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CONFIDENTIAL

Protocol

Comparing the effects of three different dressings on the cutaneous response to pressure and shear of sacral skin: an exploratory crossover study

Code: CRC-SP-A-32

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1. Administrative Information

1.1. Title

Comparing the effects of three different dressings on the cutaneous response to pressure and shear of sacral skin: an exploratory crossover study.

1.2. Trial registration

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

1.3. Protocol version

Version 1

1.4. Financial support

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2. Introduction

2.1 Background and Rationale

Pressure ulcers (PUs), also called pressure injuries, are severe and unwanted cutaneous lesions and subcutaneous wounds caused by prolonged skin and underlying soft tissue deformation. In the supine position they predominantly occur near to bony prominences such as heels and the sacrum. The cornerstone of PU prevention is repositioning, early mobilization and the use of special support surfaces (National Pressure Ulcer Advisory Panel (NPUAP), European Pressure Ulcer Advisory Panel (EPUAP), Pan Pacific Pressure Injury Alliance (PPPIA) 2014).

In addition, empirical evidence suggests that the application of preventive dressings on PU predilection sites helps to prevent PU development (Clark et al. 2014). This is supported by results of a number of recent clinical trials (e.g. Santamaria et al. 2015, Kalowes et al. 2016, Forni et al. 2018) and is now also recommended in the latest Pressure Ulcer Prevention and Treatment Guideline (NPUAP, EPUAP, PPPIA 2014). The mode of action of PU preventive dressings includes mechanical cushioning and the reduction of shear loads within soft tissues and the reduction of the coefficient of friction between the dressing and the support surface (Call et al. 2015, Levy et al. 2015, 2017).

Many different dressings are on the market and the dressing performance is related to its material and structure. Results of *in vitro*, computer modelling, and *in vivo* studies indicate different effects on the skin microclimate, pressure reduction, and maybe also on clinical outcomes (e.g. Call et al. 2013, Dutra et al. 2015, Matsuzaki et al. 2015). However, results of laboratory or computer modelling studies are not automatically transferable to real-life situations. In addition, there are no high quality clinical trials with a direct head-to-head comparison of the most important competitors on the market. Therefore, it is not appropriate to generalize clinical study results of one dressing type to another (Gefen et al. 2016).

Next to the ‘hard’ clinical outcome ‘PU development’ there are a number of alternative biomarkers and parameters to characterize the response of the skin to prolonged loading and deformation. According to Bader and Worsley (2018) they may be classified into four categories: (1) ‘Monitoring of the interface’ (including interface pressure mapping, shear, friction and microclimate measurement); (2) ‘Biophysical skin sensing’ (skin measurements); (3) ‘Biomarkers indicative of early skin damage’ (for example cytokines, chemokines, lactate on the skin surface, blood markers such as CRP); (4) ‘Medical imaging’ (including MRI, CT, ultrasound, colour measurements). Skin functional parameters such as erythema or stratum corneum hydration and structural parameters, like structural stiffness, have been successfully used in PU prevention research (Dobos et al. 2015, Kottner et al. 2015). These parameters are able to discriminate effects of different loading intensities and to measure PU preventive device performance (Tomova-Simitchieva et al. 2017). Recently it also could be

shown that there are associations between structural and functional skin changes at the heel and sacral area during loading (Pfannes et al. 2018).

(Subclinical) injuries to the stratum corneum stimulate the production of inflammatory cytokines. In clinical PU research, it has been shown that levels of IL-1alpha are also useful to measure the inflammatory response of the skin due to mechanical deformation. It was demonstrated that the increase of cytokines is related to mechanical loading intensity (De Wert et al. 2016, Bader, Worsley 2018) and thus are suitable biomarkers to measure early skin response due to deformation.

Recently, Mölnlycke Healthcare sponsored a study to investigate the effects of pressure ulcer preventive dressings on loaded and unloaded skin. Between July and October 2016 n = 8 healthy males (mean age 28 years) were included into an exploratory cross-over trial to explore the effects of Mepilex® Border Sacrum and Heel on the sacral and heel skin with and without loading (CRC-SP-A-26). Main results were that the dressings have an occlusive effect in terms of accumulation of heat and humidity, but this was not very different to loaded skin without dressings. This increase of stratum corneum and epidermal hydration softened the skin and contributed to changes of skin topography. Finally, results indicate that loading increased the inflammatory cytokine IL-1alpha and that this increase seemed to be slightly lower when a dressing was applied. This may indicate that the dressing may reduce the inflammatory response. The detailed results are reported in the full study report version 2, December 2016.

Overall, the study results indicate that cutaneous structure and function parameters can characterize the response of heel and sacral skin due to loading and that it is possible to measure a particular dressing effect. However, the sample size was small, the loading duration of 2.5 hours was short, shear forces were reduced to a minimum, and the sample was not representative for patients at PU risk. Therefore, there is a need to repeat this study using a more relevant target group such as aged females, to increase the mechanical loading in terms of pressure and shear, and to compare directly different dressing types.

2.2 Aims

The overall aim of this study is to measure the effects of Mepilex® Border Sacrum on the skin structure and function during mechanical loading compared to (1) no dressing, (2) ALLEVYN Life Sacrum and (3) Optifoam® Gentle Liquitrap Sacrum.

The following objectives are determined:

(1) To measure the changes of skin temperature, stratum corneum hydration, erythema and skin roughness, (2) to evaluate clinical signs of pain and erythema and (3) to determine IL-1alpha and total protein of the sacral skin before loading (baseline) and after three and a

half hours loading with or without application of a dressing (Mepilex® border, ALLEVYN Life Sacrum, Optifoam® Gentle Liquitrap Sacrum).

3. Methods: Participants, interventions, and outcomes

3.1 Study design

This study is an investigator initiated explorative randomized cross-over trial using intraindividual comparisons. In total four interventions will be compared at the sacral skin (Table 1).

3.2 Study setting

The study will be conducted at the Clinical Research Center for Hair and Skin Science (CRC) at the Department of Dermatology and Allergy, Charité – Universitätsmedizin Berlin.

3.3 Eligibility criteria

Inclusion criteria

- Healthy female volunteers
- 65 to 80 years
- Body Mass Index 18.5 to 29.9 kg/m2
- Non-smoker of at least one year (including electronic-cigarettes)
- Informed consent
- Being free of any clinical dermatosis in the investigational area
- Intact sacral skin without scars
- Skin phototype I, II, or III (according to Fitzpatrick)
- No regular use of leave-on products on the sacral skin
- Willing and able to fulfil the study requirements

Exclusion criteria

- Disability to maintain in supine or prone position
- Acute diseases
- Known hyper-sensibility or allergy to the study product or any of its ingredients
- Extensive UV exposure 4 weeks before study inclusion
- Use of topical treatment on the investigational areas or systemic treatment within the 4 past weeks (topical hyaluronan, anti-inflammatory drugs, corticoids, retinoids, NSIDS etc.) that would interfere with assessment and/or investigational treatments
- Medical history of skin cancer
- History of established Diabetes mellitus, cardiac or renal insufficiency, COPD

• Chronic inflammatory skin disorders such as atopic dermatitis, psoriasis, lichen planus
• Participation in another study 4 weeks prior to study start

3.4 Study procedures and interventions

Volunteers will come to the study centre for four visits. In between, there are at least 3 weeks to prevent possible carry over effects. Therefore, the entire duration of one subject will be at least 9 weeks. The duration of one study visit per subject is approximately 5 hours. After four visits, each volunteer will have received each intervention once (A, B, C and D, see Table 1).

Table 1. Experimental interventions for the sacral skin

Intervention	Dressing
A	None
B	Mepilex® Border Sacrum
C	ALLEVYN Life Sacrum
D	Optifoam® Gentle Sacrum

After giving informed consent, subjects will lie down in supine position on a standard hospital mattress for a maximum of 10 minutes. Then subjects will turn around into prone position. Two fields of equal size (each 2cm x 2.5cm) will be marked with a skin pen, one for the baseline and one for the follow-up measurements. If an erythema has occurred at the sacral area during the 10 minutes in supine position, the investigational site will be marked within the reddened skin area. In case of no erythema, the test area will be identified by feeling the most protuberant point at sacrum. After marking the measurement area the subjects will acclimatize under standardized room temperature and humidity conditions (22±2°C, 40 to 60% rel. humidity) for 30 minutes with having the sacral skin uncovered. Subjects may lay (on the side) or sit during this period but must make sure that the investigational area is uncovered. After that, subjects will move into prone position and the following baseline measurements will be conducted according to CRC standard operating procedures (SOPs):

(1) Measurement of skin surface temperature
(2) Measurement of SC hydration (SCH)
(3) Measurement of Erythema index (EI)
(4) Visioscan images to measure Rz, Ra
(5) Cyanoacrylate skin surface stripping (CSSS), to determine IL-1alpha and total protein of the sacral skin.

In addition to the instrumental measurements, erythema and pain will be evaluated clinically.

The measures of skin surface temperature, SCH and EI will be performed three times per measuring round. Two duplicate Visioscan images will be taken. CSSS will be performed at the end.

After the baseline measurements a randomization envelope will be opened to allocate the subject to one of the intervention groups A, B, C or D (see Table 1). The dressings (B, C, D) will be applied or the skin will be left uncovered (A), followed by a 3.5 hours loading period. The subject will lie in supine position on a standard hospital mattress. Every 30 minutes the head of the bed will be elevated to 45° for five minutes. During these five minutes, the participants will be instructed to bend their knees and to drag the feet repeatedly forth and back 10 times. Then the head of bed will be moved back again and the subjects can relax. The whole exercise will be done six times, after 0.5, 1, 1.5, 2, 2.5 and 3 hours.

After 3.5 hours loading time in supine position the subjects will move into prone position. In case of interventions B, C or D the dressings will be removed. Then all skin measurements and CSSS will be conducted again. After the end of the measurements and procedures, subjects will leave the study site. They will come back for another three times completing the remaining interventions.

3.5 Participant timeline

Table 2. Individual participant timeline per visit

Hours	0.0	0.5	1.0	1.5	2	2.5	3.0	3.5	4.0	4.5	5.0	5.5
In-/exclusion criteria[1]	x											
Informed consent[1]	x											
Demographics[1]	x											
Medical examination[1]	x											
Skin inspection[1]	x											
Supine position for 10 minutes	x											
Marking of investigational areas		x										
Acclimatization for 30 minutes with sacrum uncovered		←	→									
Intervention												
Randomization of treatments			x									
Supine position				←	—	—	—	—	—	—	→	
Elevation of head of bed, bending knees and moving heels on the mattress back and forth 10x					x	x	x	x	x	x		
Clinical evaluation												
Pain			←	—	—	—	—	—	—	—	→	
Erythema			x								x	
Measurements												
SCH			x								x	
Erythema index			x								x	
Skin surface temperature			x								x	
Visioscan Rz, Ra			x								x	
CSSS (Cytokines IL-1, total protein)			x								x	
Adverse events monitoring and documentation	←	—	—	—	—	—	—	—	—	—	—	→

[1]Inclusion visit only

3.6 Variables and outcomes

Due to the explorative nature of this study, no distinction between primary, secondary or other variables is made (Table 3).

Table 3. Variables and outcomes

Name	Method and metric
Skin phototype	• Classification according to Fitzpatrick (nominal)
Height	• Measurements in the CRC • m (metric)
Weight	• Measurements in the CRC • kg (metric)
Age	• Checking by looking at the ID card • metric
Sacral pain	• Subjects' self-report • Pain (yes/no) (nominal) • Time to pain reporting in minutes (metric)
Erythema	• Visual inspection • VAS (metric)
Skin surface temperature	• Skin thermometer based in infrared technique (Courage and Khazaka Electronic GmbH) • °C (metric)
SCH	• Noninvasive instrumental measure using the Corneometer CM 825 (Courage and Khazaka Electronic GmbH) • Arbitrary units, A.U. (metric)
EI	• Noninvasive instrumental measure using the Mexameter MX18 (Courage and Khazaka Electronic GmbH) • Arbitrary units, A.U. (metric)
Rz, Ra, Rmax	• Visioscan VC 98 (Courage and Khazaka Electronic GmbH) • µm (metric)
Cytokines	• Cyanoacrylate skin surface stripping (CSSS) (or another sampling method) • IL-1, total protein in pg/µg • ELISA

3.7 Sample size

Due to the exploratory nature of this trial a formal sample size calculation is not performed. We plan to include n = 12 female subjects.

3.8 Recruitment

Potentially relevant subjects will be invited directly to participate by using advertisement and/or announcements 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

After the baseline measurements are completed, opaque envelopes will be opened to assign the treatment order. In order to minimize bias, the product allocation will be randomized. A computerized simple 1:1:1:1 randomization scheme for four study visits will be applied for the sacral skin for n = 12 subjects. An example of a possible allocation is displayed in Table 4.

Table 4. Example for order of experimental interventions for the sacral skin

Subject number	Dressing application order visits 1, 2, 3, 4
1	C → A → D → B
2	B → D → C → A
3	A → C → D → B
4	D → A → B → C
5	B → A → C → D
6	A → C → B → D
7	B → C → A → D
8	…
9	…
10	…
11	…
12	C → B → D → A

4.2 Allocation concealment

During the trial preparation the data manager, who is not involved in the trial and uses appropriate software, will create this randomization scheme independently. The scheme will not be revealed to the investigators. Sequentially numbered opaque sealed envelopes containing the randomized intervention order will be used.

4.3 Allocation implementation

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

4.4 Blinding

Due to the nature of the intervention subjects, study assistants, and researchers will not be blinded. The data manager will be blinded. Emergency unblinding is not foreseen.

5 Methods: data collection, management, analysis

5.1 Data collection and management

All study data will be recorded on paper source data and subsequently entered into an electronic database. After data are entered, a random subset will be verified by an independent person (source data verification) who was not involved in the data entry. All aspects of Data Management is managed by properly trained staff at Charité.

5.2 Statistical methods

Demographic characteristics will be described using numbers, proportions, means and standard deviations. Metric outcomes will be described using mean and spread parameters per intervention and time point. Baseline and follow-up parameters will be compared descriptively.

6 Methods: monitoring

6.1 Monitoring

One monitoring visit will be done by the Charité Coordinating Center for Clinical Studies, comprising the following tasks:

- Checking the existence of study participants
- Checking the existence of informed consents
- Checking the completeness of the source data for one study participant

6.2 Harms

Harms, like pain, persisting erythema lasting 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 Event (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; or

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 silicone dressings 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

An approval to conduct this 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 Consent

Subjects meeting all of the inclusion criteria and none of the exclusion 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 distinctive 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 Clinical Research Center for Hair and Skin Science. All participant information will be stored in locked file cabinets in areas with limited access. Electronical data are stored on a secured digital server of the Charité. Medical devices are stored securely at the Clinical Research Center for Hair and Skin Science in locked rooms in areas with limited access at appropriate temperature and humidity.

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9. 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.