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KLINIK FÜR DERMATOLOGIE, VENEROLOGIE UND ALLERGOLOGIE

Klinik mit zertifiziertem Qualitätsmanagementsystem nach DIN EN ISO 9001:2008

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CONFIDENTIAL

Study Protocol

Comparing the effects of three different support surfaces on the properties of heel and sacral skin after loading

Code: CRC-PU-A-23

Version 2.0, January 06, 2017

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Abbreviations

ADE	Adverse Device Effect
AE	Adverse Event
BfArM	Bundesinstitut für Arzneimittel und Medizinprodukte
CRC	Clinical Research Center for Hair and Skin Science
CRF	Case report form
DD	Device deficiency
EPUAP	European Pressure Ulcer Advisory Panel
ICF	Informed consent form
IIS	Investigator initiated study
NPUAP	National Pressure Ulcer Advisory Panel
PI	Principal Investigator
PPPIA	Pan Pacific Pressure Injury Alliance
PU	Pressure ulcer
SADE	Serious Adverse Device Effect
SAE	Serious Adverse Event
SCH	Stratum corneum hydration
SD	Source data
SOP	Standard operating procedure
TEWL	Transepidermal waterloss

1 Administrative Information

1.1 Title

Comparing the effects of three different support surfaces on the skin function of heel and sacral skin after loading

1.2 Protocol version

Version 1, September 25, 2015

1.3 Funding

This investigator initiated study (IIS) is conducted by the Clinical Research Center for Hair and Skin Science, Department of Dermatology and Allergy, Charité – Universitätsmedizin Berlin. The trial is supported by Stryker®. Stryker® provides the three support surfaces (IsoAir, IsoGel and basic foam mattress).

1.4 Roles and responsibilities

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2 Introduction

2.1 Background and Rationale

Pressure ulcers (PUs) are localized injuries of the skin and/or underlying soft tissues due to prolonged deformation (NPUAP, EPUAP, PPPIA 2014). In adults in supine position the lateral areas of the heel and the sacral area are most often affected (PU predilection sites). PUs are severe injuries and wounds causing a substantial burden on patients, caregivers, and on healthcare systems worldwide. There is common agreement, that effective PU prevention is of crucial importance to maintain skin and tissue integrity in individuals at risk. Besides risk assessment and repositioning the use of special PU preventive support surfaces are the key interventions in PU prevention. Support surfaces may be broadly classified into active (e.g. alternating mattresses) and reactive (e.g. special foams). These support surface allow a more even “pressure distribution” leading to lesser deformation of the skin and soft tissues and/or to alternating loading and off-loading to limit the time of localized compression.

In recent years the concept of “microclimate” received increasing attention. It is defined as the temperature, humidity, and air-flow on and near to the skin surface. The parameters of skin temperature and humidity are closely related to functional and mechanical skin properties and to the susceptibility to PU development (Gefen 2011, NPUAP, EPUAP, PPPIA 2014). Therefore, many support surfaces try to influence the microclimate as well. A major methodological challenge in current PU research is the lack of outcomes to measure the effects of preventive approaches. PU incidence is clearly the clinical most relevant parameter. However, using this dichotomous outcome well conducted RCTs require hundreds of patients, long recruitment and follow-up periods, and are expensive. In addition, there is a debate whether the current definition of PU incidence in clinical trials is really the best choice (Kottner, Gefen 2012). Widely agreed upon Core Outcomes Sets (Clarke, Williamson 2015) have not been developed in PU research so far (Nixon 2015). Attempts have been made, to identify possible other parameters serving as predictors or biomarkers for PU risk and/or early tissue damage, e.g. skin temperature, shear wave velocity based on ultrasound elastography, epidermal cytokines, or serum myoglobin. It is well known, that skin function for instance in terms of transepidermal waterloss (TEWL) is very sensitive marker of skin barrier changes. TEWL increases are usually associated with skin barrier impairments whereas TEWL decreases are associated with an intact or improved skin barrier (Rogiers et al. 2001). Using a standard hospital mattress, it was shown recently that this parameter shows a loading time depend increases in the lateral heel areas indicating subclinical skin damage (Kottner et al. 2015). Skin temperature and erythema increased as well; both being directly related to the risk of tissue damage. These functional parameters were also partly

related to changes in skin surface topography and elasticity (Dobos et al. 2015). Taken together, these results indicate that the prolonged loading causes changes in skin structure and function. PU preventive support surface modify the degree of skin and tissue deformation and/or skin temperature and moisture. Therefore, an association between the type and working mechanism of a PU support surface and skin function after loading is highly likely. Furthermore, such a relationship may be used to characterize and/or to quantify the performance PU support surfaces in terms of skin protection.

2.2 Objectives

The overall aim of this explorative study is to measure skin responses of the two most common PU predilection sites (heel, sacral skin) after two hours loading on three different support surfaces and the sternal skin (control area). The following objectives are determined:

(1) To measure the changes of skin temperature, erythema, stratum corneum hydration, TEWL, skin roughness and elasticity before loading (baseline) and after two hours loading at the right heel and sacral on three different support surfaces and the sternal skin area.

(2) To quantify possible differences in skin response between the support surfaces.

2.3 Trial design

This exploratory study is a randomized and controlled trial, with a cross-over design (every subject will lie on every support surface).

3 Methods: Participants, interventions, and outcomes

3.1 Eligibility criteria

Inclusion criteria

- Healthy, female volunteers
- 60 to 80 years
- Body Mass Index between 18.5 and 29.9 kg/m^2
- Non-Smoker of at least one year
- Absence of skin diseases or scars in the skin areas of interest
- Ability to move independently and to maintain supine and prone positions
- Able to give written informed consent
- No use of cosmetic products or topical applied drugs on the study areas at least 12 hours before measurement
- Skin phototype I to III according to Fitzpatrick classification
- Willing and able to fulfil the study requirements

These criteria are chosen because they reflect the target group and results will be comparable with the previous study (Kottner et al. 2015, Dobos et al. 2015). This would enhance interpretation.

Exclusion criteria

- Disability to maintain in supine or prone position
- Acute diseases
- Acute or chronic diseases with increased or decreased body temperature (≤ 35°C or ≥ 38,5°C, measured in the ear)
- History or establishment of Diabetes or pre-diabetes, cardiac or renal insufficiency, atopic dermatitis, psoriasis, chronic obstructive pulmonary disease (COPD)
- Acute or chronic wounds in the skin areas of interest
- Any skin affection which may interfere with the study assessment, e.g. tattoo, psoriasis or scar on the investigational sites
- Participation in another clinical study 4 weeks before inclusion visit
- Current participation in any other clinical study

3.2 Interventions

After giving informed consent and checking the in- and exclusion criteria, the subjects will be randomized into three study groups (three different support surfaces):

(1) Alternating Low Pressure mattress with low air loss function (IsoAir, stryker, USA)

(2) Reactive support surface, gel mattress (IsoGel, stryker, USA)

(3) Standard mattress (basic foam)

The support surfaces will be used according to the manufacturer instructions. Every subject will lie on every mattress. Therefore, every subject will have at least three visits in the study center of approximately 4 hours. The order of mattress use will be randomized for the visits.

The study volunteers will be requested, to acclimatize for 30 min at 40-60% relative humidity and a temperature of 20-22°C with having the right lateral heel, sacral and sternal skin uncovered. During this time the right lateral heel skin, the sacral and sternal skin will be marked in prone position. Once in prone position the baseline skin measurements on the right lateral heel and sacral skin will be conducted (order see below: Sequence of measurements), that no/minimal interferences between measurements occur (Kottner et al. 2014). After that, the participants will stay in supine position for two hours. The baseline sternal skin measurements will be performed immediately after the subjects turned into supine position. At the end of two hours the sternal skin measurements will be repeated. After two hours, the subjects turn into prone position again and the skin measurements on the right lateral heel and sacral skin will be conducted again to capture the effect of the two hour loading on the mattress. The measurements will be repeated after 20 min to observe the adjustments after offloading. Study procedures and measurements will be conducted always and only in the morning to minimize possible circadian influences. The procedures will be performed on all visits in the same way and order, only the support surface will change.

<u>Sequence of measurements:</u>
(1) TEWL
(2) Skin surface temperature
(3) Stratum corneum hydration (SCH)
(4) Erythema
(5) Epidermal and dermal hydration
(6) Skin elasticity
(7) Skin roughness
(8) Taking of OCT images (only for standard mattress (basic foam))

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

3.3 Outcomes and variables

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

Table 1. Outcomes

Name	Method and metric	Time points of data collection
TEWL	· Tewameter TM 300 (Courage + Khazaka, Cologne, Germany) · Means of duplicate measurements per skin area in g/m^2/h	BL, after 2 hours and 20 minutes after loading
Erythema	· Mexameter MX 18 · Means of duplicate measurements per skin area in arbitrary units	BL, after 2 hours and 20 minutes after loading
SCH	· Corneometer CM 825 (Courage + Khazaka, Cologne, Germany) · Means of duplicate measurements per skin area in arbitrary units	BL, after 2 hours and 20 minutes after loading
Skin roughness	· Visioscan VC 98 · Images of skin structure · Rz and Ra in µm	BL, after 2 hours and 20 minutes after loading
Skin elasticity/ deformability	· Cutometer MPA 580 (Courage& Khazaka, Germany) · Means of duplicate measurements per skin area in mm	BL, after 2 hours and 20 minutes after loading
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	BL, after 2 hours and 20 minutes after loading
Epidermal and dermal hydration	· Measurement with MoistureMeterEpiD (Delfin Technologies) · Percentage of tissue water (0-100%) (0,5mm measurement depth)	BL, after 2 hours and 20 minutes after loading
Epidermal/ dermal characteristics (only for basic foam)	· OCT (Thorlabs, Lübeck, Germany), image processing and measurements according Trojahn et al. 2015 · Descriptive	BL and after 2 hours
Skin thickness (only for basic foam)	· OCT (Thorlabs, Lübeck, Germany), image processing and measurements according Trojahn et al. 2015 · µm (metric)	BL and after 2 hours

Table 2. Variables

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

3.4 Participant timeline

Table 3. Participant timeline

	Inclusion	**V1, V2, V3***				
	0 to 30 min	30 min (acclimatization)	Baseline measurements	2 hours (supine position)	Prone position	Prone position after 20 minutes
In-/exclusion criteria	x					
Signed Informed consent	x					
Demographics	x					
BMI	x					
Physical examination	x					
Marking of measurement areas	x					
Randomization	x					
Heart rate	x					
Blood pressure	x					
Body temperature	x					
Skin measurements at sternal skin			x	x		
Skin measurements at right heel and sacral skin			x		x	x
Adverse events monitoring		x	x	x	x	x

*same protocol on V1, V2, V3 (only change of support surface depending on randomized order), V3: end of study

3.5 Sample size

Due to the explorative nature of this study, a formal sample size estimation is not performed. However, considering the data of the previous study on a standard hospital mattress (Kottner et al. 2015) with n = 15, it is for instance possible, to detect a true difference in mean TEWL changes of approx. -8 or 8 g/m^2/h with a probability of (power) 0.8 (alpha-level = 0.05) with an assumed standard deviation of 10 g/m^2/h. Observed TEWL changes at the heel skin were actually higher. Therefore we assume that the chosen sample size is sufficient to detect differences in support surface performance if they exist.

3.6 Recruitment

Potentially relevant subjects will be invited directly to participate by using the subject data base of the Clinical Research Center for Hair and Skin Science. The volunteers will be contacted by telephone.

4 Methods: assignment of interventions

4.1 Assignment of interventions

The subjects will be randomized into one of six possible randomization orders (Table 4).

Table 4. Randomization orders

1.	2.	3.	4.	5.	6.
Mattress **A**	Mattress **A**	Mattress **B**	Mattress **B**	Mattress **C**	Mattress **C**
Mattress **B**	Mattress **C**	Mattress **A**	Mattress **C**	Mattress **A**	Mattress **B**
Mattress **C**	Mattress **B**	Mattress **C**	Mattress **A**	Mattress **B**	Mattress **A**

A = Alternating Low Pressure mattress with low air loss function (IsoAir, stryker, USA)

B = Reactive support surface, gel mattress (IsoGel, stryker, USA)

C = Standard mattress (basic foam)

4.2 Allocation concealment

Sequentially numbered opaque sealed envelopes containing the group assignment will be prepared and used. Envelope preparation will be done by the data manager of the CRC who is not involved in any study preparation or procedures at this stage.

4.3 Allocation implementation

The batch of sequentially numbered envelopes is stored at the CRC. Envelopes are opened after confirming eligibility and provision of informed consent.

4.4 Blinding

Due to the nature of the intervention study assistants and researchers will not be blinded. The data manager and statistician will be blinded.

5 Methods: data collection, management, analysis

5.1 Data collection and management

All data collectors will be trained in obtaining accurately the variables of interest (see 3.3). Paper source data (SD) will be used to document all study variables of interest. 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.

5.2 Statistical methods

Depending on the level of measurement (nominal, ordinal, continuous) variables will be described using absolute and relative frequencies or arithmetic means, medians and spread parameters (minimum, maximum, interquartile ranges, standard deviations). Statistical analyses will be primary descriptively including group comparisons for dependent samples.

6 Methods: monitoring

6.1 Data monitoring

Data monitoring is not planned.

6.2 Harms

Harms, like pain, persisting erythema for more than 30 minutes or possible irritant reactions, which occur immediately or after loading will be documented as an adverse event.

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

Device Deficiency (DD)

Inadequacy of a medical device with respect to its identity, quality, durability, reliability, safety or performance.

Note: Device Deficiencies include malfunctions, use errors, and inadequate labelling. All Device Deficiencies that could have led to a Serious Adverse Device Effect shall be reported in accordance with Serious Adverse Event reporting procedures.

Adverse Events (AE)

Any untoward medical occurrence, unintended disease or injury, or untoward clinical signs (including abnormal laboratory findings) in subjects, users or other persons, whether or not related to the investigational medical device.

Note: This definition includes events related to the investigational medical device or the comparator. This definition includes events related to the procedures involved. For users or other persons, this definition is restricted to events related to investigational medical devices.

Adverse Device Effect (ADE)

Adverse Event related to the use of an investigational medical device.

Note: This definition includes adverse events resulting from insufficient or inadequate instructions for use, deployment, installation, implantation, or operation, or any malfunction of the investigational medical device. This definition includes any event resulting from use error or from intentional misuse of the investigational medical device.

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. a life-threatening illness or injury, or
b. a permanent impairment of a body structure or a body function; or
c. prolonged hospitalization; or,
d. medical or surgical intervention to prevent life-threatening illness or injury or permanent impairment to a body structure or a body function;

Serious Adverse Device Effect (SADE)

Adverse Device Effect that has resulted in any of the consequences characteristic of a Serious Adverse Event.

According to the Guidelines on Medical Devices (European Commission 2010) the above listed definitions only apply for non-CE marked devices and Conformité Européenne CE marketed devices outside the intended use. The support surfaces used in this study are already CE marketed and are used within the intended use. Therefore formal reporting modalities do not apply. However, (1) SAEs and (2) DD that might have led to a SAE will be reported not later than 2 calendar days to the manufacturer using the reporting form in Appendix 1.

7 Ethics and dissemination

7.1 Research ethics approval

The trial protocol and any amendments are prepared in accordance with the Declaration of Helsinki in the version of October 1996 (48th General Assembly of the World Medical Association, Somerset West, Republic of South Africa) and according to the SPIRIT guidance (Chan et al. 2013). This protocol and the informed consent form will be reviewed and approved by the responsible ethics committee. This study involves medical devices classes I and IIb. Because the product is CE certified already an application to the Bundesinstitut für Arzneimittel und Medizinprodukte (BfArM) is not needed (see MPG-Law § 23b). An approval to conduct the study will be obtained from the local ethics committee of the Charité-Universitätsmedizin Berlin.

This study inclusion procedure is considered ethically sound, because adverse events by using low pressure mattress with low air loss function or gel mattress at heels and the sacral skin to prevent skin ulcerations have not been reported so far.

7.2 Protocol amendments

The ethics committee will be informed about possible study amendments.

7.3 Consent

Subjects meeting the inclusion criteria must provide written informed consent prior to participation. The informed consent form (ICF) will meet the requirements proposed by the ethics committee of the Charité. 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

Related to this PU trial the following possible conflicts of interests are disclosed:

• JK is member of the EPUAP executive board.

All other study team members have no possible conflicts of interest regarding PU research to declare.

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 Dissemination policy

A clinical study report will be prepared regarding relevant headings of the ICH E3 guideline. The study results will be presented in an international scientific journal following the guidance of the CONSORT 2010 statement (Schulz et al. 2010).

8 References

Clarke M, Williamson P. Core outcome sets and trial registries. Trials. 2015;16(1):216.

Dobos G, Gefen A, Blume-Peytavi U, Kottner J. Weight-bearing-induced changes in the microtopography and structural stiffness of human skin in vivo following immobility periods. Wound Repair Regen. 2015;23(1):37-43.

Gefen A. How do microclimate factors affect the risk for superficial pressure ulcers: a mathematical modeling study. J Tissue Viability. 2011;20(3):81-8.

Kottner J, Dobos G, Andruck A, Trojahn C, Apelt J, Wehrmeyer H, Richter C, Blume-Peytavi U. Skin response to sustained loading: A clinical explorative study. J Tissue Viability. 2015 May. [Epub ahead of print]

Kottner J, Gefen A. Incidence of pressure ulcers as primary outcomes in clinical trials: a comment on McInnes et al. (2012). Int J Nurs Stud. 2012;49(3):372-4.

Kottner J, Ludriksone L, Garcia Bartels N, Blume-Peytavi U. Do repeated skin barrier measurements influence each other's results? An explorative study. Skin Pharmacol Physiol. 2014;27(2):90-6.

National Pressure Ulcer Advisory Panel, European Pressure Ulcer Advisory Panel, Pan Pacific Pressure Injury Alliance. Prevention and Treatment of Pressure Ulcers: Clinical Practice Guideline. Emily Heasler (Ed.). Cambridge Media: Osborne Park, Western Australia; 2014.

Nixon J. Outcomes for Pressure Ulcer Trials (OUTPUT). Comet-database. Retrieved from http://www.comet-initiative.org/studies/details/283

Rogiers V; EEMCO Group. Skin Pharmacol Appl Skin Physiol. 2001;14(2):117-28. EEMCO guidance for the assessment of transepidermal water loss in cosmetic sciences.

Schulz KF, Altman DG, Moher D; CONSORT Group. CONSORT 2010 statement: updated guidelines for reporting parallel group randomised trials. BMJ. 2010 Mar 23;340:c332. doi: 10.1136/bmj.c332.

Appendix 1. SAE reporting form

MEDDEV 2.7/3 SAE Report Table- V1															
EUDAMED - ID:															
Title of Clinical Investigation:															
CIP Number:															
Contact person (Name, Address, E-Mail, Telephone Number)										**Device type:**					
MS+NCA Reference Numbers for all participating Countries:										**Reference Member State:**					
No. of Patients enrolled to date (date of report):										**No. of Invest. Devices used to date**					
Date of Report:															
Status: a, m, u	**Date Sponsor received Report of SAE**	**Country**	**Study Center**	**Patient ID Code**	**Date of Procedure/ First Use**	**Date of Event Onset**	**Event: Organ System**	**Description of event**	**action/ treatment/patient outcome**	**Assessment of Relationship to Procedure:** Yes No Possibly	**Assessment of Relationship to Investigational Device:** Yes No Possibly	**Unanticipated SADE yes/No**	**Treatment Arm:** Investigational Device/ Control Group/ blinded/ n.a.	**Event Status:** Resolved/ Resolved with Sequelae/ Ongoing/Death	**Date of Event Resolution**

Note: Submission of this report does not, in itself, represent a conclusion by the sponsor or the competent authority that the content of this report is complete or that the device(s) listed failed in any manner and/or that the device(s) caused or contributed to the alleged death or deterioration in the state of the health of any person.

Appendix 2. Setting of the IsoAir mattress (Stryker)