factors may accelerate skin aging. Due to its ageing-related loss of functional capacity the skin becomes susceptible to develop adverse skin conditions and dermatological diseases (e.g. skin dryness, fungal infections) (Chang *et al.*, 2013, Kottner *et al.*, 2015). Especially old aged, care depended, and severely ill individuals are at high risk for developing severe skin injuries and wounds (e.g. decubitus, skin tears) with high social and economic impact. Empirical evidence indicates that the reduced adhesion of the dermal-epidermal junction is a major pathophysiological predictor for these types of injuries.

In the field of skin research various non-invasive *in vivo* measurements are established, e.g. measurement of transepidermal water loss or stratum corneum hydration (du Plessis *et al.*, 2013). However, most of these measurements are indirect and these parameters only quantify the properties of the most superficial epidermal layers. The suction blister model is an artificial and controlled technique for dermal-epidermal separation along the dermo-epidermal junction (DEJ) (Unna, 1878, Kiistala and Mustakallio, 1964, Kiistala and Mustakallio, 1967). Empirical evidence suggests that the time of the dermal-epidermal separation (blistering time) is a measure of the dermo-epidermal adhesion. It has been proposed that the blistering time might be a clinically relevant parameter reflecting the mechanical integrity/stability of the dermo-epidermal junction (Hatje *et al.*, 2015).

Cosmetics and basic skin care products are widely used during the entire lifespan. People spent substantial amounts of money for that. In addition, topical skin care products are explicitly recommended to mitigate the increased risk in vulnerable populations, to protect the skin and to keep it intact. For instance, clinical practice guidelines recommend the use of topical skin care products to reduce the risk for pressure ulcer and skin tear development. However, the underlying working mechanisms of most basic skin care products are poorly understood. It is known that topically applied skin care products exhibit physical and chemical effects on and in the uppermost skin layers (e.g. the stratum corneum). Despite a few well known active ingredients (e.g. retinoids, vitamin C) exhibiting effects in the dermis, a particular skin protective effect of the vast majority of daily basic skin care applications on these deeper skin layers is unknown. Interestingly, results of a clinical trial including aged care residents from Australia suggest a protective effect of basic topical

skin care application for preventing skin tears, but the underlying mechanism remains unclear (Carville *et al.*, 2014).

2.2 Objectives

The main aim of this study is to investigate in a suction blister model, whether the use of a basic skin care formulation increases the mechanical integrity/adhesion of the dermo-epidermal junction.

2.3 Trial design

Exploratory randomized controlled study with a split body design on two investigational areas of the anterior side of both forearms.

3 Methods: Participants, interventions, and outcomes

3.1 Study setting

The study will be conducted at the Clinical Research Center for Hair and Skin Science (CRC), Department of Dermatology and Allergy, Charité – Universitätsmedizin Berlin. Screening, inclusion and all study visits including the induction of the suction blisters and the measurement procedures will be conducted at the CRC. Daily application of the skin care product will be conducted at home by the subjects.

3.2 Eligibility criteria

Inclusion criteria

- Healthy volunteers and/or with stable chronic condition (e.g. controlled hypertension)
- Female,
- 65 to 85 years,
- Caucasian,
- Phototype I to III according to the Fitzpatrick classification,
- Body Mass Index between 20 and 28 kg/m^2,
- Non-smoker of at least one year,
- Absence of skin diseases or scars in the skin area of interest,
- Absence of tattoos in the skin area of interest,
- Able to give written informed consent,
- Willing and able to fulfill the study requirements

Exclusion criteria

- Known or suspected defect of healing,
- Diabetes mellitus
- Any acute or chronic pathology that may interfere with the trial conduct, from investigator point of view,
- Acute or chronic wounds in the skin area of interest,
- Any skin affection which may interfere with the trial assessment, like urticaria,, psoriasis or scar on investigational areas,
- Medical history of skin cancer,
- History or establishment of diabetes or pre-diabetes,
- Any hyper-sensibility to one of the compounds of the investigational product,
- Any regular treatment which may affect the blood coagulation and hemostasis (anticoagulant medications, NSAID, etc.) before the suction blister induction (Visit 3 and Visit 5), one NSAID to treat headache within four days is allowed
- Any physical treatment (like laser or surgery) on the arms within the last 6 months,
- Use of topical or systemic treatment on the investigational areas within the past 4 weeks (topical hyaluronan, anti-inflammatory drugs, corticoids, retinoids, vitamin C, etc.) that would interfere with assessment and/or investigational treatments,
- Allergy to band-aid or to metals (such as nickel),
- UV sessions or strong sun exposure of the arms during the study period,
- Subject who cannot be contacted easily in case of necessity,
- Current participation in any other clinical study

3.3 Interventions

After giving informed consent and checking the in- and exclusion criteria, baseline skin measurements will be conducted (Table 3). After that one arm will be randomly selected. Subjects are instructed to apply on the selected forearm petrolatum (VASELINE, weiß Ph.Eur., Salbe). The other arm will remain untreated (control). The application of the skin care product will be twice a day in the morning and in the evening for 4, respectively 8 weeks. This should be done after washing or showering to allow the product to stay on the skin during day/ night.

Subject instructions

The subjects should inform the Investigator before using any systemic treatment which may interfere with the study assessments. Some treatments are prohibited throughout the study.

During the study, the subjects will be instructed ***not to***:

- have sun exposure or UV-light sessions on the investigational areas,
- Use any topical drug or cosmetic product on the investigational areas on both arms (except usual cleaning products) which may interfere with the trial assessment (topical hyaluronan, anti-inflammatory drugs, corticoids, retinoids, α-hydroxy acids, vitamin C).
- have physical treatments on the investigational areas.

3.3.1 Concomitant Treatments

Prohibited concomitant treatments

- Any topical drug (hyaluronan, anti-inflammatory drugs, corticoids, retinoids, vitamin C, corticoids, etc.) on investigational areas until the last assessment
- Any systemic treatment which may interfere with either investigational products or study conduct (anti-inflammatory drugs, corticoids, retinoids, vitamin C, corticoids, etc.) for more than 5 consecutive days until the last assessment
- Any treatment which may affect the blood coagulation and hemostasis (anticoagulant medications, NSAID, etc.)

Allowed concomitant treatments

The associated treatments which are considered necessary and not interfering with either investigational products or study conduct can be used on decision of the Investigator. The drug names (INN), their indication, dose and duration will be recorded in the CRF in concomitant treatments section.

3.4 Outcomes and variables

Because this is an exploratory study, no distinction is be made between primary and secondary outcomes.

Name	Method and metric	Time points of data collection
Blistering Time	- Visual inspection - Duration from start of suction pressure to appearance of first vesicles in minutes - Duration from start of suction pressure to development of full blister in minutes (Appendix 4)	Visit 3, Visit 5
Skin surface Temperature	- Measurement with Skin-Thermometer ST 500 (Courage+Khazaka electronic GmbH) - Means of duplicate measurements per skin area in °C per skin area	Visit 3, Visit 5
Stratum corneum hydratation (SCH)	- Corneometer CM 825 (Courage + Khazaka, Cologne, Germany) (Appendix 5) - Means of duplicate measurements per skin area in arbitrary units	Visit 1, Visit 2, Visit 3, Visit 4, Visit 5, Visit 6
Epidermal and dermal hydratation	- Measurement with MoistureMeterEpiD (Delfin Technologies) (Appendix 6) - Percentage of tissue water (0-100%) (0,5mm measurement depth)	Visit 1, Visit 2, Visit 3, Visit 4, Visit 5, Visit 6
Epidermal thickness	- OCT (Thorlabs, Lübeck, Germany), measurements according to Trojahn et al. 2015 µm) (Appendix 8)	Visit 1, Visit 3, Visit 5, Visit 6

Name	Method and metric	Time points of data collection
Age	Checking by looking at the ID card (metric)	Screening
Body temperature	Clinical thermometer in °C	Screening
Heart rate	Beats per minute (bpm)	Screening
Blood pressure	Millimeters of mercury (mmHg)	Screening
BMI (body height and weight)	kg/m^2	Screening
Phototype	Categories I, II, III	Screening

Both arms will be subdivided in two investigational areas, called “Area A” (upper part of the middle of the **right** volar forearm) respectively “Area C” (upper part of the middle of the **left** volar forearm) and “Area B” (lower part of the middle of the **right** volar forearm) respectively “Area D” (lower part of the middle of the **left** volar forearm) (Figure 1).
After 4 weeks (Visit 3) 2 suction blisters (Appendix 4) will be raised at the investigational Areas A or B at the right volar forearm (Figure 2). Another 2 suction blisters will be raised at the left volar forearm at the investigational Areas C or D (Figure 2). The allocation of the respective area for suction blister induction is decided via a randomization list.
After 4 additional weeks (Visit 5), 2 more suction blisters will be raised in each of the remaining so far non-blistered investigational Areas.

After the blister has been raised, the blister fluid will be punctured and a dressing applied to allow the wound to heal. The skin areas where suction blisters have been raised after 4 weeks will not be treated during the following 8 weeks.

Before any measurements or induction of the suction blisters, the study volunteers will be requested to acclimatize for 30 minutes at 40 to 60 % relative humidity and a temperature of 20 to 22 °C with having both forearms uncovered.

Sequence of measurements (Visit 1, 2, 3, 4, 5 and 6)

(1) Skin surface temperature
(2) Stratum corneum hydration (SCH)
(3) Epidermal and dermal hydration
(4) Skin thickness

Measurements will be performed two times per measurement area. Every value will be recorded separately.

Figure 1. Localization of investigational skin areas

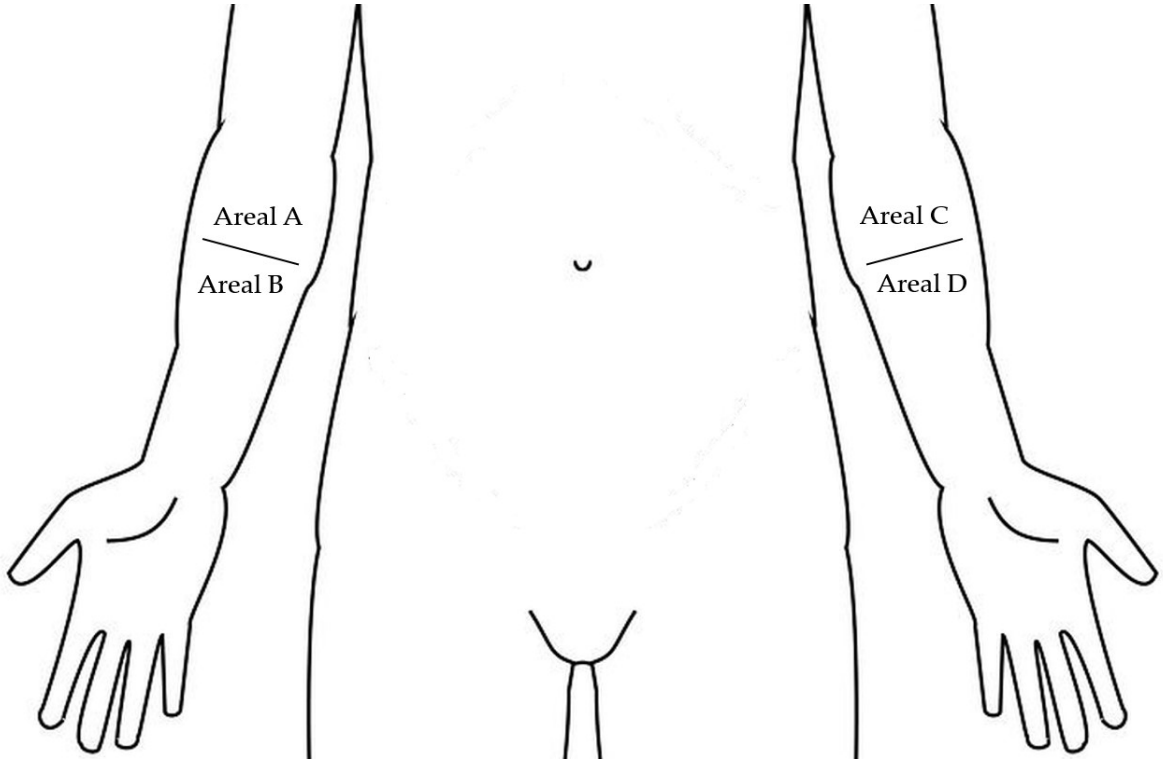
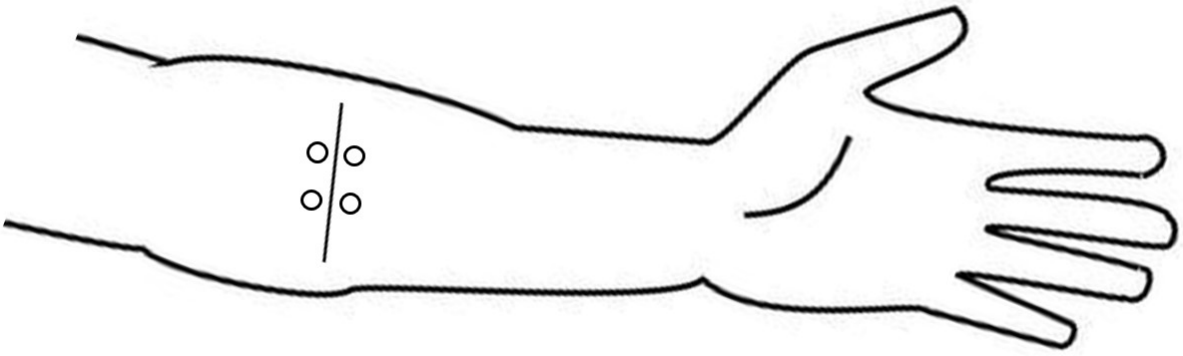


Figure 2. Localization of suction blisters



3.5 Participant timeline

Table 1. Participant timeline

	Visit 0 Screening	**Visit 1 Inclusion**	**Visit 2**	**Visit 3**	**Visit 4**	**Visit 5**	**Visit 6**
	D_{-14} to D_0	D_0	$D_{14\pm1}$	$D_{28\pm2}$	$D_{42\pm2}$	$D_{56\pm2}$	$D_{66\pm3}$
Informed consent	X						
Demography	X						
Medical history	X						
Vital signs	X						
Physical examination	X						
In-/exclusion criteria	X	X					
BMI	X						
Randomization of arms		X					
Instruction how to treat the treatment arm		X	X	X	X		
Handout of products		X		X			
Treatment		◄	———	———	———	►	
Record concomitant medication, therapies, procedures	X	X	X	X	X	X	X
Investigational sites identification		X					
Blister Induction*				X		X	
Check for blister healing					X		X
Stratum corneum hydratation		X	X	X	X	X	
Epidermal and dermal hydratation		X	X	X	X	X	
Epidermal thickness		X		X		X	
Record AEs		X	X	X	X	X	X
Return investigational products						X	

*Randomization

3.6 Sample size

Due to the explorative character of this study, a formal sample size estimation is not performed. It is planned to include 12 healthy female subjects.

Subject replacement
In this study, a subject withdrawn from the study for any reason will be replaced.

3.7 Recruitment

Subjects will recruited via advertisements and/or contacted directly.

4 Methods: Assignment of interventions

There will be a concealed random allocation of the treatment arm (left vs. right) and area of suction blister induction (“Area A”/ “Area C” vs. “Area B”/ “Area D”).

4.1 Allocation Sequence Generation

Two independent simple randomization lists (left vs. right arm and “Area A”/ “Area C” vs. “Area B”/ “Area D”) will be created by the data manager not involved in the study. The data manager will also prepare sequentially numbered opaque sealed envelopes containing the allocation.

4.2 Allocation implementation and concealment

The numbered opaque sealed envelopes are stored at the CRC. Envelopes containing the assignment to the treatment arm will be opened after confirming eligibility provision of informed consent at Day 0. Envelopes containing the assignment of suction blister area will be opened at visit 3.

4.3 Blinding

Due to the nature of the intervention, neither the investigators nor the participants will be blinded.

5 Methods: Data collection, management, analysis

5.1 Data collection methods

All data collectors will be trained in obtaining accurately the variables of interest. Paper source data (SD) will be used to document all study variables of interest (data collection forms see appendix 3).

Medical examination

The medical examination performed before inclusion will include a subject's interview on her medical history and a clinical examination, to make sure of the subject's eligibility.

Suction blister creation

The Suction blister model is an artificial and controlled technique for dermal-epidermal separation. Over the course of this study a total of 8 suction blisters with 8 mm in diameter are produced at the middle of the volar forearms of one volunteer. The comparisons of the blistering times (in minutes) will be used as outcome to detect possible treatment effects. Two suction blisters will be induced on each investigational area for two independent measurements of the blistering time. The technical procedure of suction blister wound creation is presented in the SOP Appendix 4.

5.2 Data management

The data manager creates an SPSS file and data of the SD are entered (single data entry). After data are entered, a random subset will be verified by an independent person (SD verification) who was not involved in the data entry so far.

5.3 Statistical methods

Demographic and other characteristics will be described using mean and spread parameters or proportions. The skin measurement results including the time(s) to blistering will be described using medians and interquartile ranges per skin area and time and displayed in grouped bar graphs. No statistical tests will be applied.

6 Methods: Monitoring

6.1 Data monitoring

Data monitoring is not planned.

6.2 Harms

Within this trial, the following definitions of adverse events will be used:

Adverse Event (AE)

Adverse events are defined in this study as any untoward medical occurrence, unintended disease or injury, or untoward clinical signs in patients, related to the intervention. Adverse events reported to the investigator must be recorded on the adverse event page of the data collection form and should be described.

Serious Adverse Event (SAE)

Adverse Event that:

i. leads to death;

ii. leads to a serious deterioration in the health of the subject, that either resulted in;

a life-threatening illness or injury, or

a permanent impairment of a body structure or a body function; or

prolonged hospitalization; or,

medical or surgical intervention to prevent life-threatening illness or injury or permanent impairment to a body structure or a body function; or

iii. led to foetal distress, foetal death or a congenital abnormality or birth defect.

Note: Planned hospitalization for a pre-existing condition, without serious deterioration in health, is not considered a serious adverse event.

7 Ethics and dissemination

7.1 Research ethics approval

An approval to conduct the study will be obtained from the local ethics committee of the Charité-Universitätsmedizin Berlin.

7.2 Protocol amendments

The ethics committee will be informed about possible study amendments.

7.3 Informed Consent

Subjects meeting the inclusion criteria must provide written informed consent prior to participation. The informed consent form (ICF) must be dated and signed by the study participant herself. The originally signed consent form is archived in the investigator site file. Study participants receive copies of the written information sheet, and the signed informed consent form.
The patient information sheet, informed consent form and all other documents handed out to the study participant will be submitted for approval to the ethics committee before use.
Any study participants can withdraw her consent at any time without giving reasons.

7.4 Confidentiality

All personal data are collected under pseudonymization. Each patient gets a distinct subject number. The investigator administrates the subject identification list, which includes the subject number as well as name, birthday and address of the subject. The access to this is limited, only the investigators as well as the authorized study staff, will have permission to inspect this list. All study-related information will be stored securely at the CRC. All participant information will be stored in locked file cabinets in areas with limited access. Digital data are stored on a secured digital server of the Charité-Universitätsmedizin Berlin.

7.5 Declaration of interests

None declared.

7.6 Access to data

Because this is an IIS, the data is owned by the responsible researcher and therefore has full access.

7.7 Ancillary and post-trial care

Not planned.

7.8 Dissemination policy

A clinical study report will be prepared. Results will be also made available at the trial register clinicaltrial.gov. The study results will be presented in an international scientific journal following the guidance of the CONSORT 2010 statement (Schulz *et al.*, 2010). Any publication will take account of the 'Uniform requirements for manuscripts submitted to biomedical journals'.

8 References

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9 Appendices

Appendix 1: Subject information leaflet (in German)
Appendix 2: Informed consent form (in German)
Appendix 3: Data collection forms
Appendix 4: Suction blister creation and time measurement
Appendix 5: Technical Procedure Corneometer
Appendix 6: Technical Procedure MoistureMeterEpid
Appendix 7: Procedure OCT
Appendix 8: Technical Procedure OCT-Bestimmung der epidermalen Hautdicke