Aus der Klinik für Dermatologie, Venerologie und Allergologie
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DISSERTATION

Anwendung topischer Produkte zum Erhalt der Hautintegrität im Alter und bei Pflegebedürftigkeit

Application of topical products to maintain skin integrity in aged and care dependent individuals

zur Erlangung des akademischen Grades

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und

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und

El Genedy M, Hahnel E, Tomova-Simitchieva T, Padula WV, Hauß A, Löber N, Blume-Peytavi U, Kottner J. Cost-effectiveness of multi-layered silicone foam dressings for prevention of sacral and heel pressure ulcers in high-risk intensive care unit patients: An economic analysis of a randomised controlled trial. Int Wound J. 2020;17:1291-1299.

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INHALTSVERZEICHNIS

ZUSAMMENFASSUNG

ABSTRAKT

Ältere, pflegebedürftige, immobile und schwer kranke Menschen haben ein erhöhtes Risiko, pathologische Hautveränderungen zu entwickeln. Ziel der vorliegenden Arbeit war es, verschiedene präventive topische Ansätze zur Erhaltung und Verbesserung der Hautintegrität im Alter und bei Pflegebedürftigkeit zu untersuchen.

Im Rahmen der vorliegenden Dissertation wurde eine systematische Übersichtsarbeit über Wirkung und Effektivität topischer Hautpflegeinterventionen zum Erhalt der Hautintegrität älterer Personen erstellt. Es wurden 63 Volltexte eingeschlossen, die über Behandlungseffekte von Interventionen zur Prävention unerwünschter Hauterscheinungen berichteten. Als unterstützend zur Erhaltung der Hautintegrität älterer Personen erwiesen sich die Verwendung milder Reinigungs- und die regelmäßige Applikation rückfettender Pflegeprodukte mit Zusatz von feuchtigkeitsbindenden Substanzen und einem niedrigen pH-Wert.

In einer explorativen, randomisierten, kontrollierten, klinischen Studie mit Split-Body-Design wurde die Wirkung eines Basishautpflegeprodukts zur strukturellen Stärkung alternder Haut bei n = 12 älteren Probandinnen (mittleres Alter 70,3 Jahre [SD 2,1]) untersucht. Mittels Saugblasenmethode wurde kontrolliert die Trennung von Dermis und Epidermis induziert und Zeitspannen bis zur Separation als Indikator für die dermo-epidermale Adhäsionsstärke verwendet. Nach Applikation des Pflegeprodukts wiesen Interventionsareale längere mediane Zeitspannen bis zur Separation der Hautschichten sowie durchgehend höhere epidermale Hydratationswerte im Vergleich zu den Kontrollarealen auf. Im Einklang mit Ergebnissen der systematischen Übersichtsarbeit zeigt sich, dass die regelmäßige Verwendung eines Basishautpflegeprodukts die dermo-epidermale Adhäsion älterer Personen verbessern kann. Die Saugblasenmethode und Messung der Zeitspannen bis zur Separation der Hautschichten stellen einen geeigneten Ansatz zur Quantifizierung der dermo-epidermalen Adhäsionsstärke im Rahmen der klinischen Forschung dar.

Eine randomisierte, kontrollierte, pragmatische, klinische Studie untersuchte die Wirksamkeit mehrschichtiger Silikonschaumverbände zur Dekubitusprävention bei n = 422 Hochrisikopatienten und -patientinnen auf Intensivstationen. Die Verbände wurden in der Interventionsgruppe zusätzlich zu den Standardmaßnahmen der Dekubitusprävention an Sakrum und Fersen appliziert. Die kumulative Dekubitusinzidenz betrug 2,8 % in der Interventions- und

10,5 % in der Kontrollgruppe (Relatives Risiko = -0,26; 95 %-Konfidenzintervall [KI] = 0,11-0,62; Absolute Risikoreduktion = 0,08; 95 %-KI = 0,03-0,13). Eine Kosten-Effektivitäts-Analyse wurde durchgeführt und das ermittelte inkrementelle Kosten-Effektivitäts-Verhältnis lag bei 1945,30€ je vermiedenem Dekubitus in der Interventionsgruppe. Die Applikation der verwendeten Verbände zur Dekubitusprävention an Sakrum und Fersen in der untersuchten Population ist klinisch wirksam und die Verwendung im Sakralbereich kosteneffektiv.

ABSTRACT

Elderly as well as care-dependent, immobile, and critically ill individuals have a particularly high risk of developing pathological skin conditions. The aim of this thesis was to investigate different preventive topical interventions to maintain and improve skin integrity in aged and care-dependent individuals.

In the context of this dissertation, a systematic review about the effects and effectiveness of topical skin care interventions for maintaining skin integrity in the aged population was conducted. Sixty-three full-text articles were included that reported treatment effects of interventions to prevent unwanted skin conditions. The use of low-irritating cleansers and the regular application of humectant-containing leave-on products with a low pH value were found to support the maintenance of skin integrity in the elderly.

Twelve older female subjects (mean age 70.3 years [SD 2.1]) were included in an exploratory, randomized, controlled trial with a split-body design to investigate the effect of a basic skin care product on the structural strength of aging skin. By applying the suction blister method, a controlled detachment of the dermis from the epidermis was induced, and the time to separation of the skin layers was used as an indicator for dermo-epidermal adhesion strength. After the application of the skin care product, the median time to separation of the skin layers was longer, and skin hydration values were consistently higher in interventional skin areas compared to control areas. Consistent with the results of the systematic review, it appears that regular use of a basic skin care product may improve dermo-epidermal adhesion strength in this population. The suction blister method and measurement of time to dermo-epidermal separation represent a suitable approach to quantify the dermo-epidermal adhesion strength in the context of clinical research.

A randomized, controlled, pragmatic, clinical trial in n = 422 high-risk intensive care unit patients was performed to investigate the effectiveness of multi-layered silicone foam dressings for sacral and heel pressure ulcer prevention in this population. Dressings were applied in addition to standard pressure ulcer prevention care. The cumulative pressure ulcer incidence within the pragmatic trial was 2.8% in the intervention and 10.5% in the control group (relative risk -0.26; 95% confidence interval [CI] 0.11-0.62; absolute risk reduction 0.08; 95% CI 0.03-0.13). A supplementary cost-effectiveness analysis was performed and the incremental cost-effectiveness ratio was € 1,945.30 per avoided pressure ulcer in the intervention group. The application of the dressings used for pressure ulcer prevention on the sacrum and heels in the population studied is clinically effective and the use in the sacral region is additionally cost-effective.

1. EINLEITUNG

1.1 HINTERGRUND

Die Haut stellt das größte menschliche Organ dar und grenzt den Organismus als äußere Barriere von seiner Umwelt ab. Infolgedessen ist die Haut konstant gegenüber Umwelteinflüssen exponiert, welche einen negativen Einfluss auf die Hautgesundheit und -alterung haben können. Die Literatur beschreibt zwei unterschiedliche Arten der Hautalterung. Die intrinsische Hautalterung ist dabei Teil des natürlichen, unaufhaltbaren chronologischen Alterungsprozesses. Sie ist maßgeblich genetisch determiniert und wird von metabolischen und hormonellen Faktoren beeinflusst. Die extrinsische Hautalterung wird durch Umwelteinflüsse, insbesondere durch UV-Licht, bestimmt [1, 2]. Als hochkomplexes Organ erfüllt die Haut eine Vielzahl essenzieller regulatorischer und protektiver Aufgaben. Zu diesen zählen Thermoregulation, Sinneswahrnehmung, Abwehr von Mikroorganismen sowie immunologischer und mechanischer Schutz des Körpers [3, 4]. In Anbetracht ihrer vielfältigen Aufgaben wird deutlich, dass es von grundlegender Relevanz ist, die Integrität der Haut und somit ihre Funktionsfähigkeit über die gesamte Lebensspanne zu erhalten.

Die intrinsische Hautalterung ist mit diversen funktionellen und strukturellen Veränderungen verbunden. Zu ihnen zählen eine reduzierte Sebumsekretion, verminderter Lipidgehalt, der Anstieg des pH-Werts der Haut, eine Abnahme der Dichte kollagener und elastischer Fasern der Dermis und eine verminderte Proliferationsrate der Keratinozyten [1, 5]. Eine verdünnte, atrophische Epidermis mit Abflachung und Desorganisation molekularer Komponenten der dermo-epidermalen Junktionszone (DEJ) sind weitere Begleiterscheinungen [6]. Die DEJ beschreibt die Grenzfläche zwischen Dermis und Epidermis. Sie vermittelt, neben dem Nährstoff- und Molekülaustausch, die Adhäsion dieser beiden Gewebe durch ein komplexes Netzwerk interagierender Proteine [7]. Neben der molekularen Interaktion zwischen den Hautschichten ist für die DEJ eine charakteristische dreidimensionale Struktur beschrieben. Diese präsentiert sich in Form von epidermalen Reteleisten, die als fingerartige Projektionen in die Dermis ragen, während dermale Papillen als Ausstülpung in die Epidermis zu erkennen sind [8]. Die beschriebene Interdigitation der Schichten erhöht die dermo-epidermale Kontaktfläche und vermittelt strukturelle Integrität sowie mechanische Stabilität [7]. Durch den altersbedingten Verlust von Reteleisten und Abflachung der DEJ reduziert sich die Kontaktfläche zwischen Dermis und Epidermis und vermindert deren Adhäsion. In Folge der beschriebenen

Prozesse weist die gealterte Haut eine verminderte Elastizität mit erhöhter Anfälligkeit für Infektionen und die Entstehung von Wunden sowie eine verzögerte Wundheilung auf [6].

Aufgrund der Komplexität der Haut wird deutlich, weshalb sich ihr Zustand sowie die Integrität nicht anhand eines einzelnen Merkmals bestimmen lassen. Bei der Entstehung von Wunden und anderen unerwünschten Hautzuständen handelt es sich um multifaktorielle komplexe Prozesse, welche die funktionelle Kapazität und Widerstandsfähigkeit überschreiten [9]. Neben den beschriebenen Vorgängen im Rahmen der chronologischen Hautalterung sind in diesem Zusammenhang weitere (altersunabhängige) Einflüsse ebenfalls von hoher Relevanz. Zu ihnen gehören Faktoren wie Immobilität, (Multi-) Medikation, kognitiver Zustand sowie chemische oder mechanische Einwirkungen [10, 11]. Neben älteren Personen sind somit auch pflegebedürftige, multimorbide, immobile und/oder schwer und chronisch Erkrankte jeder Altersgruppe einem erhöhten Risiko ausgesetzt, eine pathologische Hautveränderung zu entwickeln. Eine wichtige Rolle nehmen hierbei Personen in Hochrisiko-Settings ein, zu diesen zählen u. a. Bewohnende geriatrischer Langzeitpflegeeinrichtungen sowie Hochrisikopatienten und -patientinnen auf Intensivstationen.

Mit einer Prävalenz von 30 % bis 100 % findet sich in den verschiedenen Pflege-Settings die Xerosis cutis (trockene Haut) besonders häufig wieder [12-14]. Aber auch akute Wunden wie beispielsweise Hautrisse sind mit einer Prävalenz von bis zu 22 % oft in geriatrischen Langzeitpflegeeinrichtungen zu finden [15, 16]. Neben dem Risiko komplexe chronische Wunden auszubilden, sind sie u. a. oftmals mit einem erhöhten Infektionsrisiko und Schmerzen verbunden [17]. Ebenso treten mit hoher Prävalenz und Inzidenz Dekubitus (auch Druckgeschwür) auf [18-20], welche oftmals als Indikator für die Qualität der Pflege herangezogen werden [21, 22]. Dekubitus können die Lebensqualität Betroffener nachhaltig beeinträchtigen [23-25] und zählen zu den dermatologischen Erkrankungen mit der höchsten Krankheitslast [26]. Neben einer gesundheitlichen sind sie oftmals auch mit einer finanziellen Belastung der Betroffenen assoziiert [23]. Auch Pflegeeinrichtungen und Krankenhäuser stehen vor dem Problem zusätzlicher Kosten in enormer Höhe sowie einer steigenden Arbeitsbelastung für Pflegende [27-29]. Aufgrund der beschriebenen gesundheitlichen, sozialen und ökonomischen Faktoren, die im Zusammenhang mit (vermeidbaren) pathologischen Hautzuständen stehen, besteht ein hohes Interesse, das Auftreten dieser zu vermeiden.

Die genannten Hautzustände gelten ebenso wie das Auftreten von Inkontinenz-assoziierter Dermatitis (IAD) und Intertrigo bei frühzeitiger Ergreifung von

adäquaten Präventionsmaßnahmen als weitestgehend vermeidbar. Daraus wird ersichtlich, wie nachhaltig und wichtig der frühe Einsatz geeigneter, individuell angepasster, präventiver pflegerischer Maßnahmen zur Erhaltung und Förderung der Hautintegrität dieser Personengruppen ist. Eine 2013 publizierte systematische Übersichtsarbeit [30], die den Zeitraum von 1990 bis 2012 inkludiert, fasst die empirische Evidenz der Wirksamkeit und Effektivität grundlegender topischer Hautpflegemaßnahmen zur Erhaltung der Hautintegrität älterer Personen zusammen. Eine Aktualisierung und Erweiterung bestehender Evidenz ist notwendig, um Aufschluss über neue Erkenntnisse zu erhalten, bestehende Empfehlungen anzupassen sowie innerhalb der klinischen Forschung relevante Endpunkte (auch Zielvariablen; *engl.: Outcomes*) und geeignete Messinstrumente im Bereich der präventiven Hautpflege zu identifizieren.

Basierend auf wachsenden Erkenntnissen über die Ätiologie und Pathogenese von Dekubitus wurden in den letzten Jahrzehnten umfangreiche Leitlinien und Handlungsempfehlungen mit dem Ziel der Prävention entwickelt und implementiert sowie fortlaufend aktualisiert [18, 31-36]. Grundlegende Maßnahmen der Dekubitusprävention setzen auf die größtmögliche Reduktion zusätzlicher extrinsischer Faktoren wie mechanische Belastung und chemische Reizungen. Zu ihnen zählen die Verwendung druckumverteilender Matratzen und Auflagen, regelmäßige Umlagerung zur Druckentlastung und Inkontinenzmanagement [18]. Trotz umfangreicher Präventionsmaßnahmen scheint die Dekubitusinzidenz in diesen Settings weiterhin hoch zu sein [18-20]. Der daraus resultierende Bedarf an zusätzlichen wirksamen Präventionsmaßnahmen führte zur Erprobung neuer Ansätze. Ein Ansatz mit zunehmender Evidenz zur Wirksamkeit ist die Applikation präventiver Verbände an entsprechenden Prädilektionsstellen [18, 37-39]. Das Wirkprinzip solcher Verbände ist in diesem Zusammenhang nicht vollständig geklärt. Diverse Untersuchungen konnten jedoch zeigen, dass verschiedene präventive Verbände dazu beitragen können, Scherkräfte, Reibung und Druck zu reduzieren [39].

Für die Charakterisierung struktureller und funktioneller Hauteigenschaften und Ermittlung hautphysiologischer Parameter stehen im Bereich der klinischen dermatologischen Forschung verschiedene Messverfahren und Methoden zur Verfügung. Sie ermöglichen es, den Einfluss verschiedener Faktoren oder Interventionen auf die Haut zu untersuchen. Zu diesen Messverfahren zählen die Bestimmung des Feuchtigkeitsgehalts des Stratum corneums, des transepidermalen Wasserverlusts (TEWL) oder des pH-Werts der Hautoberfläche [40, 41]. Diese Messinstrumente können dabei helfen, die Wirkung und Wirksamkeit bestehender präventiver

Maßnahmen zu untersuchen und zu vergleichen, dabei bieten sie die Möglichkeit, neuartige Ansätze zu prüfen. Die meisten dieser Messverfahren sind nicht-invasiv, indirekt oder erfassen nur die obersten Schichten der Epidermis.

Einen invasiven Ansatz stellt die Saugblasenmethode dar, welche erstmals im Jahr 1878 [42] in der Literatur beschrieben und von Kiistala und Mustakallio [43, 44] weiterentwickelt wurde. Die Applikation eines konstanten Unterdrucks auf ein begrenztes Hautareal induziert hierbei eine kontrollierte, artifizielle Trennung von Dermis und Epidermis an der DEJ. Durch den Unterdruck akkumuliert interstitielle Flüssigkeit zwischen den beiden Hautschichten und äußert sich makroskopisch in Form einer flüssigkeitsgefüllten Blase. Die Zeitspanne bis zur Blasenbildung soll dabei als Indikator für die dermo-epidermale Adhäsionsstärke dienen. Vorteil dieser invasiven Methode ist die Möglichkeit einer direkten Quantifizierung dieses Parameters *in vivo*. Die Saugblasenmethode bietet einen möglichen Ansatz, um Erkenntnisse über den Einfluss verschiedener Interventionen auf die dermo-epidermale Adhäsionsstärke zu gewinnen und in Zusammenhang mit assoziierten pathologischen Hautzuständen zu bringen. Bisher wird diese Methode im Rahmen der klinischen Forschung jedoch nicht für diesen Zweck verwendet.

Der altersbedingt geschwächte dermo-epidermale Verbund wird aufgrund seiner hohen Anfälligkeit gegenüber Scherkräften potenziell mit der Entstehung von Hautrissen in Verbindung gebracht [45, 46]. Eine klinische Studie [47] zeigte, dass die zweimalige tägliche Anwendung eines Basishautpflegeprodukts bei älteren Pflegeheimbewohnern die Inzidenz von Hautrissen fast halbieren konnte im Vergleich zur Standardpflegeprozedur allein. Daraus ergab sich die Empfehlung der regelmäßigen Anwendung topischer Basishautpflegeprodukte als Bestandteil eines Programms zur Prävention von Hautrissen in dieser Population [13]. Dennoch ist der zugrundeliegende Mechanismus bisher nicht vollständig geklärt. Ebenso ist eine mögliche Rolle der verminderten dermo-epidermalen Adhäsionsstärke in diesem Kontext bisher nicht beschrieben.

1.2 FRAGESTELLUNGEN

Im Rahmen dieser Promotion wurden die folgenden Fragestellungen untersucht:

I. Welche aktuelle empirische Evidenz zur Wirksamkeit von topischen Hautpflegeinterventionen gibt es, um präventiv die Integrität und funktionelle Kapazität der Haut im Alter zu erhalten und zu stärken? Welche Endpunkte und Messinstrumente werden dabei im Bereich der klinischen Forschung verwendet? (Teilprojekt 1, Publikation 1)

II. Welchen Effekt hat die präventive topische Applikation eines Basishautpflegeprodukts auf die dermo-epidermale Adhäsion und somit auf die strukturelle Widerstandsfähigkeit gealterter Haut? Sind die Saugblasenmethode und Messung der „Blasenbildungszeit“ geeignet, um die dermo-epidermale Adhäsionsstärke im Rahmen der klinischen Forschung zu quantifizieren? (Teilprojekt 2, Publikation 2)

III. Kann die zusätzliche Applikation mehrschichtiger Silikonschaumverbände an Sakrum und Fersen bei Hochrisikopatienten und -patientinnen auf Intensivstationen die Dekubitusinzidenz senken? Ist diese zusätzliche Präventionsmaßnahme aus Perspektive des versorgenden Krankenhauses kosteneffektiv? (Teilprojekt 3, Publikationen 3 und 4)

2. METHODIK

2.1 TEILPROJEKT 1: SYSTEMATISCHE ÜBERSICHTSARBEIT ÜBER DIE WIRKSAMKEIT PRÄVENTIVER TOPISCHER HAUTPFLEGEINTERVENTIONEN ZUR ERHALTUNG UND STÄRKUNG DER HAUTINTEGRITÄT (PUBLIKATION 1)

Eine systematische Übersichtsarbeit zur Erfassung der empirischen Evidenz zu Wirksamkeit und Nutzen präventiver Hautpflegeinterventionen wurde durchgeführt und die Ergebnisse publiziert (Publikation 1) [48]. Es handelte sich hierbei um die Aktualisierung einer Übersichtsarbeit, welche 2013 publiziert wurde und Publikationen von 1990 bis August 2012 umfasst [30]. Vor Beginn der Arbeit wurde das Protokoll für die aktualisierte Version der systematischen Übersichtsarbeit in der PROSPERO-Datenbank registriert (Registrierungsnummer: CRD42018100792) [49].

2.1.1 SUCHSTRATEGIE UND AUSWAHL DER STUDIEN

Mittels der vorab erstellten Suchstrategie wurden die elektronischen Datenbanken MEDLINE, EMBASE (via OvidSP) und CINHAL (EBSCOhost) nach relevanten Publikationen durchsucht (von September 2012 bis Mai 2018). Somit umfasst diese aktualisierte Version der Übersichtsarbeit Publikationen von 1990 bis einschließlich Mai 2018.

Nach Entfernung der Duplikate wurden die verbliebenen Publikationen in ein Literaturverwaltungsprogramm importiert (EndNote X7, Clarivate Analytics, Philadelphia, Vereinigte Staaten). Anschließend wurden die Titel und Zusammenfassungen der Publikationen von zwei unabhängigen Gutachtern[1] hinsichtlich folgender Kriterien auf Eignung untersucht: (I) Primärstudien in Form von randomisierten kontrollierten Studien (RCTs) oder mit quasi-experimentellem Design, (II) Sekundärdatenanalysen, (III) englisch- oder deutschsprachig, (IV) Interventionen mit Hautpflegeprodukten zur Förderung und Erhaltung der Hautintegrität bei physiologisch gealterter Haut, (V) Personen ≥ 50 Jahre. Bei Eignung wurden die Volltexte der Publikationen gesichtet. Zusätzlich wurden die Referenzlisten eingeschlossener Volltexte hinsichtlich weiterer relevanter Studien überprüft. Nach Einschluss von Artikeln basierend auf der Datenbanksuche sowie aus Referenzlisten wurde eine Vorwärtssuche in Scopus (Oktober 2018) durchgeführt. Bei ausgeschlossenen Volltexten wurden die Gründe dokumentiert. Etwaige Diskrepanzen wurden mit einem dritten Gutachter diskutiert.

[1] In den Kapiteln, die Methodik und Ergebnisse der vorliegenden Arbeit beschreiben, wird aus Gründen der besseren Lesbarkeit bei Personenbezeichnungen teilweise das generische Maskulinum verwendet. Dieses ist als neutrale grammatikalische Ausdruckweise zu verstehen und umfasst ausdrücklich alle Geschlechter. Beschreibungen, die sich explizit auf ein bestimmtes Geschlecht beziehen, sind entsprechend kenntlich gemacht.

2.1.2 DATENEXTRAKTION UND -ANALYSE

Für die Extraktion und Analyse der Studiendaten der einzelnen Publikationen wurde ein standardisiertes Formular erstellt, welches die folgenden Punkte beinhaltete: (I) Autor und Veröffentlichungsjahr (II) Studiendesign (III) Charakteristiken der Stichprobe und des Umfeldes (z. B. Pflegeheim) sowie Indikation (IV) Art der Intervention (V) Studiendauer (VI) Anzahl der Teilnehmenden (VII) Alter (VIII) Endpunkte und (IX) Ergebnisse. Für eingeschlossene RCTs wurde zusätzlich das Risk-of-Bias-Instrument [50] verwendet, welches für die standardisierte Bewertung des Verzerrungsrisikos von kontrollierten klinischen Studien eingesetzt wird. Für jede eingeschlossene Studie wurde der Evidenzgrad bestimmt [51-53]. Die Evidenzgrade reichen von I bis IV, wobei Studien mit dem Evidenzgrad I die höchste Evidenz aufweisen.

2.2 TEILPROJEKT 2: WIRKSAMKEIT DER PRÄVENTIVEN APPLIKATION TOPISCHER BASISHAUTPFLEGE ZUR STRUKTURELLEN STÄRKUNG DER HAUT (PUBLIKATION 2)

2.2.1 STUDIENDESIGN UND -UMGEBUNG

Eine explorative, randomisierte, kontrollierte klinische Studie mit Split-Body-Design, wurde 2018 im klinischen Forschungszentrum für Haut und Haare an der Charité – Universitätsmedizin Berlin, Klinik für Dermatologie, Venerologie und Allergologie durchgeführt und die Ergebnisse veröffentlicht (Publikation 2) [54]. Die Studie wurde vor Beginn von der Ethikkommission der Charité – Universitätsmedizin Berlin zustimmend bewertet (EA1/060/18) und in der Datenbank ClinicalTrials.gov (NCT03625167) registriert. Keine substanziellen, meldepflichtigen Änderungen der Methoden wurden nach Studienbeginn vorgenommen.

2.2.2 AUSWAHLKRITERIEN

Gesunde, weibliche Probandinnen konnten an der Studie teilnehmen, wenn folgende Einschlusskriterien zutrafen: (I) Alter zwischen 65 und 85 Jahren, (II) Kaukasierin mit einem Phototyp I bis III (entsprechend der Fitzpatrick-Klassifikation [55, 56]), (III) Body-Mass-Index (BMI) von 20 bis 28 kg/m^2, (IV) Nichtraucherin, (V) keine Hautschädigungen und -erkrankungen, Narben oder Tätowierungen in den Studienarealen. Teilnehmende Probandinnen wurden vor Studieneinschluss mündlich durch den Prüfarzt und schriftlich mittels der Probandeninformation über Inhalt, Ablauf und Risiken der Studie informiert. Alle Teilnehmerinnen haben vorab ihre schriftliche Zustimmung zur Studienteilnahme gegeben. Bevor studienbezogene Prozeduren durchgeführt wurden, unterzogen sich die Probandinnen einer körperlichen Untersuchung durch den Prüfarzt, um ihre Eignung zur Studienteilnahme festzustellen.

Zu den Hauptausschlusskriterien zählten: (I) Gesicherte oder vermutete Wundheilungsstörung, (II) Diabetes mellitus, (III) jegliche akute oder chronische (Haut-) Erkrankung, welche die Durchführung und Beurteilung der Studie beeinflussen könnte, (IV) akute oder chronische Wunden in den Studienarealen, (V) topische Anwendungen im Bereich der Studienareale innerhalb der letzten vier Wochen, welche die Beurteilung der Studie beeinträchtigen könnten, (VI) jegliche Überempfindlichkeit auf einen Bestandteil des Prüfprodukts.

2.2.3 INTERVENTION, RANDOMISIERUNG UND PROZEDUREN

Im Rahmen der Intervention behandelten eingeschlossene Probandinnen die gesamte Innenseite eines randomisiert zugeordneten Unterarms mit Petrolatum (Vaseline, weiß Ph. Eur., Fagron GmbH & Co. KG, Barsbüttel, Deutschland). Das Produkt wurde zwei Mal täglich (morgens und abends) für einen Zeitraum von vier bzw. acht Wochen eigenständig von den Probandinnen angewendet und die Anwendung in einem Tagebuch dokumentiert. Über das korrekte Vorgehen hinsichtlich des Zeitpunkts, Art und Menge des Produktauftrags wurden die Probandinnen bei der ersten Studienvisite aufgeklärt. Der verbliebene Unterarm diente als unbehandeltes Kontrollareal. Die Anwendung weiterer Pflegeprodukte, medizinischer Produkte oder Anwendungen war für die Dauer der Studie auf beiden Unterarmen nicht gestattet.

Je Unterarm wurden zwei standardisierte Untersuchungsareale festgelegt. Diese befanden sich jeweils im oberen Drittel der Innenseite der Unterarme. Die beiden Untersuchungsareale, die sich jeweils auf demselben Unterarm befanden, wurden in „oberes Areal“ und „unteres Areal“ unterteilt. Somit lagen bei jeder Probandin insgesamt vier Untersuchungsareale vor, zwei obere und zwei untere Untersuchungsareale.

Die Randomisierung erfolgte in zwei Schritten. In einem ersten Schritt wurde die Zuordnung einer der beiden Unterarme zur Intervention festgelegt (linker Unterarm *versus* rechter Unterarm). Die Zuordnung erfolgte bei der ersten Studienvisite in Woche 0, nachdem sämtliche Hautmessungen durchgeführt wurden, um die hautphysiologischen Ausgangswerte zu erfassen. Vor Induktion der ersten Saugblasen in Woche 4 wurde, in einem zweiten Schritt der Randomisierung, festgelegt in welchen Untersuchungsarealen die Saugblasen als erstes induziert werden (oberes Areal zuerst *versus* unteres Areal zuerst). Beide Randomisierungen basierten auf einer computergenerierten Randomisierungsliste mit einer 1:1-Zuordnung zu Intervention und Kontrolle bzw. oberem Areal und unterem Areal. Anhand dieser Listen wurden von

Mitarbeitenden des Studienzentrums, die nicht an der Durchführung oder Auswertung der Studie beteiligt waren, blickdichte, nummerierte Umschläge mit der jeweiligen Zuordnung erstellt.

In Woche 4 und Woche 8 wurden je Unterarm, in der randomisiert festgelegten Reihenfolge, jeweils in einem der beiden Untersuchungsareale (oberes Areal *versus* unteres Areal) zwei Saugblasen induziert. Hierfür wurde eine Vakuumpumpe (Hico-Rapidovac 761, Hirtz, Köln, Deutschland) genutzt. Die Pumpe wurde mit einem Schlauchsystem verbunden, um eine simultane Applikation desselben konstanten Unterdrucks von -200 mmHg auf alle Induktionsareale auszuüben. Nach Bildung vollständiger Saugblasen wurde die Apparatur entfernt. Die Blasenbildungszeit wurde in Minuten gemessen und in zwei Unterkategorien unterteilt: (I) „Zeit bis zum ersten Vesikel“, welche die Zeitspanne bis zur Entwicklung eines ersten makroskopisch sichtbaren Vesikels beschreibt und (II) „Zeit bis zur vollständigen Blase“. Letztere erfasst die benötigte Dauer bis zur Ausbildung einer vollständigen Blase, die das gesamte Areal abdeckt, auf welches der Unterdruck appliziert wurde. Die Bildung einer vollständigen Blase wurde entweder durch Expansion eines einzelnen initialen Vesikels oder durch die Fusion mehrerer kleiner entstandener Vesikel erreicht.

Nicht-invasive hautphysiologische Messungen wurden in den festgelegten Arealen an beiden inneren Unterarmen vor Anwendung der Produkte in Woche 0 sowie in Woche 2, 4, 6 und 8 durchgeführt. Die Stratum Corneum Hydratation (SCH) wurde mittels des Corneometers CM 825 (Courage + Khazaka, Köln, Deutschland) gemessen. Die Messung basiert auf der Differenz der dielektrischen Konstanten von Wasser und anderen Substanzen und misst den Feuchtigkeitsgehalt des Stratum corneums und wird mittels relativer Maßeinheit (*engl.: arbitrary units* [AU]) angegeben. Die Messwerte des Gerätes können zwischen 0 AU und 120 AU liegen. Werte > 40 AU gelten als normwertig, Werte die < 40 AU liegen werden als Zeichen für trockene Haut interpretiert [57]. Die epidermale Hydratation wurde mit dem MoistureMeterEpiD (Delfin Technologies Ltd, Kuopio, Finnland) gemessen. Die gemessenen dielektrischen Konstantenwerte sind dabei proportional zum Wassergehalt im epidermalen Gewebe und werden als prozentualer Anteil des Wassers im Gewebe (0 % bis 100 %) angegeben. Die Oberflächentemperatur der Haut wurde mittels Skin-Thermometer ST 500 (Courage + Khazaka, Köln, Deutschland) in Grad Celsius [°C] gemessen. Die epidermale Dicke wurde mittels Optischer Kohärenztomografie (OCT) (Thorlabs, Lübeck, Deutschland) durch standardisierte Messung [58] ermittelt und in Mikrometern [µm] angegeben. Alle Messungen wurden in Duplikaten durchgeführt. Um eine größtmögliche Standardisierung und

Reproduzierbarkeit zu gewährleisten, wurden alle Messungen sowie die Induktion der Saugblasen unter einheitlichen Bedingungen durchgeführt. Dazu gehörten die Akklimatisierung der freigelegten Studienareale für 30 Minuten bei einer relativen Luftfeuchtigkeit zwischen 40 % und 60 % sowie einer Raumtemperatur zwischen 20 °C und 22 °C.

2.2.4 ENDPUNKTE, VARIABLEN UND STATISTISCHE METHODEN

Eine formelle Fallzahlkalkulation oder Unterscheidung zwischen primären und sekundären Endpunkten wurde aufgrund des explorativen Charakters der Studie nicht durchgeführt. Basierend auf Empfehlungen in der Literatur war geplant n = 12 Probandinnen in die Studie einzuschließen [59]. Endpunkte in allen Untersuchungsarealen waren Blasenbildungszeit („Zeit bis zum ersten Vesikel“ und „Zeit bis zur vollständigen Blase“), SCH, epidermale Hydratation und epidermale Dicke. Zu den erhobenen Variablen gehörten Alter, BMI, Phototyp, Körpertemperatur und Blutdruck.

Demografische Charakteristiken wurden mit Mittelwerten und Standardabweichungen (SD) beschrieben. Für die Endpunkte wurden Mediane und Interquartilsabstände (IQR) (25 % - 75 %) für die gesamte Stichprobe, die einzelnen Gruppen sowie Gruppendifferenzen ermittelt. Aufgrund des explorativen Studiendesigns wurden keine statistischen Tests angewendet. Alle statistischen Analysen wurden mit der Software IBM SPSS Statistics Version 25.0 (IBM Corp., Armonk, NY) durchgeführt.

2.3 TEILPROJEKT 3: KLINISCHE WIRKSAMKEIT UND KOSTENEFFEKTIVITÄT MEHRSCHICHTIGER SILIKONSCHAUMVERBÄNDE ZUR PRÄVENTION VON DEKUBITUS (PUBLIKATION 3 UND 4)

Dieses Teilprojekt setzte sich mit den klinischen (Publikation 3) [60] sowie ökonomischen (Publikation 4) [61] Aspekten der Verwendung von mehrschichtigen Silikonschaumverbänden zur Prävention von Dekubitus auseinander.

2.3.1 STUDIENDESIGN UND -UMGEBUNG

Eine randomisierte, kontrollierte, pragmatisch angelegte klinische Interventionsstudie wurde auf insgesamt sieben Intensivstationen der Charité – Universitätsmedizin Berlin durchgeführt (Juni 2015 bis Juli 2018) und die Ergebnisse veröffentlicht (Publikation 3) [60]. Die Durchführung erfolgte durch das klinische Forschungszentrum für Haut und Haare an der Charité – Universitätsmedizin Berlin, Klinik für Dermatologie, Venerologie und Allergologie. Die Studie wurde im Vorfeld zustimmend durch die Ethikkommission der

Charité – Universitätsmedizin Berlin (EA1/054/15) bewertet und in der Datenbank ClinicalTrials.gov (NCT02295735) registriert. Keine substanziellen, meldepflichtigen Änderungen der Methoden wurden nach Studienbeginn vorgenommen.

2.3.2 AUSWAHLKRITERIEN DER INTERVENTIONSSTUDIE

Patienten der teilnehmenden Intensivstationen, (I) die 18 Jahre alt oder älter waren, (II) eine voraussichtliche Mindestliegedauer von drei Tagen sowie (IV) ein hohes oder sehr hohes Dekubitusrisiko hatten, konnten innerhalb der ersten sechs Stunden nach Aufnahme auf die Intensivstation in die Studie eingeschlossen werden. Die Klassifikation des Dekubitusrisikos wurde hierbei durch den Charité-internen Standard zur Dekubitusprävention definiert [62]. Das Einverständnis zur Studienteilnahme wurde bei bestehender Einwilligungsfähigkeit von den Patienten selbst, oder alternativ von einem gesetzlichen Vertreter, eingeholt.

Von einer Studienteilnahme ausgeschlossen waren Personen (I) im Sterbeprozess, (II) bei vorbestehenden Traumata oder Dekubitus im Sakralbereich oder an den Fersen (entsprechend dem National and European Pressure Ulcer Advisory Panels (NPUAP/EPUAP) 2014 Klassifikationssystem [33]) oder (III) einer bekannten Unverträglichkeit gegenüber den in der Interventionsgruppe verwendeten Verbänden. Ebenso wurden Personen von der Studienteilnahme ausgeschlossen, wenn diese aufgrund medizinischer Komplikationen nicht regelmäßig umgelagert werden konnten. Dies stellte eine Voraussetzung dar, um reguläre Hautinspektionen sowie Pflasterwechsel zu ermöglichen.

2.3.3 INTERVENTION UND RANDOMISIERUNG

Alle eingeschlossenen Studienteilnehmenden erhielten weiterhin die regulären Dekubitus-Präventionsmaßnahmen, entsprechend des Charité-internen Standards [62]. Neben der individuellen Einschätzung des Dekubitusrisikos umfasst der Standard eine Hautinspektion innerhalb ersten sechs Stunden nach der Aufnahme sowie, abhängig von der Risikoeinschätzung, die Aufklärung der Patienten, tägliche Hautinspektionen, Mobilisierungsmaßnahmen, Verwendung spezieller Matratzen, regelmäßige Umlagerung und Freilagerung der Fersen. Bei Patienten der Interventionsgruppe wurden zusätzlich, neben den Maßnahmen des Standards, am Sakrum sowie an beiden Fersen mehrschichtige Silikonschaumverbände angebracht. Für eine tägliche Hautinspektion wurden die Verbände teilweise abgelöst und nach Bewertung des Hautzustands wieder aufgebracht. Ein vollständiger Pflasterwechsel fand regulär alle drei Tage statt oder früher bei vorzeitigem Ablösen oder Verschmutzungen. Eingeschlossene Patienten der

Kontroll- sowie Interventionsgruppe wurden mindestens einmal täglich durch das Studienpersonal besucht, um die Verbände zu wechseln, den korrekten Sitz zu prüfen und die Hautinspektionen durchzuführen.

Die Teilnahme an der Studie endete, (I) wenn Teilnehmende kein hohes oder sehr hohes Dekubitusrisiko mehr aufwiesen, (II) bei Entstehung eines Dekubitus im Sakralbereich oder an den Fersen, (III) wenn ein unerwünschtes Ereignis im Zusammenhang mit den Verbänden aufgetreten ist, (IV) wenn ein Patient (oder die gesetzlich bevollmächtigte Person) die Teilnahme an der Studie beenden wollte, (IV) bei schweren Protokollverletzungen, (V) wenn der Patient verstarb oder (VI) außerhalb des Krankenhauses verlegt bzw. entlassen wurde.

Die Randomisierung basierte auf einer computergenerierten 1:1 Zuordnung zur Kontroll- und Interventionsgruppe und wurde extern vom Institut für Biometrie und klinische Epidemiologie der Charité – Universitätsmedizin Berlin erstellt. Darauf basierend wurden durch den von der Studie unabhängigen Datenmanager des Studienzentrums aufsteigend nummerierte, blickdichte Umschläge mit der jeweiligen Zuordnung erstellt. Weder bei der Erstellung der Randomisierungsliste noch bei der Vorbereitung der Umschläge waren Personen des Studienteams involviert. Nach Einschluss in die Studie und Erhebung von definierten demografischen und medizinischen Daten, wurde der nächste nummerierte Umschlag geöffnet und der Patient einer der beiden Gruppen zugeordnet.

2.3.4 STICHPROBENGRÖßE

Auf Basis der mittleren kumulativen Inzidenz von 0,06 Dekubitusfällen pro Monat auf den Intensivstationen der Charité – Universitätsmedizin Berlin, wurde eine benötigte Stichprobengröße von 211 Patienten je Gruppe berechnet, um einen Unterschied bezüglich der Dekubitusinzidenz nachweisen zu können. Dies entspricht einer benötigten Gesamtanzahl von 422 Patienten. Um mögliche Verluste (z. B. durch eine rückwirkende Ablehnung der Studienteilnahme) zu kompensieren, wurde eine Ausfallrate von 10 % einkalkuliert, somit war insgesamt der Einschluss von 464 Patienten geplant.

2.3.5 ENDPUNKTE, VARIABLEN UND STATISTISCHE METHODEN

Der primäre Endpunkt der Interventionsstudie war die kumulative Inzidenz von Dekubitus der Kategorie II, III, IV und vermutete tiefe Gewebsschädigung (*engl.: suspected deep tissue injury*; DTI) am Sakrum oder den Fersen. Dekubitus wurden entsprechend den NPUAP/EPUAP 2014 Kategorien eingeordnet [33]. Neu aufgetretene Dekubitus aller Kategorien

wurden täglich nachverfolgt und beurteilt bis zum Eintreten der Heilung, Ablehnen einer weiteren Nachverfolgung durch den Patienten selbst oder dessen gesetzlichen Vertreter, Entlassung aus dem Krankenhaus oder dem Versterben des Patienten. Sekundäre Endpunkte waren die Inzidenzdichte von Dekubitus der Kategorie II oder höher (Ausgedrückt in Dekubitus per 1000 Liegetage) sowie die kumulative Inzidenz und Inzidenzdichte von Dekubitus der Kategorie I und höher. Ebenfalls ermittelt wurde die Gesamtzahl der ereignisfreien Tage bezogen auf Dekubitus Kategorie I bzw. II und höher.

Bei Studieneinschluss erfasste Hauptvariablen waren Alter, Geschlecht, aktueller oder vergangener Tabakkonsum, Phototyp [55, 56], BMI, bekannte Hauptdiagnosen (codiert nach *International Classification of Diseases 10* (ICD-10) [63]), Vorliegen von Diabetes mellitus oder Tetraplegie, vorhergehende Aufenthaltsdauer in der Notaufnahme/anderen Stationen vor Aufnahme auf die Intensivstation. Täglich dokumentiert wurden vorliegende Urin- und/oder Harninkontinenz, Art der verwendeten Matratze sowie Lagerungsart und -intervall und ob eine maschinelle Beatmung vorlag.

In Abhängigkeit des Messniveaus (nominal, ordinal, kontinuierlich) wurden die Variablen anhand von relativen und absoluten Häufigkeiten, Mittelwerten, Medianen und Streuparametern beschrieben (Minimum, Maximum, IQR und SD). Der primäre Endpunkt, also die Dekubitusinzidenz der Kategorien II, III, IV und DTI am Sakrum und den Fersen, wurde mittels des χ^2-Tests verglichen. Mittels generalisierter linearer Modelle (GLM) wurde auf verschiedene zu Studieneinschluss vorliegende Kovariate (u. a. Gruppenzugehörigkeit, Alter, Vorliegen von Diabetes mellitus, Aufenthalt in der Notaufnahme), hinsichtlich des primären Endpunkts, adjustiert. Bei den sekundären Endpunkten wurden der χ^2-Test und *t*-Test bzw. Mann-Whitney-U-Test angewandt, um die Gruppen zu vergleichen. Alle statistischen Analysen wurden mit der Software IBM SPSS Statistics Version 25.0 (IBM Corp., Armonk, NY) durchgeführt.

2.3.6 RESSOURCEN UND KOSTEN DER DEKUBITUSPRÄVENTION UND -BEHANDLUNG

Mittels Bottom-up-Ansatz wurden die Kosten der Dekubitusprävention und -behandlung durch Dokumentation des tatsächlichen Verbrauchs an Ressourcen ermittelt. Ressourcen für die Kostenkalkulation der Prävention beinhalteten die Anzahl der tatsächlich verwendeten Verbände, zuzüglich der benötigten Arbeitszeit für deren Applikation und Wechsel. Für die Kostenkalkulation der Behandlung inzidenter Dekubitus im Sakralbereich und den Fersen in beiden Gruppen wurden die Kosten der Wundversorgung (inklusive Wundauflagen und

medizinischer Verbrauchsmaterialien wie Gaze und Handschuhe), die zusätzlich benötigte Arbeitszeit (inklusive Wundassessment, -dokumentation und -versorgung) sowie Konsultationen von Wundmanagern berücksichtigt. Die angesetzten Materialkosten entsprachen den Krankenhaus-individuellen Einkaufspreisen, die zum Zeitpunkt der Durchführung galten. Die angesetzten Stundenlöhne basierten auf dem jeweils jahresgültigen Tarifvertrag für den öffentlichen Dienst im Bereich der Vereinigung der kommunalen Arbeitgeberverbände für den Pflegedienst (TvöD-P; Entgeltgruppe 7A und 8A, Stufe 4).

Die Gesamtkosten der Dekubitusprävention in der Interventionsgruppe wurden ermittelt, indem die Summe aus den Kosten aller verwendeten präventiven Verbände und die Lohnkosten für zusätzlich benötigte Arbeitszeit gebildet wurde. Die Gesamtbehandlungskosten inzidenter Dekubitus setzte sich aus der Summe der Behandlungskosten (verwendete Ressourcen multipliziert mit jeweiligen Einheitspreisen) und zusätzlich entstandenen Lohnkosten zusammen.

2.3.7 INKREMENTELLE KOSTEN-EFFEKTIVITÄTS- UND SENSITIVITÄTSANALYSE

In der durchgeführten Kosten-Effektivitäts-Analyse wurden inkrementelle Kosten-Nutzen-Verhältnisse (*engl.: incremental cost-effectiveness ratio;* ICER) ermittelt. ICERs werden verwendet, um zu beschreiben wie viele Mehrkosten eine alternative wirksamere Therapie, im Vergleich zu einer bestehenden Therapie, für einen zusätzlichen Nutzen verursacht. Generell gilt, dass mit einem steigenden ICER eine sinkende Kosteneffektivität einhergeht.

Ergänzend zu der Basisfallanalyse wurde im Rahmen einer Sensitivitätsanalyse der Einfluss einzelner Variablen auf die Zielgröße, in diesem Fall den ICER, gemessen. Diese Herangehensweise erlaubt es mögliche Unsicherheiten der einzelnen Variablen abzubilden und deren Auswirkungen zu untersuchen. Dies hilft relevante und einflussreiche Variablen zu identifizieren. Es wurden multiple univariate Sensitivitätsanalysen durchgeführt, bei denen die Anzahl der im Rahmen der Intervention verwendeten Verbände sowie deren Preis, die benötigte Arbeitszeit für Applikation und Wechsel der Verbände und die Durchschnittskosten der Intervention variiert wurden.

3. ERGEBNISSE

3.1 TEILPROJEKT 1: SYSTEMATISCHE ÜBERSICHTSARBEIT ÜBER DIE WIRKSAMKEIT PRÄVENTIVER TOPISCHER HAUTPFLEGEINTERVENTIONEN ZUR ERHALTUNG UND STÄRKUNG DER HAUTINTEGRITÄT (PUBLIKATION 1)

Die systematische Literaturrecherche in den elektronischen Datenbanken MEDLINE, EMBASE und CINHAL ergab für den Zeitraum von September 2012 bis Mai 2018 insgesamt 1465 Treffer. Nach Überprüfung von Titel und Abstrakt, wurden insgesamt 100 Publikationen als relevant identifiziert und einer Volltextprüfung unterzogen. Hiervon konnten 30 aktuelle Artikel in die quantitative Datenanalyse eingeschlossen werden. Zusammen mit den 33 Artikeln der ursprünglichen Übersichtsarbeit wurden insgesamt 63 Studien ausgewertet (34 RCTs, 25 Quasi-experimentelle Studien, eine deskriptive und drei retrospektive Studien).

Davon befassten sich 31 Studien mit der Prävention und Behandlung von trockener Haut, zwölf Studien thematisierten die Verbesserung der Hautbarriere, 13 Studien beschäftigten sich mit der Prävention von IAD, sechs mit der Dekubitusprävention und fünf mit der Prävention von Hautrissen. Zusammengefasst zeigten die Ergebnisse, dass das Waschen der Haut mit milden Reinigungsprodukten und Auftrag von Pflegeprodukten, die Feuchthaltemittel (sog. Humectants; Stoffe mit hygroskopischen Eigenschaften) wie Urea oder Glycerin enthielten, die Hautrockenheit reduzierten sowie die Widerstands- und Regenerationsfähigkeit fördern konnten. Pflegeprodukte mit niedrigem pH-Wert zeigten einen positiven Einfluss auf die Stärke der Hautbarriere im Vergleich zu Produkten mit höherem pH-Wert. Reinigung mit milden Reinigungsprodukten und anschließende Verwendung von Hautschutzprodukten reduzierten die IAD- und Dekubitusinzidenz sowie den Schweregrad der IAD. Verwendung von Glycerin- und Petrolatum-haltigen Pflegeprodukten konnte die Inzidenz von Hautrissen reduzieren. Insgesamt wurden 35 Endpunkte (z. B. trockene Haut, Pruritus, SCH und TEWL) unter Verwendung von fast 100 Messinstrumenten identifiziert. Messinstrumente umfassten u. a. klinische Scores und Skalen, Fragebögen sowie apparative Messungen.

3.2 TEILPROJEKT 2: WIRKSAMKEIT DER PRÄVENTIVEN APPLIKATION TOPISCHER BASISHAUTPFLEGE ZUR STRUKTURELLEN STÄRKUNG DER HAUT (PUBLIKATION 2)

Von 18 untersuchten Frauen erfüllten 17 die Einschlusskriterien, alle von ihnen willigten in die Studienteilnahme ein. Es war geplant die Studie mit zwölf Probandinnen durchzuführen. Im Studienverlauf wurden bei fünf Probandinnen schwerwiegende Protokollverletzungen

festgestellt. Diese hatten zusätzliche Pflegeprodukte auf einen oder beide Unterarme aufgetragen. Betreffende Probandinnen wurden von der weiteren Teilnahme ausgeschlossen und ersetzt. Zwölf Probandinnen haben die Studie protokollkonform abgeschlossen. Das mittlere Alter betrug 70,3 Jahre (SD 2,1) und der mittlere BMI lag bei 26,0 kg/m^2 (SD 2,2).

Bei der Induktion der Saugblasen nach vier Wochen konnte beobachtet werden, dass die mediane Zeitspanne sowohl für die Entstehung erster Vesikel 3 Minuten (IQR -8 bis 10) als auch bis zur Entstehung einer vollständigen Saugblase 6 Minuten (IQR -9 bis 15) in den Interventionsarealen länger dauerte, verglichen mit den Kontrollarealen. Nach acht Wochen stieg die zeitliche Differenz auf 7 Minuten (IQR -2 bis 17) bis zur Entstehung erster Vesikel an und belief sich bis zur Ausbildung einer vollständigen Saugblase auf 6 Minuten (IQR -6 bis 12). Die medianen SCH-Werte wiesen bereits zu Beginn der Studie in Woche 0 Differenzen auf und waren in den Interventionsarealen höher als in Kontrollarealen. Im Verlauf der Studie sanken die SCH-Werte sowohl für Interventions- als auch für Kontrollareale jedoch blieb die mediane Differenz im Studienverlauf bestehen. Die Werte für die epidermale Hydratation waren in Woche 0 in allen Arealen vergleichbar. Im weiteren Studienverlauf entwickelte sich eine größer werdende Differenz der Werte zwischen den Arealen, so dass die mediane epidermale Hydratation in Interventionsarealen stets höhere Werte aufwies. Gemessene Werte der epidermalen Dicke lagen zwischen 44 µm bis 112 µm mit medianen Werten von 67 µm bis 76 µm. Die Werte beziehen sich auf alle Messzeitpunkte sowie Areale und zeigten im Studienverlauf eine geringe Variabilität zwischen den Messzeitpunkten. Ein gruppenspezifischer Unterschied war nicht ersichtlich.

3.3 TEILPROJEKT 3: KLINISCHE WIRKSAMKEIT UND KOSTENEFFEKTIVITÄT MEHRSCHICHTIGER SILIKONSCHAUMVERBÄNDE ZUR PRÄVENTION VON DEKUBITUS (PUBLIKATION 3 UND 4)

Im Studienverlauf wurden insgesamt 7575 Patienten der Intensivstationen auf ihre Eignung zur Studienteilnahme überprüft. 475 Patienten konnten in die Studie eingeschlossen werden, dabei wurden 238 Patienten der Interventions- und 237 Patienten der Kontrollgruppe zugeteilt. Nach Ausschluss von 30 Patienten, die fälschlicherweise randomisiert wurden, und 24 Patienten, die eine Studienteilnahme nach Einschluss ablehnten, konnten die Daten für 422 Patienten (n = 212 Interventions-/n = 210 Kontrollgruppe) ausgewertet werden. Das mittlere Alter der Patienten betrug 63,5 Jahre (SD 15,4) und der mittlere BMI lag bei 26,5 kg/m^2 (SD 4,9). Der Anteil an Patienten, die dem männlichen Geschlecht zugeordnet wurden, betrug 65,4 %.

Bei 40,5 % (171/422) lag ein Diabetes mellitus vor und 2,4 % (10/422) waren von einer Tetraplegie betroffen. Informationen über das Rauchverhalten lagen für 269 Patienten vor, davon waren fast ein Drittel ehemalige Raucher, ein Drittel aktive Raucher, die übrigen Patienten haben niemals geraucht. Mit Ausnahme einer leichten Ungleichverteilung hinsichtlich des zugeordneten Geschlechts waren die übrigen Stichprobencharakteristiken in beiden Gruppen vergleichbar.

3.3.1 ERGEBNISSE DER INTERVENTIONSSTUDIE

Die kumulative Dekubitusinzidenz der Kategorien II, III, IV und DTI lag bei 6,6 % (28/422). In der Interventionsgruppe entwickelten 2,8 % (6/212) und in der Kontrollgruppe 10,5 % (22/210) der Patienten einen Dekubitus. Das relative Risiko (RR) in der Interventionsgruppe, verglichen mit der Kontrollgruppe, lag bei RR = 0,26 (95 %-Konfidenzintervall [KI] = 0,11 bis 0,62) und die absolute Risikoreduktion bei 0,08 (95 %-KI = 0,03 bis 0,13). Bei insgesamt 1,4 % (6/422) der Patienten lag ein Dekubitus der Kategorie I vor (jeweils in der Kontrollgruppe). Dekubitus der Kategorie IV sind im Studienverlauf nicht aufgetreten.

In der GLM-Analyse wurden verschiedene Parameter wie u. a. Gruppenzuordnung, Nachverfolgungszeitraum, Alter, Geschlecht, BMI oder Vorliegen eines Diabetes mellitus zugrunde gelegt. Es konnte gezeigt werden, dass in der Interventionsgruppe statistisch signifikant seltener Dekubitus der Kategorien II oder höher aufgetreten sind, im Vergleich mit der Kontrollgruppe (Odds Ratio [OR] = 0,269 [95 %-KI = 0,105 bis 0,687]).

Im Mittel wurden die Patienten im Rahmen der Studie für 12,6 Tage (SD 12,7) nachverfolgt. Nachverfolgungsperioden in der Interventions- (11,0 Tage; SD 10,3) und Kontrollgruppe (14,3 Tage; SD 14,6) haben sich statistisch signifikant unterschieden (p = 0,006). Die Entwicklung eines Dekubitus (Kategorie II bis DTI) fand im Mittel in den ersten zwölf Tagen statt. In der Interventionsgruppe betrug die mittlere Zeit bis zur Entstehung eines Dekubitus 10,8 Tage (SD 10,1) und in der Kontrollgruppe 13,5 Tage (SD 13,8) (p = 0,025).

Insgesamt wurde bei n = 2 Patienten (0,47 %) ein unerwünschtes Ereignis festgestellt (jeweils in der Interventionsgruppe). Ein Patient berichtete über brennenden Schmerz und Wärmeempfinden unter dem Schaumverband am Sakrum. Weder Anzeichen einer Entzündung noch andere Auffälligkeiten konnten festgestellt werden. Auf Wunsch des Patienten wurde die Applikation beendet und die Symptome klangen ab. Bei einem weiteren Patienten war unter dem Schaumverband die Ablösung der oberen Hautschichten am Sakrum zu erkennen. Keine

Anzeichen einer Entzündung wurden festgestellt, die Teilnahme wurde fortgesetzt und der Patient beendete die Studie regulär.

3.3.2 ERGEBNISSE DER ÖKONOMISCHEN ANALYSE

Die Daten aller 422 auswertbaren Patienten des zugrundeliegenden RCTs wurden in Rahmen der ökonomischen Analyse berücksichtigt. Im Studienverlauf wurden insgesamt 1050 Sakralverbände und 2260 Fersenverbände in der Interventionsgruppe verwendet. Die gesamten Materialkosten betrugen 28.463,82 €, davon entfielen 22.292,53 € auf Fersenverbände und 6.171,13 € auf Sakralverbände. Für die Applikation oder den Wechsel eines Schaumverbandes wurde eine Arbeitszeit von zwei Minuten angenommen, basierend auf der Annahme, dass dieser im Rahmen regulärer pflegerischer Maßnahmen stattgefunden hat. Die Kosten der benötigten zusätzlichen Arbeitszeit aller Applikationen bzw. Wechsel belief sich auf 3.508,60 € (Fersen: 2.395,60 €; Sakrum: 1.113,00 €). Dies ergab in der Interventionsgruppe eine Gesamtsumme direkter Präventionskosten von 31.972,42 €, mit durchschnittlichen Mehrkosten von 150,81 € pro Patient. Die kalkulierten direkten Kosten inzidenter Dekubitus in beiden Gruppen setzten sich aus den zusätzlichen Material- und Lohnkosten zusammen. Totale direkte Kosten in der Interventionsgruppe für die Behandlung inzidenter Dekubitus (n = 6) lagen bei 134,88 € (Materialkosten: 106,77 €; Lohnkosten: 28,11 €), bei durchschnittlichen Mehrkosten von 22,48 € pro Patient. In der Kontrollgruppe beliefen sich die gesamten direkten Kosten für die Behandlung inzidenter Dekubitus (n = 22) auf 569,49 € (Materialkosten: 445,96 €; Lohnkosten: 123,53 €). Dies entsprach durchschnittlichen Mehrkosten von 25,89 € je Patient. Totale direkte Behandlungskosten in der Kontrollgruppe lagen 4,2-fach höher als in der Interventionsgruppe. Bezogen auf die einzelnen Kategorien aufgetretener Dekubitus reichten die durchschnittlichen täglichen Behandlungskosten von 0,33 € (Kategorie II; Ferse) bis 4,32 € (Kategorie III; Sakrum).

In der Basisfallanalyse belief sich der ICER auf 1945,30 € je vermiedenem Dekubitus in der Interventionsgruppe. Betrachtet man die ICERs nach ihrer Lokalisation getrennt voneinander ergibt sich ein ICER von 8144,72 € je vermiedenem Dekubitus an den Fersen und von 701,54 € je vermiedenem sakralen Dekubitus. Im Rahmen der Sensitivitätsanalyse wurden die Kosten sowie die Anzahl der verwendeten Fersenverbände als Variablen mit größtem Einfluss auf den ICER identifiziert. Am wenigsten Einfluss hatte die Anzahl der verwendeten Sakralverbände sowie die zusätzlich benötigte Arbeitszeit.

4. LIMITATIONEN

Obwohl im Rahmen der systematischen Übersichtsarbeit eine umfangreiche Recherche in mehreren Datenbanken sowie eine zusätzliche Suche in Referenzlisten eingeschlossener Volltexte durchgeführt wurde, besteht die Möglichkeit, dass weitere relevante Studien nicht identifiziert wurden. Da die Recherche auf deutsch- sowie englischsprachige Literatur beschränkt war, ist denkbar, dass nicht sämtliche verfügbare relevante Literatur in die Übersichtarbeit eingeschlossen wurde.

Die explorativ angelegte klinische Studie des zweiten Teilprojekts diente dazu empirische Evidenz über mögliche Effekte von Basishautpflegeprodukten auf die Adhäsionsstärke der DEJ zu gewinnen und umfasste nur eine geringe Stichprobengröße sowie eng definierte Einschlusskriterien. Aufgrund der Charakteristik der Stichprobe sind die Ergebnisse nicht generalisierbar und sollten daher als Grundlage für weitergehende Forschung und Hypothesenbildung betrachtet werden. Petrolatum gilt mit seiner Zusammensetzung, guten Verfügbarkeit und bekannten Eigenschaften als sicher in der Anwendung und ist Bestandteil verschiedener Pflegeprodukte. Petrolatum selbst besitzt zwar hohe hydratisierende Eigenschaften [64], jedoch sind spezielle Mixturen hydratisierender Inhaltsstoffe der alleinigen Verwendung von Petrolatum überlegen [65, 66]. Es wurden in dieser Studie keine Risikogruppen-spezifischen Faktoren berücksichtig, wie beispielsweise Individuen höheren Alters mit einer vorliegenden Xerosis cutis.

Aufgrund des Studiendesigns der in Teilprojekt 3 analysierten klinischen Studie, welche die Wirksamkeit mehrschichtiger Silikonschaumverbände zur Dekubitusprävention bei Hochrisikopatienten und -patientinnen auf Intensivstationen untersuchte, waren Teilnehmende sowie das Pflege- und Studienpersonal, hinsichtlich der Gruppenzuordnung und studienrelevanter Prozeduren, nicht verblindet. Dies birgt das Risiko einer möglichen Verzerrung bei der Studiendurchführung durch Performance Bias (systematische Differenzen bei der Studiendurchführung zwischen den beiden Gruppen) oder Detektionsbias (systematische Unterschiede zwischen den Vergleichsgruppen hinsichtlich der Datenerhebung oder Feststellung von Endpunkten). Das Auftreten von Selektionsbias könnte möglich sein, wird im Rahmen der Studie jedoch als gering eingeschätzt, da sämtliche aufgenommenen Patienten und Patientinnen der teilnehmenden Stationen hinsichtlich ihrer Eignung zur Studienteilnahme überprüft und bei Eignung eingeschlossen und randomisiert wurden. Im Rahmen der Studie wurden ausschließlich Dekubitus erfasst, die am Sakrum und den Fersen aufgetreten sind, andere Lokalisationen

wurden nicht berücksichtigt. Daher können keine Aussagen zur Dekubitusinzidenz abseits dieser Lokalisationen gemacht werden. Patienten und Patientinnen, die aufgrund eines instabilen Zustandes oder bestimmter medizinischer Prozeduren nicht bewegt werden konnten, waren von der Teilnahme ausgeschlossen. Die Begründung hierfür liegt darin, dass bei diesen Personen, die im Protokoll täglich geforderte Hautinspektion nur bedingt möglich gewesen wäre. Jedoch sind gerade diese Patienten und Patientinnen einem besonders hohen Dekubitusrisiko ausgesetzt und könnten in besonderem Maße von dieser Intervention profitieren.

Die dazugehörige ökonomische Analyse deckt nur den Zeitraum der Studienteilnahme ab, mit Entlassung aus dem Krankenhaus endete auch die Nachverfolgung der eingeschlossenen Patienten und Patientinnen. Da die Mehrheit entstandener Dekubitus nicht während des Krankenhausaufenthaltes abgeheilt ist, konnten in diesen Fällen nicht die gesamten Kosten bis zur Abheilung erfasst werden. Im Rahmen der Analyse wurde ein sogenannter Bottom-up-Ansatz genutzt, bei diesem wird auf Modellierungen (z. B. Markov-Modelle) und theoretische Annahmen verzichtet und nur die tatsächlichen realen Kosten berücksichtigt. Daher wurden in der Analyse auch nicht die entstandenen Kosten bis zur Abheilung, sondern nur während des Krankenhausaufenthaltes zugrunde gelegt. Es wäre zu erwarten, dass die tatsächlichen direkten Behandlungskosten je vermiedenem Dekubitus deutlich höher sind als im Rahmen der Analyse kalkuliert. Alle weiteren Kosten, die im Zusammenhang mit den entstandenen Dekubitus stehen, hätten sich positiv im Sinne der Kosteneffektivität auf den ICER ausgewirkt, ihn also gesenkt. Trotz umfangreicher Dokumentation der verbrauchten Ressourcen ist es wahrscheinlich, dass ein Teil des eingesetzten Materials nicht erfasst oder die dahinterstehende Arbeitszeit unterschätzt und somit nicht kalkuliert wurden. Die Sensitivitätsanalyse zeigte jedoch, dass auch bei Variation von ± 15 % der jeweiligen Schätzungen, hinsichtlich des Material- und Zeitaufwandes, diese nur einen geringen Effekt auf den ICER haben.

5. DISKUSSION

Das übergeordnete Ziel dieser Arbeit war es Kenntnisse hinsichtlich der Wirkung und Effektivität verschiedener präventiver topischer Ansätze zur Stärkung und Erhaltung der Hautintegrität vulnerabler Personengruppen zu erlangen. Die Verwendung von mehrschichtigen Silikonschaumverbänden im Rahmen der Dekubitusprävention wurde darüber hinaus auch unter dem ökonomischen Aspekt der Kosteneffektivität analysiert. Ein weiteres Ziel war es zu bewerten, inwiefern der Endpunkt „Blasenbildungszeit“ geeignet ist, um die dermo-epidermale Adhäsionsstärke im Rahmen der klinischen Forschung in einem direkten Ansatz zu quantifizieren.

Die durchgeführte systematische Literaturrecherche macht deutlich, dass das Interesse hinsichtlich Wirksamkeit und Nutzen präventiver topischer Hautpflegeinterventionen bei älteren Personen in den letzten Jahren gestiegen ist. In der ursprünglichen Übersichtsarbeit [30], die den Zeitraum von 1990 bis August 2012 und somit fast 22 Jahre umfasst, wurden 33 Artikel als relevant identifiziert. In der aktualisierten Version wurden anhand derselben Kriterien, für den deutlich kürzeren Zeitraum von September 2012 bis Mai 2018, 30 weitere Artikel identifiziert und ausgewertet. Bezieht man die eingeschlossenen Publikationen auf die analysierten Zeiträume, hat sich die jährliche Anzahl der Publikationen, die den verwendeten Suchkriterien zugeordnet werden können, mehr als verdreifacht.

Auffällig ist die hohe Anzahl identifizierter Endpunkte in den verschiedenen Publikationen. Insgesamt 35 verschiedene Endpunkte und fast 100 verwendete Messinstrumente wurden identifiziert. Allein für den Endpunkt „klinische Anzeichen trockener Haut“ wurden 17 verschiedene Messinstrumente in 13 Studien verwendet. Die hohe Heterogenität der Endpunkte und dazu gehörender Messinstrumente limitiert die Vergleichbarkeit, Interpretation und Generalisierbarkeit der Ergebnisse. Die Vergleichbarkeit ist unter anderem jedoch Grundlage für die Zusammenfassung von Daten im Rahmen von systematischen Übersichtsarbeiten oder Metaanalysen, welche wiederum relevant sind für die Synthese Evidenz-basierten Wissens [67]. Zur Verbesserung der Qualität und Vergleichbarkeit klinischer Forschung in diesem Gebiet empfiehlt es sich zu evaluieren welche Endpunkte die höchste Relevanz haben und welche jeweiligen Messinstrumente für deren Erhebung geeignet sind. In so genannten Core-Outcome-Sets (COS) wird ein standardisiertes Set der minimalen, einheitlich zu erfassenden Endpunkte innerhalb von klinischen Studien eines bestimmten Forschungsbereiches mit gleicher Fragestellung zusammengefasst [68]. Diese standardisierte Erfassung festgelegter „Kern“-Endpunkte hilft bei Zusammenfassung und Vergleich von

Ergebnissen unterschiedlicher Studien. Projekte für die Entwicklung von COS gibt es beispielsweise bereits im Rahmen der Dekubitusprävention [69] oder IAD-Forschung [70].

Die Studien zeigen einheitlich, dass die Verwendung von Hautpflegeprodukten zur Behandlung und Prävention der trockenen Haut effektiv ist. Dabei scheinen strukturierte Hautpflegeregime und Verwendung lipophiler Basishautpflegeprodukte, wie beispielsweise Petrolatum, mit oder ohne Feuchthaltemitteln wie Urea, Glycerin oder Laktat, hilfreich für eine Verbesserung der Hauttrockenheit und Stärkung der Hautbarriere zu sein. Zur Prävention sowie Behandlung der IAD zeigte sich ein strukturiertes Vorgehen, bestehend aus der Hautreinigung mit milden Produkten sowie die Anwendung eines Hautschutzprodukts, als hilfreich. Die Häufigkeit von Hautrissen bei älteren Personen konnte durch die regelmäßige Verwendung von Basishautpflegeprodukten, die Petrolatum und Glycerin enthielten, reduziert werden. Milde Hautreinigung in Verbindung mit einem Hautschutz scheinen teilweise vorteilhaft hinsichtlich der Vermeidung superfizieller Dekubitus zu sein.

Die im Rahmen der explorativen Studie gemessenen Werte für die SCH waren vergleichbar mit vorangegangenen Studien in ähnlichen Altersgruppen [71-76]. Trotz einer zu Beginn vorliegenden Differenz der SCH-Werte zwischen Interventions- und Kontrollarealen in Woche 0 zeigte sich im Studienverlauf, dass die SCH-Werte in den Interventionsarealen durchgängig höher waren, im Vergleich zu Kontrollarealen. Im Falle der epidermalen Hydratation waren die Werte in allen Arealen zu Beginn vergleichbar. Im Verlauf der Studie konnte beobachtet werden, dass die epidermale Hydratation in den Interventionsarealen im Vergleich zu Kontrollarealen ab Woche 2 bis zum Abschluss der Studie durchgehend erhöht war. Diese Beobachtungen bestätigen den beschriebenen hydratisierenden Effekt von Petrolatum [64, 77-79]. Hinsichtlich der epidermalen Dicke sind die gemessenen Werte vergleichbar mit publizierten Daten, die auf hochstandardisierten Messverfahren beruhen [58]. Die gemessenen Werte in allen Arealen wiesen zwischen den Messzeitpunkten nur eine geringe biologische Variabilität auf. Weder in den Interventions- noch den Kontrollarealen konnten relevante Veränderungen der epidermalen Dicke festgestellt werden. Diese Beobachtungen sind widersprüchlich mit anderweitig publizierten Daten, die eine deutliche Schwellung des Stratum corneums nach der Verwendung von Petrolatum zeigen konnten [80]. Eine mögliche Ursache könnte sein, dass die Zeitspanne der Intervention zu kurz gewählt wurde, um messbare Veränderungen der epidermalen Dicke zu detektieren.

Die benötigte Zeit bis zur Entstehung erster Vesikel sowie bis zur Ausbildung einer vollständigen Saugblase dauerte in allen Interventionsarealen systematisch länger als in den Kontrollarealen. Die zeitliche mediane Differenz in Woche 4 lag zwischen 3 bis 7 Minuten, in Woche 8 lag die gemessene Differenz bei 6 Minuten. Diese Resultate sprechen für eine gesteigerte dermo-epidermale Adhäsion, bedingt durch die Intervention. Die auf der Basis dieser Studie gewonnen Daten lassen keine direkten Rückschlüsse auf den zugrundeliegenden molekularen oder physiologischen Mechanismus zu. Jedoch stehen sie im Einklang mit der beobachteten Reduktion von Hautrissen in Folge einer regelmäßigen Applikation topischer Basishautpflegeprodukte [47].

Die Ergebnisse der Studie lassen darauf schließen, dass die Saugblasenmethode und Messung der Blasenbildungszeit geeignet sind, um im Rahmen klinischer Forschung die dermo-epidermale Adhäsionsstärke zu quantifizieren. Beispielsweise kann mit ihr der Einfluss verschiedener Interventionen oder die Exposition der Haut gegenüber bestimmten (Umwelt-) Faktoren auf die dermo-epidermale Adhäsion spezifischer charakterisiert werden. Die Methode erlaubt aufgrund ihres invasiven Ansatzes eine direkte Quantifizierung der dermo-epidermalen Adhäsionsstärke *in vivo*, welche durch nicht-invasive indirekte Methoden nur bedingt möglich ist. Jedoch ist diese Methode gerade aufgrund ihres invasiven und auch zeitlich aufwendigen Charakters weder als routinierte Standardmethode noch als isolierter Ansatz zu verstehen. Vielmehr sollte diese Methode lediglich bei spezifischer Fragestellung und stets im Kontext mit etablierten Messmethoden verwendet werden. Dabei ist ein hoher Grad an Standardisierung bei Durchführung und Analyse unabdingbar, um die Reproduzierbarkeit und Aussagekraft sicherzustellen.

In Folgestudien könnten weitere Aspekte näher betrachtet werden, die hier nicht berücksichtigt wurden oder im Widerspruch zu anderweitig publizierten Daten stehen. Zum einen könnte der Untersuchungszeitraum ausgeweitet werden, um die Effekte von Petrolatum auf die Dicke des Stratum corneums besser beurteilen zu können. Zum anderen könnten weitere Basishautpflegemittel wie Glycerin bzw. Kombinationen aus verschiedenen Inhaltsstoffen getestet werden. Die Studienpopulation sollte angepasst werden, so dass Risikogruppen-spezifische Faktoren berücksichtigt werden, wie ältere Personen mit Xerosis cutis. Ebenfalls sollte bewertet werden, ob die Parameter „Zeit bis zum ersten Vesikel“ und „Zeit bis zur vollständigen Saugblase“ unterschiedliche Aussagekraft besitzen. Die Tatsache, dass die Entstehung eines ersten Vesikels das Zeichen der initialen dermo-epidermalen Trennung ist,

spricht dafür, diesen Parameter zu nutzen. Im Rahmen der Studie konnte jedoch keine abschließende Aussage darüber getroffen werden welcher Parameter die höhere Aussagekraft und Reproduzierbarkeit aufweist.

Das pragmatische Design der im dritten Teilprojekt behandelten Studie erlaubte es die Effekte der Intervention, im Vergleich zu hoch standardisierten RCTs, im Rahmen der täglichen Routineversorgung zu erfassen. Demografische Charakteristiken wie Alter und Geschlecht der Studienpopulation sind vergleichbar mit vorausgegangenen Studien in ähnlicher Studienumgebung [81-83]. Der größere Teil der entstanden Dekubitus war im Sakralbereich lokalisiert, was im Einklang mit anderweitig publizierten Daten vergleichbarer Studien auf Intensivstationen steht [84, 85].

Der zeitlich unbegrenzte Nachverfolgungszeitraum ermöglichte den Gewinn realitätsnaher Daten über Verweildauer und Zeitspannen bis zum Auftreten von Dekubitus bei Hochrisikopatienten und -patientinnen auf Intensivstationen. Vergleichbare Studien waren bisher zeitlich limitiert und nicht auf die tatsächliche Aufenthaltsdauer ausgerichtet [81, 84, 85]. Die Ergebnisse zeigen, dass die Mehrzahl aufgetretener Dekubitus innerhalb der ersten Woche nach Aufnahme entstanden sind. Es konnten jedoch auch Fälle beobachtet werden, in denen ein inzidenter Dekubitus später aufgetreten ist. Eine weitere Stärke der Studie ist, dass mögliche Effekte der Intervention sich auf die Dekubitus-Kategorien II oder höher beziehen. Analysen vergleichbarer Studien beziehen auch Dekubitus der Kategorie I ein [81, 85, 86]. Dekubitus der Kategorie I stellen jedoch keine Wunden im eigentlichen Sinne dar, ihre klinische Relevanz ist fraglich und Messfehler dieser Variable sind hoch [87]. Der vorläufige Einschluss nicht einwilligungsfähiger Patienten und Patientinnen ermöglichte ein breites Spektrum an Teilnehmenden inklusive schwersterkrankten und/oder sedierten Personen. Die Ergebnisse der Studie zeigen, dass die Applikation der präventiven Verbände an Sakrum und Fersen in dieser Studienpopulation die Dekubitusinzidenz in diesen Arealen signifikant reduzieren kann.

Die beobachteten Effekte in der Interventionsgruppe sind mit ähnlichen Studien vergleichbar, bei denen die gleichen Verbände verwendet wurden [81, 84, 85]. Es trat nur eine geringe Anzahl unerwünschter Ereignisse auf, deren Schwere und Verlauf mild war und vollständig abgeklungen sind. Analysen, bei denen auf verschiedene Risikovariablen adjustiert wurde, zeigen, dass die Intervention selbst der einzige signifikante Faktor hinsichtlich der Dekubitusinzidenz ist. Darauf basierend kann geschlussfolgert werden, dass der zusätzliche Einsatz der verwendeten Verbände neben den Standardpräventionsmaßnahmen effektiv und

sicher für die Dekubitusprävention bei Hochrisikopatienten und -patientinnen auf Intensivstationen ist. Die Verwendung präventiver Verbände sollte dabei keinesfalls als Ersatz für standardisierte Maßnahmen der Dekubitusprävention gesehen (z. B. regelmäßige Lagerung der Patienten), sondern als zusätzliche unterstützende Option verstanden werden, um die Dekubitusinzidenz weiter zu reduzieren.

Neben Bewertung der klinischen Wirksamkeit wurde eine ökonomische Analyse durchgeführt, welche Aufschluss über die Kosteneffektivität der Intervention geben sollte. Die Intervention verursachte durchschnittliche Mehrkosten von 1.945,30 € je vermiedenem Dekubitus der Kategorie II oder höher am Sakrum oder den Fersen. Schlüsselt man die Ergebnisse der Analyse nach ihrer Lokalisation auf, zeigt sich ein deutlicher Unterschied hinsichtlich der beiden ICER. Der ICER für die Prävention eines Dekubitus im Sakralbereich lag bei etwa 701,54 €, während der ICER für die Prävention eines Dekubitus an der Ferse mit 8.144,72 € mehr als das 11-Fache höher lag. Begründen lässt sich diese Diskrepanz hauptsächlich durch die, in Relation zum Sakralbereich gesehen, geringe Anzahl entstandener Dekubitus an Fersen bei gleichzeitig wesentlich höherem Verbrauch von Fersenverbänden sowie einem deutlich höheren Stückpreis pro Fersenpflaster. Die Kosteneffektivität könnte an dieser Stelle beispielsweise durch Verlängerung der Tragezeiten gesteigert werden.

Aus der Perspektive des versorgenden Krankenhauses kann der ICER von circa 700 € für die Prävention eines Sakral-Dekubitus als kosteneffektiv bezeichnet werden. Gegensätzlich dazu ist der in Relation gesehen sehr hohe ICER für die Prävention eines Fersen-Dekubitus zu bewerten. Grundsätzlich ist zu berücksichtigen, dass die tatsächlichen Gesamtkosten für die Behandlung eines Dekubitus wahrscheinlich deutlich über den hier ermittelten Werten liegen würden. Zusätzliche direkte Kosten zulasten des Gesundheitssystems und der Betroffenen für weiterführende Wundversorgung oder indirekte Kosten, wie Produktivitätsverluste in Folge der Erkrankung, wurden nicht berücksichtigt. Höhere Kosten für die Behandlung würden sich wiederum senkend auf den ICER auswirken und somit die Kosteneffektivität steigern.

Leitlinien zur Dekubitusprävention [18, 88] empfehlen die systematische Verwendung von präventiven Verbänden im Sakralbereich. Darauf basierend, zusammen mit den Ergebnissen der durchgeführten Interventionsstudie sowie der zugehörigen ökonomischen Analyse, wurde die Verwendung der mehrschichtigen Silikonschaumverbände im Sakralbereich bei Hochrisikopatienten und -patientinnen in stationären Bereichen der Charité – Universitätsmedizin Berlin implementiert.

SCHLUSSFOLGERUNGEN

I. Das Interesse an topischen Hautpflegeinterventionen zur Erhaltung der Hautintegrität älterer Personen ist in der letzten Dekade deutlich angestiegen. Regelmäßige Verwendung von Basishautpflegeprodukten (bevorzugt niedriger pH-Wert) mit Inhaltsstoffen wie Petrolatum, Paraffin oder Glycerin, zeigen einen förderlichen Einfluss auf die Erhaltung der Hautintegrität. Im Bereich präventiver Hautpflegeinterventionen besteht eine hohe Heterogenität verwendeter Endpunkte und Messinstrumente, die eine Vergleichbarkeit von Studien und deren Zusammenfassung erschweren. Die Identifizierung relevanter Endpunkte sowie geeigneter Messinstrumente und deren einheitliche Anwendung in diesem Forschungsbereich ist erforderlich.

II. Im Einklang mit Ergebnissen der systematischen Übersichtsarbeit, zeigt die durchgeführte, explorativ angelegte Studie, dass die regelmäßige topische Verwendung von Petrolatum als Basishautpflegeprodukt die Hautintegrität älterer Personen verbessern kann. Die Ergebnisse legen nahe, dass dies im Zusammenhang mit einer gesteigerten dermo-epidermalen Adhäsion steht. Diese könnte, neben der gesteigerten Hydratation der Haut, auf möglichen strukturellen und funktionellen Veränderungen der Epidermis sowie dermo-epidermalen Junktionszone beruhen. Im Rahmen der klinischen Forschung stellt die Saugblasenmethode in Verbindung mit dem Endpunkt „Blasenbildungszeit“ einen geeigneten direkten Ansatz dar, um die dermo-epidermale Adhäsionsstärke zu quantifizieren.

III. Die Applikation mehrschichtiger Silikonschaumverbände im Sakralbereich sowie an den Fersen kann, in Verbindung mit Standardpräventionsmaßnahmen, bei Hochrisikopatienten und -patientinnen auf Intensivstationen die Dekubitusinzidenz in diesen Arealen senken. Die Anwendung der Verbände im Sakralbereich kann aus Sicht des versorgenden Krankenhauses als kosteneffektiv bezeichnet werden.

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EIDESSTATTLICHE VERSICHERUNG

„Ich, Monira El Genedy-Kalyoncu, versichere an Eides statt durch meine eigenhändige Unterschrift, dass ich die vorgelegte Dissertation mit dem Thema:

„Anwendung topischer Produkte zum Erhalt der Hautintegrität im Alter und bei Pflegebedürftigkeit“

„Application of topical products to maintain skin integrity in aged and care dependent individuals“

selbstständig und ohne nicht offengelegte Hilfe Dritter verfasst und keine anderen als die angegebenen Quellen und Hilfsmittel genutzt habe.

Alle Stellen, die wörtlich oder dem Sinne nach auf Publikationen oder Vorträgen anderer Autoren/innen beruhen, sind als solche in korrekter Zitierung kenntlich gemacht. Die Abschnitte zu Methodik (insbesondere praktische Arbeiten, Laborbestimmungen, statistische Aufarbeitung) und Resultaten (insbesondere Abbildungen, Graphiken und Tabellen) werden von mir verantwortet.

Ich versichere ferner, dass ich die in Zusammenarbeit mit anderen Personen generierten Daten, Datenauswertungen und Schlussfolgerungen korrekt gekennzeichnet und meinen eigenen Beitrag sowie die Beiträge anderer Personen korrekt kenntlich gemacht habe (siehe Anteilserklärung). Texte oder Textteile, die gemeinsam mit anderen erstellt oder verwendet wurden, habe ich korrekt kenntlich gemacht.

Meine Anteile an etwaigen Publikationen zu dieser Dissertation entsprechen denen, die in der untenstehenden gemeinsamen Erklärung mit dem/der Erstbetreuer/in, angegeben sind. Für sämtliche im Rahmen der Dissertation entstandenen Publikationen wurden die Richtlinien des ICMJE (International Committee of Medical Journal Editors; www.icmje.org) zur Autorenschaft eingehalten. Ich erkläre ferner, dass ich mich zur Einhaltung der Satzung der Charité – Universitätsmedizin Berlin zur Sicherung Guter Wissenschaftlicher Praxis verpflichte.

Weiterhin versichere ich, dass ich diese Dissertation weder in gleicher noch in ähnlicher Form bereits an einer anderen Fakultät eingereicht habe.

Die Bedeutung dieser eidesstattlichen Versicherung und die strafrechtlichen Folgen einer unwahren eidesstattlichen Versicherung (§§156, 161 des Strafgesetzbuches) sind mir bekannt und bewusst.“

Datum Unterschrift

ANTEILSERKLÄRUNG AN DEN ERFOLGTEN PUBLIKATIONEN

Monira El Genedy-Kalyoncu hatte folgende Anteile an den folgenden Publikationen:

PUBLIKATION 1:

Lichterfeld-Kottner A, **El Genedy M**, Lahmann N, Blume-Peytavi U, Büscher A, Kottner J. Maintaining skin integrity in the aged: A systematic review. Int J Nurs Stud. 2020;103:103509. https://doi.org/10.1016/j.ijnurstu.2019.103509

BEITRAG IM EINZELNEN: Wesentliche Beteiligung beim Titel-/Abstract-Screening und Bewertung der Volltexte sowie bei Datenextraktion und Synthese der Ergebnisse, wesentliche Beteiligung an der Gestaltung sowie Mitarbeit am Manuskript bei Ersteinreichung sowie dessen Revision.

PUBLIKATION 2:

El Genedy-Kalyoncu M, Richter C, Surber C, Blume-Peytavi U, Kottner J. The effect of a basic skin care product on the structural strength of the dermo-epidermal junction: An exploratory, randomized, controlled split-body trial. Int Wound J. 2021;1–10. https://doi.org/10.1111/iwj.13643

BEITRAG IM EINZELNEN: Mitwirkung bei der Entwicklung der Forschungsfrage, wesentliche Beteiligung bei Planung des Designs, wesentliche Beteiligung bei der Erstellung des Studienprotokolls und studienrelevanter Dokumente, wesentliche Beteiligung bei Einreichungen bei der Ethikkommission sowie der Stabsstelle Datenschutz, Hauptsächliche Rekrutierung der Studienteilnehmerinnen, Hauptsächliche Durchführung der Studie sowie Datenerhebung, Wesentliche Beteiligung an der statistischen Auswertung und Interpretation der Daten, Darstellung der Ergebnisse und Inhalte (Tabellen 1-4; Abbildungen 1-4), Federführung beim Schreiben der Publikation einschließlich der Einreichung sowie Revision des Manuskriptes.

PUBLIKATION 3:

Hahnel E, **El Genedy M**, Tomova-Simitchieva T, Hauß A, Stroux A, Lechner A, Richter C, Akdeniz M, Blume-Peytavi U, Löber N, Kottner J. The effectiveness of two silicone dressings for sacral and heel pressure ulcer prevention compared with no dressings in high-risk intensive care unit patients: a randomized controlled parallel-group trial. Br J Dermatol. 2020;183(2):256-264. https://doi.org/10.1111/bjd.18621

BEITRAG IM EINZELNEN: Wesentliche Beteiligung an der Rekrutierung der Patienten und an der Durchführung der Studie sowie Datenerhebung, wesentliche Beteiligung an der Datenanalyse, Beteiligung an der Gestaltung und Mitarbeit am Manuskript bei Ersteinreichung sowie dessen Revision.

PUBLIKATION 4:

El Genedy M, Hahnel E, Tomova-Simitchieva T, Padula WV, Hauß A, Löber N, Blume-Peytavi U, Kottner J. Cost-effectiveness of multi-layered silicone foam dressings for prevention of sacral and heel pressure ulcers in high-risk intensive care unit patients: An economic analysis of a randomised controlled trial. Int Wound J. 2020;17:1291-1299.
https://doi.org/10.1111/iwj.13390

BEITRAG IM EINZELNEN: Wesentliche Beteiligung an der Rekrutierung der Patienten und an der Durchführung der zugrundeliegenden Studie sowie Datenerhebung, Hauptsächliche Durchführung der Datenextraktion und -aufbereitung, wesentliche Beteiligung an der Auswertung und Interpretation der Daten, Darstellung der Ergebnisse (Tabellen 1-4; Abbildung 1), Federführung beim Schreiben der Publikation einschließlich der Einreichung sowie Revision des Manuskriptes.

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Datum, Unterschrift, Stempel
Prof. Dr. rer. cur. Jan Kottner (erstbetreuender Hochschullehrer)

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Datum, Unterschrift
Monira El Genedy-Kalyoncu (Doktorandin)

DRUCKEXEMPLARE DER AUSGEWÄHLTEN PUBLIKATIONEN

PUBLIKATION 1: LICHTERFELD-KOTTNER A, EL GENEDY M, LAHMANN N, BLUME-PEYTAVI U, BÜSCHER A, KOTTNER J. MAINTAINING SKIN INTEGRITY IN THE AGED: A SYSTEMATIC REVIEW. INT J NURS STUD. 2020;103:103509.

https://doi.org/10.1016/j.ijnurstu.2019.103509

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1	INTERNATIONAL JOURNAL OF NURSING STUDIES	7,971	3.656	0.012690
2	JOURNAL OF NURSING SCHOLARSHIP	2,431	2.662	0.002870
3	European Journal of Cardiovascular Nursing	1,463	2.651	0.002510
4	NURSING OUTLOOK	1,598	2.425	0.002620
5	EUROPEAN JOURNAL OF CANCER CARE	2,576	2.409	0.004330
6	BIRTH-ISSUES IN PERINATAL CARE	2,250	2.329	0.002010
7	JOURNAL OF ADVANCED NURSING	16,130	2.267	0.011660
8	Worldviews on Evidence-Based Nursing	1,061	2.143	0.001690
9	Journal of Cardiovascular Nursing	1,689	2.097	0.002840
10	NURSE EDUCATION TODAY	5,917	2.067	0.007090
11	AMERICAN JOURNAL OF CRITICAL CARE	2,483	2.055	0.002840
12	International Journal of Mental Health Nursing	1,389	2.033	0.001860
13	Journal of Family Nursing	648	1.955	0.000620
14	Australian Critical Care	600	1.930	0.000920
15	Journal of Tissue Viability	448	1.925	0.000560
16	Journal of Nursing Management	3,126	1.912	0.003730
17	NURSING ETHICS	1,773	1.876	0.002070
18	CANCER NURSING	2,927	1.844	0.004280
19	JOURNAL OF HUMAN LACTATION	1,814	1.836	0.003080
20	Women and Birth	922	1.822	0.002250
21	European Journal of Oncology Nursing	2,088	1.812	0.004630
22	Journal of Pediatric Nursing-Nursing Care of Children & Families	1,960	1.800	0.002790
23	MIDWIFERY	3,385	1.787	0.006170

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Maintaining skin integrity in the aged: A systematic review

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ABSTRACT

Background: In aged nursing care receivers, the prevalence of adverse skin conditions such as xerosis cutis, intertrigo, pressure ulcers or skin tears is high. Adequate skin care strategies are an effective method for maintaining and enhancing skin health and integrity in this population.
Objectives: The objective was to summarize the empirical evidence about the effects and effectiveness of non-drug topical skin care interventions to promote and to maintain skin integrity and skin barrier function in the aged, to identify outcome domains and outcome measurement instruments in this field.
Design: An update of a previous systematic review published in 2013 was conducted.
Data sources: Databases MEDLINE and EMBASE via OvidSP and CINAHL (original search January 1990 to August 2012, update September 2012 to May 2018) and reference lists were searched. Forward searches in Web of Science were conducted.
Methods: A review protocol was registered in Prospero (CRD42018100792). Main inclusion criteria were primary intervention studies reporting treatment effects of basic skin care strategies in aged people with a lower limit of age range of 50 years and published between 1990 and 2018. Primary empirical studies were included with experimental study designs including randomized controlled trials and quasi-experimental designs. Methodological quality of included randomized controlled trials was evaluated using the Cochrane Collaboration's Tool for assessing risk of bias. Levels of evidence were assigned to all included studies.
Results: Sixty-three articles were included in the final analysis reporting effects of interventions to treat and/or to prevent skin dryness, pruritus, general skin barrier improvement, incontinence-associated dermatitis, skin tears and pressure ulcers. Skin cleansers containing syndets or amphotheric surfactants compared with standard soap and water improved skin dryness. Lipophilic leave-on products containing humectants decreased skin dryness and reduced pruritus. Products with pH 4 improved the skin barrier. Application of skin protectants and structured skin care protocols decreased the severity of incontinence-associated dermatitis. Formulations containing glycerin and petrolatum reduced the incidence of skin tears. Thirty-five outcome domains were identified with nearly 100 different outcome measurement instruments.
Conclusion: Included studies showed substantial heterogeneity regarding design, interventions and outcomes. Basic skin care strategies including low-irritating cleansers and lipophilic humectant-containing leave-on products are helpful for treating dry skin and improving skin barrier in the aged. Lower pH of leave-on products improves the skin barrier. The number of different outcome domains was unexpectedly high. We recommend to identify critical outcome domains in the field of skin care to make trial results more comparable in the future and to measure possible performance differences between different skin care strategies and products.

What is already known about the topic?

- Aging skin undergoes structural and functional changes.
- Xerosis cutis, pressure ulcers and skin tears are frequent in aged care.

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- Leave-on products containing humectants reduce symptoms of skin dryness.

What this paper adds

- Regular application of leave-on products reduces signs of dry skin and prevents skin tears.
- A lower pH of leave-on products improves skin barrier integrity.
- Standardized skin care approaches including skin protectants prevent incontinence-associated dermatitis.

1. Introduction

The aging population is growing worldwide. The proportion of the worldś population aged over 60 years will increase to 22% until 2050. These demographic changes present challenges to all health care systems and care settings worldwide. Age dependent morphological and functional changes affect the whole body, but also the skin (Blume-Peytavi et al., 2016). For example, the skin barrier function declines and immunological processes are reduced (Al-Nuaimi et al., 2014). The content of natural moisturizing factors and lipids in the stratum corneum is decreased. Reduced water content in the stratum corneum causes impaired enzymatic processes leading to dry skin (Toncic et al., 2018). Xerosis cutis is one of the most common dermatological diagnosis in the elderly. The prevalence ranges from 30% to 100% in different care settings (Hahnel et al., 2017a, 2017b, 2017c, Paul et al., 2011; White-Chu and Reddy, 2011). Epidermal and dermal thinning and increased cutaneous stiffness leads to a higher risk for shear-type injuries such as skin tears or pressure ulcers. The prevalence of these skin conditions in aged persons over 60 years ranges from 4% to 30% (Hahnel et al., 2017a, 2017b, 2017c, LeBlanc et al., 2016; Toncic et al., 2018). Against this background, adequate skin care strategies are an effective method for maintaining and enhancing skin health and integrity in the aged (Lichterfeld et al., 2015).

Maintaining and improving skin health are integral parts of nursing practice; therefore, skin integrity serves as a quality indicator in nursing care (Nakrem et al., 2009). Patients and residents in acute and long-term care settings receive daily routine skin care delivered by nurses, including washing, bathing, and showering, together with the application of lotions, creams, and/or ointments (Kottner et al., 2015; Lechner et al., 2018; Rahn et al., 2016). Although these personal hygiene and skin care activities are daily activities of nursing practice, little is known about their benefits or clinical efficacy.

A systematic review published in 2013 (Kottner et al., 2013) revealed, that the empirical evidence supporting preventive skin care strategies in the aged is rare and of high risk of bias. The main conclusions were that the use of low-irritating cleansing products and humectant- or occlusive-containing leave-on products seem to have beneficial effects compared to using standard soap and water or no treatment. A major limitation of this evidence summary was the non-comparability of study outcomes.

The problem of outcome heterogeneity in clinical trials is considered today as one major challenge in evidence based healthcare in general and skin research specifically (Kottner et al., 2018; Kottner and Schmitt, 2018; Schmitt et al., 2018). Today, several initiatives exist for developing so called core outcome sets, that might be one solution to standardize outcome measurement and reporting in clinical trials. A core outcome set consists of outcome domains and outcome measurement instruments (Prinsen et al., 2014).

The aim of this work was to update the existing systematic review (Kottner et al., 2013) and to summarize the empirical evidence about the effects and effectiveness of non-drug topical skin care interventions to promote and to maintain skin integrity and skin barrier function in the aged. Another aim was to identify reported outcome domains and outcome measurement instruments in the field of preventive skin care in the aged.

2. Methods

This is an update of the systematic review published in 2013 (Kottner et al., 2013) using similar methods. The protocol was previously registered in the Prospero database (CRD42018100792).

2.1. Eligibility criteria

Studies had to meet identical inclusion criteria as those in the previous systematic review (Kottner et al., 2013). Primary empirical studies were included with experimental study designs comprising randomized controlled trials (RCTs) and quasi-experimental designs including before after studies describing, analyzing and reporting treatment effects of basic skin care strategies. This included skin cleansing procedures and/or use of rinse-off and/or use of leave-on products used for promoting and maintaining of skin integrity in the aged. Examples include cosmetic products such as moisturizers, soaps, syndets, and emulsions or medical devices. Further inclusion criteria were: humans; in vivo studies; physiologically aged skin including xerosis; publication dates September 2012 to May 2018; languages: English, German; lower limit of age range 50 years.

Exclusion criteria were: age <50 years; non-research papers, e.g., narrative reviews, editorials, letters to the editor; tool development and/or validation studies; observational studies without interventions; studies focusing on the treatment of diseased skin like rosacea, atopic dermatitis. Studies including diseased and non-diseased subjects were included when the proportion of diseased patients was under 25%. Medicinal product studies; anti-aging treatments to improve skin appearance of photo damaged skin and in vitro studies were excluded as well. Conference abstracts were included in the first systematic review of 2013 due to the lack of evidence, but excluded in this update.

2.2. Information sources and search

The databases MEDLINE and EMBASE via OvidSP (first search from 1990 to August 2012, update from September 2012 to May 2018) were searched. The database CINAHL was searched using EBSCOhost (first search from 1990 to August 2012, update September 2012 to May 2018) using a comparable search strategy (Table 1). Reference lists of included possible eligible articles were screened for additional studies. After inclusion of studies from database searches and reference lists a forward search was conducted in Scopus (October 2018) for identification of additional relevant studies citing already included studies.

2.3. Study selection and data collection process

Results of the database searches were screened independently by two reviewers (AL, MG) based on title and abstract. Possible relevant articles were read in full text by the two reviewers (AL, MG) independently. A third reviewer (JK) resolved possible discrepancies. Structured data extraction tables were prepared and structured summary data extraction tables were completed including source, study design, setting, sample and indication, intervention, study duration, number of included subjects, mean age, outcomes, main results and methodological appraisal. Results of individual studies were extracted from the text, recalculated if necessary and summarized in data extraction sheets.

Table 1
Search strategy in the databases Medline and Embase using OVID 1990–2018.

	Search terms	Original review 2013	Search update	#Total
1.	Emollien*.ti. or emollien*.ab. or "Emollients"	5666	3963	9629
2.	Moisturi*.af.	2848	5576	8424
3.	Skin care product*.af.	828	1498	2326
4.	Skin care/	–	13,998	13,998
5.	Skin/an, ah, cl, di [Analysis, Anatomy & Histology, Classification, Diagnosis]	–	7313	7313
6.	hygiene/	–	57,540	57,540
7.	1 or 2 or 3 or 4 or 5 or 6		87,007	87,007
8.	Limit 7 to ("middle aged (45 plus years)" or "all aged (65 and over)" or "aged (80 and over)")	4,234,597	60,264	4.294861
9.	Limit 8 to (clinical trial or randomized controlled trial or controlled clinical trial or multicenter study)	–	3534	3534
10.	Limit 9 to human	26,293,275	3399	26,296,674
11.	Limit 10 to yr = "2012–Current"	–	1325	1325
12	Limit 11 to yr = "1990–2012"	732	–	732
13.	Remove duplicates from 11 to 12	**690**	**1166**	**1856**

2.4. Risk of bias in individual studies

The risk of bias of the included RCTs was evaluated by the Cochrane Collaboration's Tool for assessing risk of bias (Higgins, 2008). The tool includes six possible bias categories: sequence generation, allocation concealment, blinding, incomplete outcome data, selective outcome reporting and other potential threats to validity. These categories were judged as "low risk of bias", "high risk of bias", or "unclear". The Cochrane Collaboration's Tool for assessing risk of bias was developed for assessing risk of bias for randomized trials. Therefore, we only appraised the included RCTs using this tool. Risk of bias of the quasi-experimental studies was not evaluated.

A Level of Evidence ranging from 1 to 5 was assigned based on the Oxford Center for Evidence Based Medicine framework. Level of Evidence 1 indicates evidence based on systematic reviews of RCTs. RCTs or observational studies with a dramatic effect were categorized to Level of Evidence 2, non-randomized controlled cohort/follow-up studies were assigned to Level of Evidence 3, Level of Evidence 4 based on case-control studies, and Level of Evidence 5 based on mechanism-based reasoning. If there were methodological limitations or high risk of bias the Level of Evidence was graded down. RCTs in this review were downgraded if more than four quality criteria were not met. The Level of Evidence can be interpreted as an overall indicator for study design, quality and therefore the internal validity of the study results.

2.5. Summary measures and synthesis of results

Results are presented descriptively per identified skin condition. The skin condition categories were developed inductively based on the reported study outcomes. Reported outcome measurement instruments were iteratively assigned to outcome domains.

3. Results

3.1. Study selection

The electronic database searches in MEDLINE, CINAHL and EMBASE resulted in 1387 records in the original review and 1465 records in the update. Fig. 1 shows the Prisma flow diagram of the study identification process, screening and eligibility. One hundred eighty-eight articles were read in full-text in the original review and 100 articles in the update. Sixty-three articles were finally included in the quantitative data analysis (33 articles in the original review and 30 articles in the update). Seventy articles were excluded in the update and are listed as online Appendix 1 including reasons for exclusion.

3.2. Study characteristics and risk of bias

Included studies are summarized in Tables 2 to 5 describing the study designs, indications, interventions, sample characteristics, outcomes, risk of bias, and Levels of Evidence. A detailed description of all included studies is presented in online Appendix 2. Some included articles reported more than one study (Quatresooz et al., 2009; Weber et al., 2012; Angelova-Fischer et al., 2018; Behm et al., 2015). Of the total of 63 included studies, 31 studies addressed prevention and treatment of dry skin, 12 studies were related to skin barrier improvement, 13 to incontinence-associated dermatitis prevention, 6 to pressure ulcer and 5 to skin tear prevention.

Of the 31 studies reporting prevention or treatment of skin dryness, 15 studies were included in the original systematic review (Kottner et al., 2013) and the update includes 16 studies (Blaak et al., 2017; Chang et al., 2018; Cristaudo et al., 2015; Danby et al., 2016; Federici et al., 2012; Federici et al., 2015; Gillis et al., 2016; Gin et al., 2017; Hahnel et al., 2017a, 2017b, 2017c, Izumi et al., 2017; Korponyai et al., 2017; Martini et al., 2017; Weber et al., 2012) (Table 2). In total, 1657 subjects participated in these studies.

Further ten articles were included reporting 12 studies (Angelova-Fischer et al., 2018; Behm et al., 2015; Blaak et al., 2015; Brooks et al., 2017; Farwick et al., 2014; Narbutt et al., 2016; Paulela et al., 2018; Schoonhoven et al., 2015; Elewa et al., 2012; Roure et al., 2012) for maintaining and improvement of skin barrier integrity (Table 3). The included studies for dry skin prevention and treatment comprised 21 RCTs. The highest Level of Evidence of 2 was assigned to six RCTs (Federici et al., 2015; Hahnel et al., 2017, 2017b, 2017c, Martini et al., 2017; Pham et al., 2002; Quatresoz et al. 2009a, 2009b). Due to quasi-experimental designs and high risk of bias 10 studies had Level of Evidence of 3. Intra-individual comparisons were used for six RCTs and group comparisons in 15.

Studies for skin barrier improvement included six RCTs with a Level of Evidence of 3 and six studies with quasi-experimental design. Of these, four studies had a Level of Evidence of 3 (Brooks et al., 2017; Elewa et al., 2012; Farwick et al., 2014; Narbut et al. 2016), and two studies had a Level of Evidence of 4 (Behm et al., 2015, Roure et al., 2012). Two RCTs used intra-individual comparisons and in four RCTs group comparisons were used.

The original review included 9 studies addressing incontinence-associated dermatitis prevention (Beeckman et al., 2011; Bliss et al., 2006, 2007; Byers et al., 1995; Cooper et al., 2008; Cooper and Gray 2001, Lewis-Byers and Thayer, 2002, Lyder et al., 1992, Warshaw et al., 2002, Zehrer et al., 2004). Four additional studies were included in the update reporting incontinence-associated dermatitis management including 1845 subjects in total (Brunner et al., 2012; Conley et al., 2014; Kon et al., 2017; Park and Kim, 2014) (Table 4).

Overall, 5 studies addressed skin tear prevention (Mason 1997; Birch and Coggins 2003; Groom et al., 2010; Carville et al., 2014; Finch et al., 2018). Interventions for pressure ulcer prevention were investigated in six studies (Clever et al., 2002; Hunter et al., 2003; Thompson et al., 2005; Torra i Bour et al. 2005; Lupianez-Perez et al., 2015; Verdu and Soldevilla, 2012) (Table 5). In total, 4121 subjects participated in these studies. Most of these were RCTs

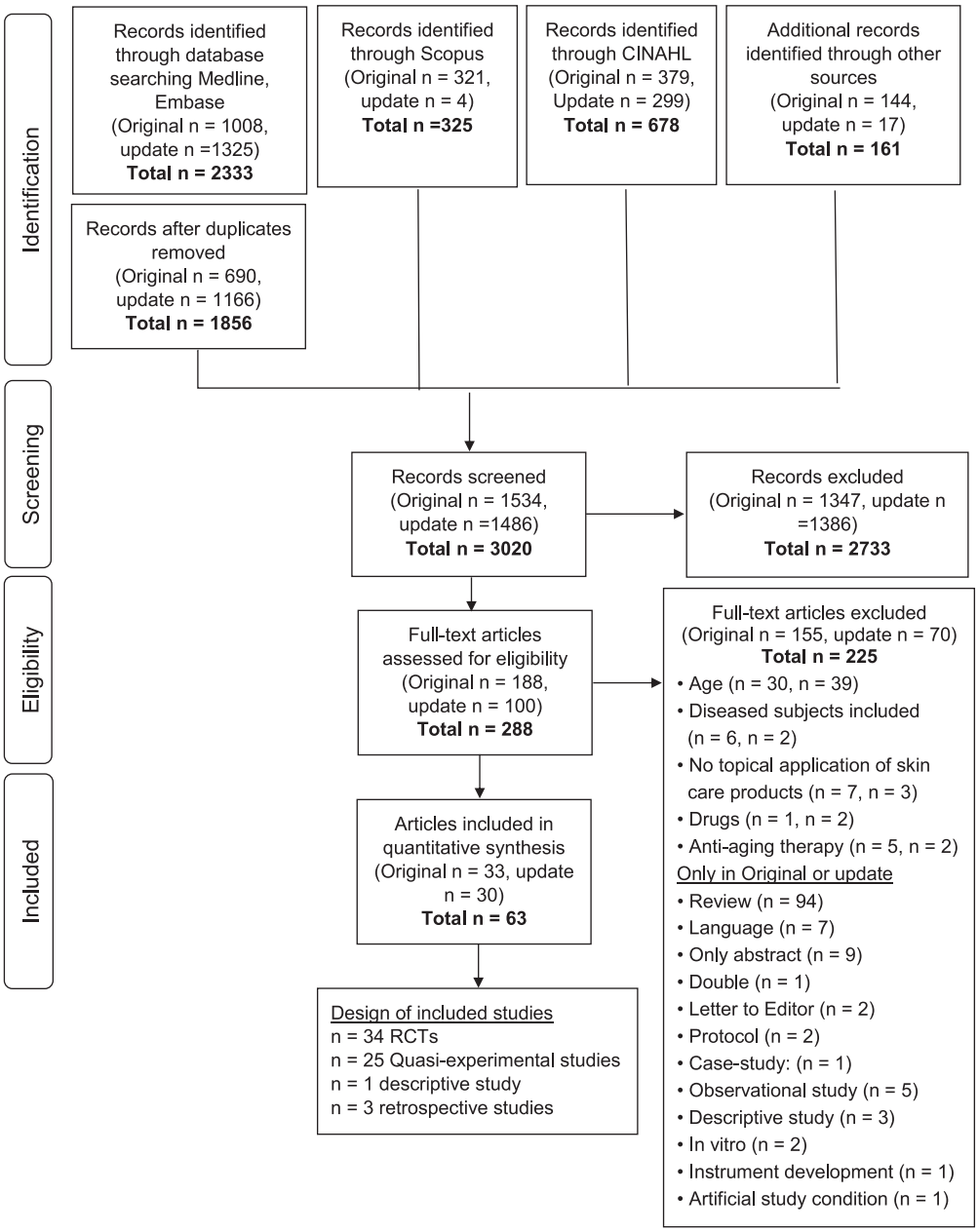

Fig. 1. Prisma flow chart.

with Level of Evidence of 3 and two with Level of Evidence of 2 (Verdu and Soldevilla, 2012; Torra i Bou et al. 2005).

The calculation of comparable summary measures across studies was not possible due to the large heterogeneity of investigated treatments and reported study outcomes. In the following sections, we summarize the effects of the skin care interventions per identified skin problem.

3.3. Preventing and treating dry skin

3.3.1. Application of leave-on skin care products

Twenty-four (Table 2) studies evaluated effects of leave-on products with or without humectants (e.g. urea, glycerol, lactate), different product pH or other ingredients such as panthenol. The application of urea with the concentrations from 5%, 10% or 40% was investigated in 10 studies (Danby et al., 2016; Federici et al., 2012; Federici et al., 2015; Gin et al., 2017; Kuzima et al. 2002; Papanas et al., 2011; Hahnel et al. 2017, 2017b, 2017c, Pham et al., 2002; Schölermann et al., 1998; Weber et al., 2012) and resulted in decreased skin dryness (Level of Evidence 2 to 3). In most studies, skin dryness was also decreased in the comparator group (Federici et al., 2012; Gin et al., 2017; Hahnel et al., 2017, 2017b; Weber et al., 2012a, Schölermann et al., 1999). Additionally, biophysical skin parameters such as stratum corneum hydration increased (Federici et al., 2015; Weber et al., 2012), or transepidermal water loss decreased (Danby et al., 2016; Weber et al., 2012) as signs for skin improvement and recovery (Level of Evidence 2 to 3).

The same was observed when using products containing glycerin in different concentrations (Behm et al., 2015; Cristaudo et al., 2015; Gin et al., 2017; Korponyai et al., 2017; Weber et al., 2012a) (Level of Evidence 3) but when different formulations containing glycerol were compared, no differences were observed in terms of stratum corneum hydration (Quatresooz et al., 2009).

Table 2
Summary of included studies for prevention and treatment of dry skin.

Source	Design	Setting/ Sample/ Indication	Intervention	Study duration	n	Mean age (years) (Intervention/ control)	Outcomes	Main results	Risk of bias						
									Sequence generation	Allocation	Blinding	Completeness	Selection	Other	LoE
Blaak et al. (2017)	RCT	Elderly subjects, treatment of skin dryness	Intervention Twice daily application of a plant oil-containing acidic O/W emulsion adjusted to pH 4 Comparator/control Untreated skin	3 weeks	23	73.5	(1) TEWL (2) SCH (3) Skin pH (4) Quality of EPB (5) Lipid profile/ordering (6) Number of lipids	(1) Decrease in TEWL in intervention vs. control ($p = 0.003$); (2) Increase in SCH vs. control ($p < 0.001$), (3) Unchanged skin pH in both groups, (4) Increased quality of EPB in intervention vs. control ($p = 0.019$), (5) Normalized lipid profile/ordering after treatment in intervention, (6) Increased lipid content in intervention vs. control ($p < 0.001$)	Unclear	Unclear	Unclear	Yes	Yes	Unclear	3
Chang et al. (2018)	Quasi-experimental	Outpatients, treatment of skin dryness	Intervention skin care regimen including over-the-counter body wash and a moisturizer containing sunflower seed oil panthenol, shea butter Comparator No comparator	15 days	25	63	(1) 5-point severity scale for skin dryness (2) SCH (3) TEWL (4) Desquamation (5) Severity of Pruritus (6) Impact of Pruritus (7) Patient satisfaction (8) AEs	(1) Decreased skin dryness (baseline vs. day 15, $p < 0.05$); (2) Increased SCH (baseline vs. day 15, $p < 0.05$); (3) Slight decreased TEWL (not significant); (4) Decrease in desquamation ($p < 0.05$) and (5) severity ($p < 0.05$) and (6) impact of pruritus ($p < 0.001$) (baseline vs. day 15); (7) Positive participant satisfaction (8) No AEs occurred	n.a.						3
Cristaudo et al. (2015)	Quasi-experimental	Healthy subjects with dry skin, treatment of skin dryness	Intervention Twice daily application of a cream containing glycerol and paraffin Comparator No comparator	4 weeks	50	65	(1) Severity of xerosis (2) Scaling (3) Skin tightness (4) Fissuring (5) Excoriations (6) Erythema (7) Itching (8) TEWL (9) SCH	Decrease of (baseline vs. week 4): (1) Xerosis severity ($p < 0.0001$), (2) Scaling ($p < 0.0001$), (3) Tightness ($p < 0.0001$), (4) Fissuring ($p < 0.0001$), (5) Excoriations ($p < 0.0001$), (6) Erythema ($p < 0.0001$), (7) Itching ($p < 0.0001$), (8) TEWL ($p < 0.001$), (9) Increase of SCH ($p < 0.001$)	n.a.						3
Danby et al. (2016)	RCT	Healthy subjects with dry skin, treatment of skin dryness	Intervention Emollient with 5% urea, ceramide NP, lactate Comparator Emollient without these additives	4 weeks	42	69/68	(1) TEWL (2) Redness (3) SCH (4) Skin pH (5) Protein quantification (6) SC Protease activity (7) Quantification of PCA and lactate	(1) Slight decreased TEWL in intervention ($p = 0.002$), increased in comparator; (2) Redness nearly unchanged in both groups, (3) Increased SCH in intervention ($p = 0.003$) and comparator ($p < 0.05$), (4) Decreased skin pH in intervention ($p = 0.005$), increased in comparator ($p < 0.001$), (5) No differences in proteins for both groups, (6) Increased SC proteases in intervention vs. comparator ($p < 0.05$, $p < 0.0001$) (7) Increase in lactate and PCA (intervention vs. comparator ($p < 0.05$)	No	Unclear	Unclear	Unclear	Yes	Unclear	3

(*Continued on next page*)

Table 2 (*Continued*).

Source	Design	Setting/ Sample/ Indication	Intervention	Study duration	n	Mean age (years) (Intervention/ control)	Outcomes	Main results	Risk of bias						
									Sequence generation	Allocation	Blinding	Completeness	Selection	Other	LoE
Federici et al. (2012)	RCT	Diabetics, treatment of skin dryness	Intervention Twice daily application of Urea 5% cream containing arginine and carnosine Comparator Emollient with glycerol, Vaseline and liquid paraffin	4 weeks	40	66/58	(1) Severity of skin dryness (DASI) (2) Severity of skin dryness (VAS) (3) Itch sensation	(1) Decreased in both groups using DASI; highest in intervention ($p < 0.001$), (2) Decrease in both groups using VAS ($p = 0.05$), (3) Decrease in both groups, no difference between groups	Yes	Unclear	Unclear	Yes	Yes	No	3
Federici et al. (2015)	RCT	Diabetics, treatment of skin dryness	Intervention Twice daily application of Urea 5% cream with arginine 0.4% and carnosine 0.01% Comparator Application of a cream containing 40% glycerol	8 months	50	62/61	(1) Severity of skin dryness using Xerosis Assessment Scale (XAS) (2) Severity of skin dryness using Overall Cutaneous score (OCS) (3) SCH (4) Desquamation (5) Percentage of patients with severe dry skin and improvement ≥3 points after treatment	(1) Decrease of skin dryness in intervention vs. comparator using XAS ($p < 0.001$), (2) Decrease of skin dryness in intervention vs. comparator using OCS ($p < 0.02$), (3) Increase in SCH in intervention compared to baseline ($p = 0.001$), (4) Reduced desquamation in intervention (77% improvement) vs. comparator (5) Reduced severe skin dryness in intervention vs. comparator ($p = 0.004$)	Yes	Unclear	Yes	Yes	Yes	Unclear	2
Gin et al. (2017)	RCT	Hospital/ Diabetologist/ General practices, treatment of skin dryness (healing of deep open fissures on the heel in diabetics)	Intervention Twice daily application of a moisturizer containing 10% glycerin, 5% urea and 8% petrolatum Comparator A placebo-cream	4 weeks	167	Median 62.9/65.2	(1) Complete healing of a target fissure after 4 weeks (3-point scale) (2) Complete healing of a target fissure after 2 weeks (3-point scale) (3) Clinical benefit (5-point scale) (4) Severity of dry skin (9-point scale) (5) AEs	(1) Complete healing after 4 weeks: 46% intervention vs. 33% comparator ($p = 0.09$), (2) Complete healing after 2 weeks: 8% intervention vs. 0 comparator ($p = 0.01$), (3) Improvement: Intervention 54.4% (after 2 weeks), 68.8% (after 4 weeks) vs. comparator: 24.4.% (after 2 weeks), 46% (after 4 weeks); (4) Decrease in xerosis in both groups, highest in intervention ($p = 0.002$); (5) $n = 4$ AEs (in 3 patients) intervention, $n = 1$ comparator (study related; in total 8 AEs) (pruritus, burning, inflammation, heaviness)	Yes	Unclear	Yes	Yes	Unclear	Unclear	3
Gillis et al. (2016)	cRCT	Nursing home, skin dryness	Intervention Washing with disposable wash gloves Comparator Traditional washing method	12 weeks	163	86/82	(1) SCH	(1) Increase in SCH in intervention vs. comparator; highest on the cheek ($p = 0.02$)	Unclear	Unclear	No	Yes	Unclear	No	3
Hahnel et al. (2017a, 2017b),	RCT	Nursing home, treatment of skin dryness	Intervention Two structured skin care regimens containing shea butter, glycerin (cleanser) and a W/O emulsion with 4% urea Comparator Routine skin care	8 weeks	133	83.8	(1) Severity of skin dryness (ODS) (2) SCH (3) TEWL (4) Skin pH	(1) Decreased skin dryness in all groups: right lower leg ($p = 0.121$), left lower leg ($p = 0.073$), right forearm ($p = 0.006$), left forearm $p = 0.011$, trunk ($p = 0.013$), (2) Increase in SCH in all groups: forearms ($p = 0.691$), legs ($p = 0.056$), (3) Increased TEWL in all groups: forearm ($p = 0.267$), legs ($p = 0.773$); (4) Unchanged or slight increase in skin pH in all groups: forearm ($p = 0.354$), leg ($p = 0.049$)	Yes	Yes	Yes	Unclear	Yes	Yes	2

(*Continued on next page*)

Table 2 (*Continued*).

Source	Design	Setting/ Sample/ Indication	Intervention	Study duration	n	Mean age (years) (Intervention/ control)	Outcomes	Main results	Risk of bias						LoE
									Sequence generation	Allocation	Blinding	Completeness	Selection	Other	
Hardy (1990)	Quasi-experimental	Nursing home, treatment of skin dryness	Intervention Twice weekly standardized bathing regime using superfatted soap (Dove) and mineral oil Comparator na.	18 weeks	15	70	(1) Skin dryness (2) Redness (3) Flaking (4) Scaling (5) Cracking	(1) Reduction of skin dryness ($p = 0.031$) (2) Redness: $p = 0.001$ for changes over time (3) Scaling: $p = 0.007$ for changes over time (4) Cracking: $p = 0.406$ for changes over time (5) Flaking: $p = 0.002$ for changes over time	na.						3
Hardy (1996)	Quasi-experimental	Nursing homes and outpatients, treatment of skin dryness	Intervention Standardized bathing regime using superfatted soap (Dove) and mineral oil using various bathing frequencies Comparator na.	18 weeks	143	75	(1) Skin dryness	(1) Reduction of skin dryness irrespective of bathing frequency	na.						3
Izumi et al. (2017)	RCT	Healthy subjects with dry skin, treatment of skin dryness	Intervention 1 Three times daily application of an emollient containing diethylene glycol/ dilinoleic acid copolymer 10% Intervention 2 An emollient containing diethylene glycol/ dilinoleic acid copolymer 20% Intervention 3 White petrolatum Comparator Untreated area	4 weeks	50	57.2/57.6	(1) Severity of skin dryness (5-point scale) (2) Severity of scratch marks (5-point scale) (3) Skin conductance (4) Itching (VAS) (5) Quality of life (Skindex-16)	(1) Highest decrease of skin dryness on lower legs for intervention 1 and 2 (comparator vs. 10%+20% D/DC $p < 0.001$), untreated and white petrolatum ($p < 0.5$), (2) Highest reduction in scratch marks for intervention 1 and 2 vs. comparator ($p < 0.01$), (3) Highest increase in skin conductance for intervention 1 and 2 vs. comparator ($p < 0.05$); (4) Itching decrease in all intervention-groups vs. comparator ($p < 0.001$) (5) Quality of life increased in all interventions, highest in intervention 2 ($p < 0.001$), followed by intervention 3 ($p < 0.05$) and intervention 1 ($p < 0.01$)	Unclear	Unclear	Unclear	Yes	Yes	Unclear	3
Korponyai et al. (2016)	Quasi-experimental	Healthy subjects with dry skin, treatment of skin dryness	Intervention 1 Twice daily application of Carbopol Ultrez 10 0.4%, dissolved in purified water Intervention 2 A gel containing 5% glycerol- and 5% xylitol Comparator Untreated skin	14 days	12	Age range: 50 to 60	(1) SCH (2) TEWL (3) Skin friction (4) Sin elasticity (5) Thickness of epidermis and dermis/ echogenicity of papillary dermis (6) Protein quantity	(1) Increase in intervention 1 ($p < 0.05$ vs. baseline) and Intervention 2 ($p < 0.001$ vs. baseline), slightly in control (20 vs. 23); (2) Highest TEWL decrease in Intervention 2 ($p < 0.001$ vs. baseline; $p < 0.05$ vs. comparator); (3) Highest increase in friction in intervention 2 ($p < 0.001$ vs. baseline; $p < 0.05$ vs. comparator) (4) Increase in elasticity in intervention 2 ($p < 0.05$ vs. baseline); (5) Thickness increased in both interventions, highest in intervention 2 ($p < 0.001$ vs. baseline), echogenicity decreased in intervention 2 ($p < 0.001$ vs. baseline, $p < 0.05$ vs. comparator); (6) Highest protein quantity in intervention 2 ($p < 0.05$ vs. comparator)	n.a.						3

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Table 2 (*Continued*).

Source	Design	Setting/ Sample/ Indication	Intervention	Study duration	n	Mean age (years) (Intervention/ control)	Outcomes	Main results	Risk of bias						
									Sequence generation	Allocation	Blinding	Completeness	Selection	Other	LoE
Kuzmina et al. (2002)	RCT	Outpatients, treatment of skin dryness	Intervention Twice daily application of oil-in-water emulsion (40 mg/g urea) Comparator Oil-in-water emulsion (40 mg/g urea and 40 mg/g sodium chloride)	2 weeks	23	73	(1)Transepidermal water loss (2) Stratum corneum hydration (3) Electrical impedance	(1) Decrease of TEWL in both groups; Difference between groups $p = 0.24$ (2) Increase in SCH; differences between groups $p < 0.01$ (3) Increase in electrical impedance in both groups	Unclear	Unclear	Unclear	Yes	Yes	Yes	3
Martini et al. (2017)	RCT	Diabetics, treatment of skin dryness on foot	Intervention Twice daily application of an emollient cream containing 15% glycerol Comparator Control vehicle	28 days	57	58.3	(1) Skin dryness and fissures (XAS-Score and Overall skin score (ODS)) (2) Effectiveness due to subject's opinion (VAS) (3) SCH (4) Desquamation (5) Skin relief (6) AEs	(1) Decrease in skin dryness in intervention vs. comparator ($p = 0.001$ XAS-Score, $p = 0.0002$ ODS-Score); (2) Higher satisfaction ($p = 0.022$) and preference ($p = 0.015$) for intervention vs. comparator; (3) Increase in SCH in intervention vs. comparator ($p = 0.005$); (4) Reduction in desquamation in intervention vs. comparator ($p < 0.001$); (5) Decreased roughness in both groups (greater reduction in intervention vs. comparator); (6) $n = 2$ cracks possible related to intervention (local-regional, reported by 2 subjects)	Yes	Yes	Yes	Yes	Unclear	Unclear	2
Okada et al. (2006) (abstract)	Quasi-experimental	Nursing home	Intervention Two weekly application of bathing detergent using pseudo-ceramide Comparator na. (before-after evaluation)	3 weeks	21	82	(1) Stratum corneum hydration (2) pH (3) Ceramide content (4) Sebum content (5) Bacterial flora	(1) Increase in SCH (2) Decrease in 2 residents (3) Decrease in ceramide in nursing home residents (4) not reported (5) Slightly decrease in bacteria	na.						na
Papanas et al. (2011)	Quasi-experimental	Diabetic outpatients	Intervention Twice daily application of urea 10%, alpha–hydroxy acid, panthenol containing foam Comparator No treatment	2 weeks	20	61	(1) Stratum corneum hydration	(1) SCH higher in Neuropad repair foam compared to no treatment ($p < 0.001$)	na.						3
Pham et al. (2002)	RCT	Diabetic outpatients, treatment of skin dryness	Intervention Atrac-Tain cream (10% urea, 4% lactic acid) Comparator Vehicle	8 weeks	40	62	(1) Skin dryness (2) Development of new foot ulcers	(1) Larger reduction of xerosis of feet than in Atrac-Tain cream group compared to vehicle ($p < 0.05$) (2) No ulcer development	Yes	Yes	Yes	Yes	Yes	No	2
Quatresooz et al. (2009) (study 1)	RCT	Diabetic menopausal woman, treatment of skin dryness	Intervention Once daily application of 1.5% chitin-glucan cream Comparator Placebo	5 weeks	30	59	(1) Stratum corneum hydration	(1) Increase of SCH in chitin-glucan group compared to placebo ($p < 0.01$)	Yes	Yes	Unclear	Yes	Yes	Yes	2

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Table 2 (*Continued*).

Source	Design	Setting/ Sample/ Indication	Intervention	Study duration	n	Mean age (years) (Intervention/ control)	Outcomes	Main results	Risk of bias						
									Sequence generation	Allocation	Blinding	Completeness	Selection	Other	LoE
Quatresooz et al. (2009) (study 2)	RCT	Diabetic menopausal woman, treatment of skin dryness	Intervention Once daily application of crème pieds/formule norvégienne ("glycerol enriched", Neutrogena, France) Comparator crème hydrante/Cetaphil ("glycerol enriched", Galderma, France)	5 weeks	30	59	(1) Stratum corneum hydration	(1) Increase of SCH in both groups; Differences between groups $p = 0.061$	Yes	Yes	Unclear	Yes	Yes	Yes	2
Schölermann et al. (1998)	RCT	Outpatients, treatment of skin dryness	Intervention Twice daily application of Eucerin 10% Urea lotion Comparator Urea free vehicle lotion	6 weeks	60	64	(1) Stratum corneum hydration (2) Skin dryness	(1) Increase of SCH in both groups; higher SCH in Eucerin 10% Urea group compared to placebo ($p < 0.05$) (2) not reported	Unclear	Unclear	Yes	No	No	Yes	3
Schölermann et al. (1999)	RCT	Outpatients	Intervention Twice daily application of Eucerin Cream 10% Urea vs. Eucerin Cream 10% Urea with 1% Panthenol and 0.07% Bisabolol Comparator Placebo	4 weeks	72	70	(1) Stratum corneum hydration (2) Skin dryness	(1) Increase of SCH in Eucerin 10% Urea and Eucerin Urea 10% with Panthenol and Bisabolol compared to placebo ($p < 0.01$); No difference between Eucerin 10% Urea and Eucerin Urea 10% with Panthenol and Bisabolol (2) not reported	Unclear	Unclear	Unclear	No	No	Yes	3
Sheppard and Brenner (2000)	Quasi-experimental	Nursing home	Intervention Bag Bath/Travel Bath Control Traditional bathing	6 weeks	32	85	(1) Skin dryness (2) Redness (3) Flaking (4) Scaling (5) Cracking	(1) Reduction of skin dryness in Bag Bath/Travel Bath compared to traditional bathing group ($p < 0.001$) (2) not reported (3) Difference between groups $p < 0.001$ (4) Difference between groups $p < 0.001$ (5) not reported	na.						3
Sloane et al. (2007)	RCT	Nursing home	Intervention Effects of four bathing procedures on skin condition Comparator na.	12 and 16 weeks	31	86	(1) Skin condition	(1) No differences of skin condition between the four bathing regimens ($p = 0.81$)	Unclear	No	No/Yes	Yes	Yes	Yes	3
Theunis et al. (2017)	RCT	Outpatients, treatment of chronic pruritus	Intervention Application of Rhealba® Oat Extract-based emollient Comparator Non-treatment	6 weeks	30	75.8	(1) Intensity of pruritus (10 cm Visual Analog Scale) (2) Intensity of pruritus (French version of the 5-D itch scale) (3) Skin dryness (4) SCH (5) Desquamation (6) TEWL (7) AEs	(1) Decrease in pruritus intensity in intervention vs. comparator ($p < 0.0001$) and (2) ($p = 0.0042$); (3) Decrease in skin dryness ($p < 0.0001$); (4) Increase in SCH in intervention vs. comparator ($p < 0.0001$); (5) Decrease in desquamation in intervention vs. comparator ($p < 0.0001$); (6) No significant change in TEWL; (7) $n = 1$ possible related AE (pruritus)	Unclear	No	No	Yes	Yes	Unclear	3

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Table 2 (*Continued*).

Source	Design	Setting/ Sample/ Indication	Intervention	Study duration	n	Mean age (years) (Intervention/ control)	Outcomes	Main results	Risk of bias						
									Sequence generation	Allocation	Blinding	Completeness	Selection	Other	LoE
Weber et al. (2012a)	RCT	Healthy subjects with very dry skin, treatment of skin dryness	Intervention 1 Twice daily application of Light Formulation containing glycerin Intervention 2 O/W emulsion (vehicle) Intervention 3 Same emulsion enriched with 5% urea, sodium lactate, lactic acid (vehicle plus) Comparator Untreated area	3 weeks	49	64,03	(1) SCH (2) TEWL (3) Skin dryness (5-point clinical grading score) (4) Tactile roughness(5-point clinical grading score) (Δ = difference between week 2 and baseline)	(1) SCH increased in all interventions and comparator groups; highest increase in intervention 1 (Δ+17.3, $p < 0.05$) followed by intervention 3 (Δ+10.2, $p < 0.05$); (2) Decrease of TEWL in all interventions and comparator groups; highest increase in intervention 1 (Δ−1.4, $p < 0.05$) and intervention 3 (Δ−1.2, $p < 0.05$); (3) Highest decrease of skin dryness in intervention 1 (Δ−1.44, $p < 0.05$) and intervention 3 (Δ−1.29, $p < 0.05$); (4) and in roughness intervention 1 (Δ−1,44, $p < 0.05$), intervention 3 (Δ−1.27, $p < 0.05$)	Unclear	No	Unclear	Yes	Yes	Unclear	3
Weber et al. (2012b)	RCT	Healthy subjects with very dry skin, treatment of skin dryness	Intervention 1 Twice daily application of Rich Formulation containing glycerin Intervention 2 O/W emulsion (vehicle) Intervention 3 Same emulsion enriched with 10% urea, sodium lactate, lactic acid (vehicle plus) Comparator Untreated area	3 weeks	44	59.9	(1) SCH (2) TEWL (3) Skin dryness (4) Tactile roughness (Δ = difference between week 2 and baseline)	(1) Increase of SCH in all interventions and comparator groups; highest increase in intervention 1 (Δ+21.7, $p < 0.05$) and intervention 3 (Δ+8.6, $p < 0.05$); (2) Highest decrease in TEWL in intervention 1 (Δ−3.7, $p < 0.05$) and intervention 3 (Δ−3.6, $p < 0.05$); (3) Decrease of skin dryness in intervention 1 (Δ−1.20, $p<0.05$) and intervention 3 (Δ−0.80, $p<0.05$); (4) Decrease in roughness in intervention 1 (Δ−0,97, $p < 0.05$), intervention 3 (Δ−0.70, $p < 0.05$) and intervention 2 (Δ−0.39, $p < 0.05$)	Unclear	No	Unclear	Yes	Yes	Unclear	3
Weber et al. (2012c)	RCT	Healthy subjects with very dry skin, treatment of skin dryness	Intervention Application of Rich Formulation (W/O) containing glycerin Comparator Untreated area	18 days	44	**66.5**	(1) SCH (2) Tactile roughness	(1) Increase in SCH in intervention vs. comparator ($p<0.05$); (2) Not reported	Unclear	No	Unclear	Unclear	No	Unclear	3
Wehr et al. (1991)	RCT	Outpatients	Intervention Twice daily application of Lac-Hydrin Five (5% lactic acid) Comparator Eucerin lotion	12 weeks	56	52	(1) Skin dryness	(1) Reduction of skin dryness in both groups over time ($p < 0.001$); Lower skin dryness scores in Lac-Hydrin Five group ($p < 0.001$)	Unclear	Unclear	Unclear	Yes	Yes	Yes	3
Welzel et al. (2006)	Quasi-experimental	Outpatients	Intervention Twice daily application of hamamelis ointment Comparator na.	6 weeks	89	63	(1) Sebum content (2) Stratum corneum hydration (3) Skin dryness (4) Degree of fissures (5) Itching (6) Adverse events	(1) Increase in sebum content and SCH ($p < 0.001$) (2) Decrease of SCH ($p < 0.001$) (3) Decrease of skin dryness ($p < 0.001$) (4) Decrease of fissures ($p < 0.001$) (5) Slight decrease of itching	na.	3					
Wilson and Nix (2005)	Quasi-experimental	Nursing home	Intervention Once daily application of Sween 24 cream (6% dimethicone) Comparator na.	5 days	16	76	(1) Erythema (2) Dry scaly skin (3) Presence of scratching	(1) Reduction of erythema ($p < 0.001$) (2) Reduction of skin dryness ($p < 0.001$) (3) Reduction of scratching ($p = 0.016$)	na.	3					

Abbreviations: LoE, Level of Evidence according to the Oxford Center for Evidence-Based Medicine 2011; na, not applicable; RCT, randomized controlled trial; SCH, stratum corneum hydration; TEWL, transepidermal water loss.

Table 3
Summary of included studies for improvement of skin barrier.

Source	Design	Setting/ Sample/ Indication	Intervention	Study duration	n	Mean age (years)	Outcomes	Main results	Risk of bias						
									Sequence generation	Allocation	Blinding	Completeness	Selection	Other	LoE
Angelova-Fischer et al. (2018a)	RCT	Healthy subjects, improvement of skin barrier integrity	Intervention Twice daily application of a pH 4 water in-oil (W/O) cream Comparator pH 5.8 (W/O) cream	4 weeks	28	67.1	(1) Skin pH (2) Roughness (3) Scaliness (4) TEWL (5) SC cohesion	(1) Decrease in skin pH ($p < 0.01$) for intervention; unchanged for comparator; (2) Small reduction in roughness for both creams; (3) Decrease in scaliness in both groups ($p < 0.001$) (4) Decreased ΔTEWL in intervention ($p < 0.001$) vs. comparator (5) Reduced protein content after 4 weeks in both creams ($p < 0.001$)	Unclear	Unclear	No	Yes	Yes	Unclear	3
Angelova-Fischer et al. (2018b)	RCT	Healthy subjects, skin barrier recovery after induced skin impairment	Intervention 1 Application of a pH 4 (W/O) cream Intervention 2 Application of a pH 5.8 (W/O) cream Comparator 1 Aceton Comparator 2 Untreated skin	24 h	10	64.5	(1) Irritation (2) Skin pH (3) TEWL	(1) No skin irritation on all test fields, (2) Reduced skin pH after 3 ($p < 0.001$) and 6 h ($p < 0.01$) of induced skin damage in intervention 1; slight decrease in intervention 2 and both comparators, (3) TEWL increased after 10 min of skin damage ($p < 0.01$ vs. baseline) and decreased after 6 ($p < 0.05$) and 24 h ($p < 0.01$) in intervention 1; in intervention 2 and both comparators it remained decreased	Unclear	Unclear	Unclear	Unclear	Yes	Unclear	3
Behm et al. (2015a)	Quasi-experimental	Elderly subjects, improvement of epidermal barrier function	Intervention Twice to four times daily application of a glycolic acid-containing pH 4 (W/O) emulsion Comparator/Control Untreated volar forearm	4 weeks	30	70.2	(1) SCH (2) Skin pH (3) Subject evaluation	(1) Increase of SCH (Δ+12.1 units) vs. control; (2) Decrease of skin pH (Δ−0.52) vs. control; (3) not reported	n.a.						4
Behm et al. (2015b)	RCT	Diabetics, improvement of epidermal barrier function	Intervention Twice daily application of a glycolic acid-containing pH 4 (W/O) emulsion Comparator/Control Untreated foot	2 weeks	10	70.2	(1) Skin pH (2) Bacterial colonization	(1) Decrease of skin pH in intervention vs. control ($p = 0.0002$); (2) Data not reported	Unclear	No	No	No	Unclear	Unclear	3
Blaak et al. (2015)	RCT	Nursing home, improvement of skin barrier integrity	Intervention Twice daily application of a (O/W) cream containing synthetic detergent adjusted to pH 4 Comparator The same cream (O/W) adjusted to pH 6	7 weeks	26	87.0	(1) DASI-score (2) SCH (3) Skin pH (4) TEWL (5) SC integrity (6) SC recovery (7) SC cohesion (Absorption) (8) Protein amount (9) Skin flora (cell count)	(1) Decreased skin dryness in both groups (pH 4 cream ($p = 0.002$); pH 6 cream ($p = 0.036$)), (2) Increase in SCH in intervention ($p = 0.005$); slight increase in comparator (not significant), (3) Skin pH decreased in intervention ($p = 0.003$), unchanged for comparator, (4) TEWL nearly unchanged in both groups, (5) Skin integrity increased in intervention ($p = 0.007$), nearly unchanged in control; (6) Enhanced SC recovery in intervention ($p = 0.004$), unchanged in control, (7) SC absorption unchanged in intervention and impaired in control ($p = 0.025$), (8) Protein amount unchanged in intervention and increased in control ($p = 0.025$), (9) Increase in CPU on skin flora in both groups ($p = 0.016$ and $p = 0.017$)	Unclear	Unclear	Unclear	Unclear	Low risk	Unclear	3

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Table 3 (*Continued*).

Source	Design	Setting/ Sample/ Indication	Intervention	Study duration	n	Mean age (years)	Outcomes	Main results	Risk of bias						
									Sequence generation	Allocation	Blinding	Completeness	Selection	Other	LoE
Brooks et al. (2017)	Quasi-experimental	Nursing home/ Outpatients, improvement of skin barrier function	Intervention Daily application of five combinations of cleansing and emolliating products on five 5 × 5 cm marked areas of a leg Comparator/control Untreated leg	5 days	10	76.4	(1) TEWL (2) SCH	(1) Greatest skin barrier improvement (TEWL Δ −1.14) and (2) highest increase of SCH ($p = 0.011$) for intervention of combination of soap, glycerine, Vaseline vs. untreated area	n.a.						3
Elewa et al. (2012) (abstract)	Quasi-experimental	Healthy subjects	Intervention Induction of skin barrier disruption by tape-stripping; daily application of two creams by LVMH Comparator DAC base cream	1 week	No data	> 65	(1) Stratum corneum hydration (2) Transepidermal water loss (3) Erythema	No data	n.a.						3
Farwick et al. (2014)	Quasi-experimental	Postmenopausal females, improvement of epidermal barrier function	Intervention 1 Cosmetic formulations containing 0.2% T. arjuna bark extract added in 1,2-pentanediol Intervention 2 2.5% TEGO® Arjuna S. Soy isoflavones Comparator A formulation without active ingredients	12 weeks	40	50 to 70	(1) Sebum content (2) Cutaneous blood microcirculation (3) Skin density/ echogenicity (4) Sagging	(1) Increase in all three formulations, highest in intervention 1 ($p < 0.001$) followed by intervention 2 ($p < 0.01$), (2) Increase in microcirculation in intervention 1 vs. comparator ($p < 0.001$), (3) Increase in echogenicity in intervention 2 ($p < 0.001$) and intervention 1 ($p < 0.05$) vs. comparator, (4) Reduction of sagging in groups, highest in intervention 1 vs. comparator ($p < 0.01$)	n.a.						3
Narbut et al. (2016)	Quasi-experimental	Diabetics with healthy skin, maintaining skin integrity	Intervention Twice daily application of Emolium Diabetix containing urea and glycerin Comparator None	4 weeks (6 weeks with follow-up)	50	56.2	(1) Visual changes of skin properties (erythema, desquamation, roughness, dryness) (4-point scale) (2) SCH (3) Skin pH (4) Sebum content (5) TEWL (6) Satisfaction of product use (7) Skin autofluorescence	(1) Reduced visible skin changes (baseline vs. 4 weeks $p < 0.05$); (2) Increase in SCH (baseline vs. 4 weeks $p < 0.05$), (3) skin pH (baseline vs. 4 weeks $p < 0.05$) and (4) sebum (baseline vs. 4 weeks $p < 0.05$); (5) Decrease in TEWL (baseline vs. 4 weeks $p < 0.05$); (6) 90% patient satisfaction, 56% physician; (7) No significant change in SAF (baseline vs. 4 weeks $p = 0.42$)	n.a.						3
Paulela et al. (2018)	RCT	Hospital, effectiveness in microbial load of the skin	Intervention Washing with bag bath Comparator Conventional bed bath with cleanser and water	5 days	55	≥60	(1) Skin microbial load	(1) Reduction in microbial load in intervention vs. comparator ($p < 0.001$)	No	No	No	Yes	Yes	Yes	3
Roure et al. (2012)	Quasi-experimental	Healthy subjects	Intervention Application of lotion containing glycerine and subsequent simulated exposure of dry and cold wind Comparator Untreated with wind	1 day	12	62	(1) Stratum corneum hydration (2) Transepidermal water loss	(1) Application of lotion before wind exposure increases SCH, decrease of SCH after wind exposure without lotion (2) not reported	n.a.						4
Schoonhoven et al. (2015)	Cluster-RCT	Nursing homes, maintaining skin integrity and resistance	Intervention Washing without water using bag bath: Washing gloves made of soft waffled nonwoven fibers, impregnated with skin cleaning and caring lotion Comparator Traditional bed bath	6 weeks	500	82.4	(1) Prevalence of skin damage	(1) No differences in skin damage between groups ($p < 0.820$) (slightly decrease in any skin abnormalities/lesions in intervention, slightly increase in comparator, resulting in 72.7% vs 77.6% of residents having any skin abnormalities/lesions after 6 weeks ($p = 0.04$); no significant differences in skin lesions or resistance after 6 weeks between groups	Yes	Unclear	No	Unclear	Yes	Yes	3

Table 4
Summary of included studies for prevention and treatment of incontinence-associated dermatitis.

Source	Design	Setting/ Sample/ Indication	Intervention/control	Study duration	n	Mean age (years)	Outcomes	Main results	Risk of bias						
									Sequence generation	Allocation	Blinding	Completeness	Selection	Other	LoE
Beeckman et al. (2011)	RCT	Nursing home/IAD prevention	Intervention 2-in-1 perineal care washcloth (3% dimethocone) for IAD prevention Comparator Water and soap	120 days	141	86	(1) Prevalence of IAD (2) Severity of IAD	(1) Decrease of IAD prevalence ($p = 0.003$) and severity ($p = 0.06$) in intervention group; larger decrease of IAD prevalence in intervention group compared to control group ($p = 0.003$) (2) Improvement of IAD severity in intervention group ($p < 0.001$ for change over time)	Yes	No	No	Yes	Yes	No	3
Bliss et al. (2006, 2007)	Quasi-experimental	Nursing home/ IAD prevention	Intervention Barrier film (spray acrylate) Comparator 1 Ointment (43% petrolatum) Comparator 2 Ointment (98% petrolatum) Comparator 3 Barrier cream (12% zinc oxide, 1% dimethicone)	6 weeks	981	65+	(1) IAD incidence	(1) IAD incidence: 33/981 (3.4%), difference between groups $p = 0.55$	na.						4
Byers et al. (1995)	Quasi-experimental	Nursing home/ IAD prevention	Intervention No-rinse incontinence cleanser for IAD prevention Comparator 1 Soap and water and moisture barrier Comparator 2 No-rinse incontinence cleanser and moisture barrier	15 weeks	12	87	(1) Transepidermal water loss (2) pH (3) Erythema	(1, 2, 3) No differences in TEWL, pH, and erythema between treatment groups	na.						4
Brunner et al. (2012)	RCT	Hospital, incontinent patients, IAD prevention	Intervention Washcloth combined with cleanser, moisturizer, and barrier impregnated with 3% dimethicone Comparator pH-balanced, no-rinse cleanser and moisturizer containing glycerin and dimethicone and a film forming polymeric solution spray	Hospital stay	64	67.3	(1) Degree of skin breakdown (2) Time to skin breakdown	(1) No differences between groups, (2) Average time to skin breakdown longer in comparator group ($p = 0.045$)	No	No	No	Yes	Yes	Yes	3
Conley et al. (2014)	RCT	Hospital (critically ill patients in PUC ward, IAD prevention	Intervention Skin care protocol every 6 h including gently skin cleansing with a aloe vera containing cleansing lotion and application of a skin barrier containing silicone Comparator Skin care protocol every 12 h including gently skin cleansing with a aloe vera containing cleansing lotion and application of a skin barrier containing silicone	9 month	99	75/67	(1) IAD score (Brown's grading scale)	(1) Moderate IAD score decreased for intervention group (7.1% vs. 10.9%) ($p \leq 0.001$), mild IAD decreased in control-group (43.6% vs. 25.5%) ($p \leq 0.001$); no statistical significant differences for no IAD and severe IAD	No	No	No	Yes	Yes	No	3
Cooper et al. (2008)	RCT	Nursing home/ Reha-bilitation center/IAD prevention	Intervention Tena Wash Mousse (emollients) Comparator Clinisan Foam Cleanser (amphoteric surfactants, triclosan, dimethicone)	14 days	30	81	(1) Skin integrity	(1) Slight increasing of patients with intact skin in both groups, no difference between groups	Unclear	Unclear	No/Yes	Yes	Yes	No	3

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Table 4 (*Continued*).

Source	Design	Setting/ Sample/ Indication	Intervention/control	Study duration	n	Mean age (years)	Outcomes	Main results	Risk of bias						
									Sequence generation	Allocation	Blinding	Completeness	Selection	Other	LoE
Cooper and Gray (2001)	RCT	Nursing home/IAD prevention	Intervention Clinisan (Vernacare) foam cleanser (amphoteric surfactants, triclosan, dimethicone) Comparator Soap (non-perfumed) pH 9.5–10.5 (1% aqueous solution) and water	14 days	93	82	(1) Skin condition	(1) Larger proportion of residents in foam cleanser group with intact skin (66%) to soap group (37%) ($p = 0.05$)	Unclear	No	No/Yes	Yes	Yes	No	3
Kon et al. (2017)	RCT	Nursing home, patients with IAD of the buttock or inner thigh/IAD treatment	Intervention Once daily use of a skin cleanser containing emollient, copolymer and dimethicone and the application of a skin protectant containing isopropyl palmitate, acrylate terpolymer and dimethicone three times daily Comparator Cleansing with wet towels after each pad change and use of the same skin cleanser once daily without using a moisturizer for improving IAD severity	14 days	33	Median 86/82	(1) Erythema (2) Pigmentation (3) Sulcus cutis thickness (4) Sulcus cutis interval (5) SCH (6) Dermis hydration (7) TEWL (8) Skin pH	(1) Decrease of erythema index in intervention vs. control ($p = 0.004$); (2) No change in pigmentation between both groups ($p = 0.307$); (3) Increase in thickness in intervention and control ($p = 0.708$); (4) For interval no change in both groups ($p = 0.259$); (5) Increase in SCH in intervention vs. control ($p = 0.100$); (6) Nearly no change in dermis hydration in both groups ($p = 0.155$); (7) Higher decrease in TEWL in intervention vs. control ($p = 0.093$); (8) Slight decrease in skin pH for intervention vs. control ($p = 0.093$)	Unclear	Unclear	No	Yes	Yes	No	3
Lewis-Byers and Thayer (2002)	RCT	Nursing home/IAD prevention	Intervention No-rinse liquid cleanser and barrier cream Comparator Soap and water followed by application of moisturizing lotion after incontinence episode	3 weeks	32	70	(1) Perineal skin condition (2) Pain	(1) Better skin condition in no-rinse cleanser and barrier cream group compared to water and soap (not statistically significant) (2) Slight increase in pain in intervention group (not statistically significant)	No	No	No	Yes	Yes	No	4
Lyder et al. (1992)	Quasi-experimental	Geriatric/ IAD prevention	Intervention Structured skin care regimen including application of cleansers and moisturizers Comparator na.	10 weeks	15	75	(1) IAD incidence	(1) No reduction of IAD incidence	na.						4
Park and Kim (2014)	Quasi-experimental	Hospital (ICU), patients with fecal incontinence, IAD and pressure ulcer risk	Intervention A structured skin care regimen (including skin and stool assessment, interventions (e.g. structured skin care after incontinence, mild washing, use of skin care products) Comparator Standard skin care protocol	7 days	76	68.8/ 69.7	(1) IADS score (2) PU incidence	(1) Lower score for intervention ($p<0.001$); (2) Higher incidence in control-group (13.2% vs 50%, $p<0.001$)	n.a.						3
Warshaw et al. (2002)	Quasi-experimental	Nursing home/IAD prevention	Intervention Cleanser barrier lotion Comparator na.	7 days	19	73	(1) Erythema score (2) Pain score	(1, 2) Reduction of erythema and pain ($p < 0.01$)	na.						3
Zehrer et al. (2004)	Descriptive	Nursing home/IAD prevention	Intervention Barrier film once daily Comparator 1 Protective ointment as needed Comparator 2 Barrier film three times per week	6 month	250	83	(1) IAD incidence	(1) No difference in IAD incidence between groups ($p = 0.55$)	na.						4

Abbreviations: IAD, incontinence-associated dermatitis; LoE, Level of Evidence according to the Oxford Center for Evidence-Based Medicine 2011; PU, pressure ulcer; RCT, randomized controlled trial.

Table 5
Summary of included studies for prevention and treatment of skin tears and pressure ulcers.

Source	Design	Setting/ sample/ indication	Intervention/control	Study duration	n	Mean age (years)	Outcomes	Main results	Risk of bias						LoE
									Sequence generation	Allocation	Blinding	Completeness	Selection	Other	
Skin tears															
Birch and Coggins (2003)	Retrospective	Nursing home /skin tears prevention	Intervention One-step no-rinse cleanser Comparator na.	4 month	29	80 to 82	(1) Skin tears	(1) Reduction of skin tear incidence	na.						4
Carville et al. (2014)	RCT	Nursing home, skin tear prevention	Intervention Twice daily application of a standardized commercially available moisturizing lotion containing glycerin Comparator Skin care as "usual"	6 month	984	87.13/ 85.95	(1) Monthly skin tear incidence (2) Cumulative incidence (3) Number of skin tears (4) Anatomical location of skin tears (5) STAR classification	(1) Intervention-group lower monthly incidence vs. control ($p = 0.004$) (2) Lower cumulative incidence in the intervention-group (41% vs. 59%); (3) 172 ST (40.6%) in intervention group, 252 ST (59.4%) in control-group,(4) Mostly developed on upper limb (Intervention vs. control: 59% vs. 44%) (5) Mostly 1a (31% vs. 45%) an 1b (32% vs. 24%)	Unclear	Unclear	Unclear	No	Yes	Yes	3
Finch et al. (2018)	Quasi-experimental	Hospital, skin tear prevention	Intervention Twice-daily application of a moisturizer containing glycerin and petrolatum Comparator "usual care"	18 month	1177	89.9/ 87.8	(1) Monthly incidence rate (2) Number of skin tears (3) Anatomical location (4) STAR classification	(1) Decreased incidence in intervention-group (4.4) vs. control-group (6.6) ($p = 0.006$); (2) $n = 185$ skin tears in total; $n = 60$ (7.9%) patients in intervention-group, $n = 44$ (10.6%) patients in control-group (3) Mostly on lower limb (about 55% intervention/ 56% control); (4) Mostly 1b (46.8% intervention, 49.2% control)	n.a.						3
Groom et al. (2010)	Retrospective	Nursing home/ skin tear prevention	Intervention Surfactant-based cleanser and moisturizer/barrier cream (dimethicone) Comparator Phospholipid-based cleanser and moisturizer/barrier cream (dimethicone)	12 month	200	65+	(1) Skin tear incidence (2) Number of skin tears	(1) Higher skin tear incidence in surfactant-based cleanser and moisturizer/barrier cream group compared to phospholipid-based cleanser ($p < 0.001$) (2) not reported	na.						4
Mason (1997)	Quasi-experimental/ skin tear prevention	Nursing home	Intervention Non-emollient soap Comparator Emollient soap for	5 month	43	86	(1) Incidence of skin tears (2) Skin quality	(1) Lower skin tear incidence in emollient soap group ($p = 0.082$) (2) not reported	na.						4
Pressure ulcers															
Clever et al. (2002)	Retrospective	Nursing home/ PU prevention	Intervention All-in-one disposable washcloth (dimethicone) vs. standard care Comparator Period before the interventional product was used of 90 days	180 days	64	83	(1) Pressure Ulcer incidence	(1) Lower PU incidence in intervention group compared to standard care group ($p = 0.015$)	na.						4

(*Continued on next page*)

Table 5 (*Continued*).

Source	Design	Setting/ sample/ indication	Intervention/control	Study duration	n	Mean age (years)	Outcomes	Main results	Risk of bias						
									Sequence generation	Allocation	Blinding	Completeness	Selection	Other	LoE
Hunter et al. (2003)	Quasi-experimental	Nursing home/ Skin breakdown and PU prevention	Intervention Skin protectant (50% lanolin, beeswax, petrolatum) and body wash Comparator Nursing care "per normal agency routine" for 3 months	6 month	83	81	(1) Incidence of "skin breakdown" (2) Pressure ulcer incidence	(1) Reduction of "skin breakdown" incidence after implementation of skin protectant and body wash ($p = 0.007$); (2) No reduction of PU incidence ($p = 0.437$)	na.						3
Lupianez-Perez et al. (2015)	RCT	Home nursing service, pressure ulcer prevention	Intervention Twice daily application of olive oil Comparator Hyperoxygenated fatty acids (HOFA)	16 weeks	831	80.6	(1) Incidence of PUs (Stage 2 or higher) (2) Skin integrity	(1) Higher PU incidence with the use of HOFA compared to olive oil on both heels and trochanter (same incidence for sacrum) (per protocol analysis) p value? (2) No differences between groups	Yes	Yes	Unclear	Unclear	Unclear	Yes	3
Thompson et al. (2005)	Quasi-experimental	Nursing home/PU prevention	Intervention Skin care protocol including application of a cleanser and skin protectant (50% lanolin, beeswax, petrolatum) Comparator na.	6 month	136	81	(1) Prevalence of category I and II pressure ulcers (2) Incidence of category I and II pressure ulcers (3) Number of category I and II pressure ulcers	(1) 11.3% pre-intervention, 4.8% post-intervention ($p = 0.244$) (2) 32.7% pre-intervention, 8.9% post-intervention ($p = 0.01$) (3) $n = 35$ pre-intervention, $n = 14$ post-intervention ($p = 0.05$) Slight increase of patients with intact skin in both groups, no difference between groups	na.						3
Torra i Bou et al. (2005)	RCT	Nursing home/ Hospital/ PU prevention	Intervention Mepentol (various oils) Comparator Placebo	30 days	380	84	(1) Incidence of pressure ulcers	(1) 12/164 (7.3%) in intervention-group; 29/167 (17.4%) in placebo-group ($p < 0.006$), RR = 0.42 (95% CI 0.22 to 0.80)	Yes	Yes	Yes	Yes	Yes	No	2
Verdú and Soldevilla (2012)	RCT	Hospital patients with high pressure ulcer risk, pressure ulcer category I prevention	Intervention Application of IPARZINE-SKR every 12 h Comparator Placebo	2 weeks	194	78.2/ 78.5	(1) Pressure ulcer incidence (2) AEs	(1) Intervention 6.1%, control 7.4%, no difference between groups; (2) AEs not reported	Yes	Yes	Yes	Yes	Unclear	Unclear	2

The application of a formulation with 10% glycerin, 5% urea and 8% petrolatum resulted in complete healing of deep fissures in nearly half of all included diabetics with very dry skin on feet compared to 30% in control group but dry skin severity decreased in both groups (Level of Evidence 3) (Gin et al., 2017).

The application of formulations containing plant-based additives like oil emulsion adjusted to pH 4 (Blaak et al., 2017), oat extract (Theunis et al., 2017) or sunflower oil (Chang et al., 2018) resulted in an increased stratum corneum hydration (Blaak et al., 2017; Chang et al., 2018; Theunis et al., 2017) (Level of Evidence 3), decreased transepidermal water loss (Blaak et al., 2017; Chang et al., 2018) (Level of Evidence 3) and reduced pruritus intensity (Theunis et al., 2017) (Level of Evidence 3). Highest improvement in dry skin was achieved for an emollient containing dilinoleic acid 20% compared to 10% and petrolatum (Izumi et al., 2017) (Level of Evidence 3).

3.3.2. Cleansing and complex skin care regimens

Six studies described skin cleansing procedures to treat dry skin. Bathing using a superfatted soap and mineral oil reduced signs of dry skin (Hardy 1990, 1996) (Level of Evidence 3) but Sloane et al. (2007) found no difference in skin condition between four different bathing regimes consisting of whirlpool tub or ultrasound tub using standard soap products or specialized soap and “skin conditioners” and still water with standard soap (Level of Evidence 3). Washing with disposable wash gloves increased skin hydration compared to traditional washing (Gillis et al., 2016) (Level of Evidence 3). A structured skin care regimen consisting of a body wash contained shea butter and glycerin compared to another skin care regimen including the use of a glycerin containing body wash and application of an emollient containing 4% urea reduced skin dryness in both interventions but in the control group as well. Transepidermal water loss and skin surface pH remained nearly unchanged in all intervention and control groups (Hahnel et al., 2017a, 2017b) (Level of Evidence 2). A combination of a body wash and a moisturizer containing sunflower seed oil, panthenol and shea butter with stearic acid, linoleic acid and catechins increased skin hydration and reduced severity of clinical signs of skin dryness after 14 days (Chang et al., 2018) (Level of Evidence 3).

3.4. Improving skin barrier function

3.4.1. Application of leave-on skin care products

Twelve studies evaluated effects of different formulations or washing methods to improve skin barrier integrity. Angelova-Fischer et al. (2018) compared two formulations with pH 4 and pH 5.8 regarding enhancement of skin barrier integrity. The pH 4 formulation showed better effects in skin barrier improvement due to a decrease in skin surface pH, transepidermal water loss and scaliness (Level of Evidence 3). Formulations with pH 4 decreased skin surface pH and improved skin barrier integrity (Behm et al., 2015; Blaak et al., 2015). A plant-based formulation showed improving effects on the epidermal barrier in postmenopausal females regarding microcirculation, skin density, sebum and sagging (Farwick et al., 2014) (Level of Evidence 3). Application of an urea and glycerin containing cream showed skin improvement effects in diabetics (Narbutt et al., 2016) (Level of Evidence 3). In a simulation study the application of a glycerine contain leave-on product before wind exposure caused increased stratum corneum hydration compared to untreated skin (Roure et al., 2012, Level of Evidence 4).

3.4.2. Cleansing and complex skin care regimens

Cleansing with a bag bath reduced the microbial load of the skin (Paulela et al., 2018) in comparison to traditional washing with water (Level of Evidence 3), but a difference of the prevalence of skin damages was not observed (Schoonhoven et al., 2015) (Level of Evidence 3).

In a tightly controlled simulation study the combination of soapy water, boiled tap water with 2% glycerin and afterwards the application of Vaseline showed the greatest skin barrier improvement regarding transepidermal water loss decrease and stratum corneum increase (Brooks et al., 2017) (Level of Evidence 3).

3.5. Preventing and treating incontinence-associated dermatitis

The implementation of structured skin care protocols was investigated in 13 studies (Table 4). Cleansers and washcloths containing low-irritating surfactants, dimethicone and emollients showed skin protecting effects compared to standard care such as using water and traditional soap (e.g. Beeckman et al., 2011, Cooper et al. 2001, Warshaw et al., 2002) (Level of Evidence 3). When comparing these cleansers and strategies directly with each other no differences were observed (Brunner et al., 2012; Byers et al., 1995; Cooper et al., 2008) (Level of Evidence 3).

The application of skin protectants such as barrier films, lipophilic leave-on products such as petrolatum containing products reduced the incontinence- associated dermatitis incidence compared to using no skin protectant (Kon et al., 2017) (Level of Evidence 3). Direct comparisons between skin protectants revealed no differences (Bliss 2006, 2007, Lewis-Byers and Thayer, 2002, Zehrer et al., 2004) (Level of Evidence 4). The application of a skin protectant containing isopropyl palmitate, acrylate terpolymer and dimethicone improved the skin integrity and reduced the severity of incontinence- associated dermatitis compared the application of a skin care protocol conducted every 6 h with every 12 h in patients with incontinence-associated dermatitis (Conley et al., 2014). The intervention comprised gently skin cleansing with an aloe vera containing lotion and application of a skin protectant containing silicone. Incontinence-associated dermatitis severity was reduced in both groups (Level of Evidence 3). Park and Kim (2014) evaluated a complex skin care regimen comprising skin assessment on admission, structured skin care immediately after every incontinence episode, mild washing, use of skin care products, education of care givers compared to standard skin care. The severity of incontinence-associated dermatitis and pressure ulcer incidence was decreased after seven days (Level of Evidence 3).

3.6. Preventing skin tears

Using ‘one-step’ no-rinse cleansers or emollient soaps reduced skin tear incidence compared to standard soap (Mason 1997; Birch and Coggins 2003) (Level of Evidence 4) (Table 5). Comparing to a phospholipid based cleanser there was a higher skin tear incidence in the surfactant-based cleanser group (Groom et al., 2010) (Level of Evidence 4). The application of leave-on products containing glycerin and petrolatum reduced the incidence of skin tears (Carville et al., 2014; Finch et al., 2018) (Level of Evidence 3).

3.7. Preventing pressure ulcers

Results of the six studies preventing pressure ulcers are shown in Table 5. The use of structured skin care regimens such as using a disposable washcloth containing dimethicone (Clever et al., 2002) or using a cleanser in combination with a skin protectant (Hunter et al., 2003; Thompson et al., 2005) reduced pressure ulcer incidence (Level of Evidence 3 to 4). In a placebo-controlled RCT there was no difference in pressure ulcer incidence between the application of a cream containing iparzine in comparison to placebo (Level of Evidence 2) (Verdu and Soldevilla, 2012). In another study, the application of olive oil was compared to hyper-

oxygenated fatty acids. Pressure ulcer incidence was slightly lower in the olive oil-group and differences regarding skin barrier improvement were not observed (Lupianez-Perez et al., 2015) (Level of Evidence 3).

3.8. Outcome domains and measurement instruments

Thirty-five outcome domains were identified (Table 6). Per outcome domain, high numbers of outcome measurement instruments were found. For instance, the outcome domain "clinical signs of skin dryness" was measured with 17 different instruments in 13 studies (Blaak et al., 2015; Chang et al., 2018; Cristaudo et al., 2015; Federici et al., 2012; Federici et al., 2015; Gin et al., 2017; Hahnel et al., 2017a, 2017b, 2017c, Izumi et al., 2017; Martini et al., 2017; Narbutt et al., 2016; Theunis et al., 2017; Weber et al., 2012). Different clinical scales containing 4 to 10 items were used to measure the severity of skin dryness. Several clinical signs were assessed, e.g. erythema, scaling, roughness or excoriations.

Seven instruments were used to measure pruritus or itch (Chang et al., 2018; Cristaudo et al., 2015; Federici et al., 2012; Izumi et al., 2017; Theunis et al., 2017). Pruritus severity was assessed using different scales or by a 22-item questionnaire.

The most often applied outcome measurement instruments for stratum corneum hydration was the Corneometer (Blaak et al., 2017; Blaak et al., 2015; Chang et al., 2018; Cristaudo et al., 2015; Danby et al., 2016; Hahnel et al., 2017a, 2017b, 2017c, Kon et al., 2017; Korponyai et al., 2017; Martini et al., 2017; Narbutt et al., 2016; Theunis et al., 2017; Weber et al., 2012), but additionally further three instruments were used. The most often applied instrument for assessments of skin surface pH was the Skin pH Meter PH905 (Angelova-Fischer et al., 2018; Blaak et al., 2017; Blaak et al., 2015; Danby et al., 2016; Hahnel et al., 2017a, 2017b, 2017c, Kon et al., 2017; Narbutt et al., 2016). For the measurement of transepidermal water loss most studies used the Tewameter (Angelova-Fischer et al., 2018; Chang et al., 2018; Cristaudo et al., 2015; Hahnel et al., 2017a, 2017b, 2017c, Korponyai et al., 2017; Narbutt et al., 2016; Weber et al., 2012), but three other instruments were also applied (Blaak et al., 2017; Blaak et al., 2015; Brooks et al., 2017; Danby et al., 2016; Kon et al., 2017; Theunis et al., 2017). Some outcome domains like "skin scaliness/desquamation" or "skin surface roughness" were assessed using devices or clinical grading scales (Angelova-Fischer et al., 2018; Federici et al., 2015; Narbutt et al., 2016).

4. Discussion

Skin care is an integral part of nursing practice and this work provides an up-to date comprehensive broad summary of available evidence of the effects and effectiveness of skin care interventions in aged populations.

One major result of this review update is, that between 2012 and 2018 more relevant studies were published compared to the much longer search period from 1990 to 2012 in the previous review (Kottner et al., 2013). This indicates increasing interest in this topic. Included studies address skin dryness, followed by general strategies to enhance skin integrity, prevention and treatment of incontinence-associated dermatitis, prevention of skin tears and pressure ulcers. This corresponds to the load of these skin conditions in aged populations (Hahnel et al., 2017a, 2017c), and they are all relevant to nursing practice (Kottner et al., 2019a, 2019b).

4.1. Preventing and treating dry skin

Study results consistently indicate, that the use of leave-on products is effective in treating signs of dry skin compared to no products (Level of Evidence 3). This is in accordance with the results of the previous review and guidance in the field (Guenther et al., 2012; Kottner et al., 2013). However, results of direct head-to-head leave-on comparisons are inconclusive. Depending on the chosen comparator, the performance of formulations containing humectants such as urea, glycerin or lactate in different concentrations seems to be better compared to vehicles without these humectants, but overall skin dryness and skin barrier properties also improved in control groups. Review results also indicate, that a structured approach is better than an unstructured or no skin care regimen for improving skin dryness (Level of Evidence 2 and 3). Overall, these results indicate, that lipophilic leave-on products containing basic ingredients such as petrolatum with or without humectants are helpful for treating dry skin in aged care settings. Based on the current evidence it is unclear, whether one product or a certain ingredient is better than another. It is widely accepted that effects on the skin are always based on the total formulation. It is not the presence or absence of a single ingredient (Kottner and Surber 2016).

4.2. Interventions for skin barrier improvement

Five of 10 studies investigated effects of leave-on products with an acidic pH of 4. These products seem to be more helpful to maintain and improve the skin barrier compared to no treatment (Level of Evidence 3 and 4) and products with higher pH (Level of Evidence 3). Similar to the treatment of dry skin, review results indicate that the application of skin care products is better than no treatment for skin barrier improvement (Brooks et al., 2017; Narbutt et al., 2016), but differences between formulations seems to be low (Farwick et al., 2014) (Level of Evidence 3). The use of traditional washing compared to 'bag baths' seems to make no difference in terms of overall skin integrity (Schoonhoven et al., 2015) (Level of Evidence 2). Taken together these results indicate, that selecting leave-on products with a more acidic pH has advantages for skin barrier improvement in aged skin.

4.3. Preventing and treating incontinence-associated dermatitis

Published quasi-experimental studies and RCTs showed that using mild cleansers and skin care and barrier products are helpful for preventing and treating incontinence-associated dermatitis but differences between strategies and products are unclear (Level of Evidence 3 and 4). This indicates that a structured skin cleansing and protection regimen is better than doing nothing, but performance differences between products or strategies are unclear. These results are similar to the previous review (Kottner et al., 2013) and are supported by conclusions in the latest Cochrane review for the prevention and treatment of incontinence-associated dermatitis (Beeckman et al., 2016) and by recent guidance in the field (Beele et al., 2018).

4.4. Preventing skin tears and pressure ulcers

Review results indicate, that the application of leave-on products containing basic ingredients such as glycerin and petrolatum prevents skin tear occurrence in the aged (Level of Evidence 2 and 3). Results of quasi-experimental studies suggest, that mild skin cleansing and skin protection might be helpful for preventing superficial pressure ulcers (Level of Evidence 4) but because a non-treatment groups are lacking in the included RCTs these results do not provide strong evidence that the application of topical products reduces pressure ulcer development per se. This also fits to the current understanding of the etiology of pressure ulcers starting in deeper subcutaneous tissues (Kottner et al., 2019a, 2019b). This interpretation is supported by the latest Cochrane review about

Table 6
Outcome domains and measurement instruments or techniques.

Outcome domains (what?)	Outcome measurement instruments/techniques (how?)	References
(1) Skin dryness (clinical signs)	(1) Dry skin area and severity index (DASI)	Blaak et al. (2015) and Federici et al. (2012)
	(2) Xerosis assessment Scale (XAS)	Federici et al. (2015) and Martini et al. (2017)
	(3) Dry skin 5-point severity scale	Chang et al. (2018)
	(4) Fissures (Complete healing of a target fissure according to a 3-point scale: healed fissures, superficial closed fissures or deep open fissures after 2 and 4 weeks of treatment), (Clinical benefit of treatment on fissure improvement (5-point scale: 1 (strong improvement) to 5 (worsening))	Gin et al. (2017)
	(5) Severity of scaling (4-point scale (absent (0), mild (+), moderate (++), severe (+++))	Cristaudo et al. (2015)
	(6) Severity of skin tightness (4-point scale)	Cristaudo et al. (2015)
	(7) Severity of fissuring (4-point scale)	Cristaudo et al. (2015)
	(8) Severity of excoriations (4-point scale)	Cristaudo et al. (2015)
	(9) Severity of Erythema (4-point scale)	Cristaudo et al. (2015)
	(10) Visual change in erythema severity (4-point scale)	Narbutt et al. (2016)
	(11) Severity of skin dryness via VAS (10-point scale: 0 = extreme skin dryness to 10 = best skin hydration state imaginable)	Federici et al. (2012)
	(12) Severity of xerosis according to a 9-point scale (0 (normal skin) to 8 (deep fissuring))	Gin et al. (2017)
	(13) Severity of skin dryness via Overall Cutaneous score (OCS) (0 = normal skin to 3 = severe hyperkeratosis)	Federici et al. (2015)
	(14) Overall dry skin score (ODS) (5-point scale: 0 = no skin dryness to 4 = advanced skin roughness, large scales, inflammation and cracks)	Hahnel et al. (2017a, 2017b, 2017c) and Theunis et al. (2017) (French translation)
	(15) Severity of skin dryness on the lower legs (5-point scale: 0 = none to 4 = severe)	Izumi et al. (2017)
	(16) Visual change in skin dryness severity (4-point scale: 1 = lack of any change, 2 = low severity changes, 3 = moderate severity changes, 4 = greatest severity changes)	Narbutt et al. (2016)
	(17) Skin dryness via 5-point clinical grading score	Weber et al. (2012a, 2012b)
(2) Pruritus/itch	(1) Pruritus (ItchyQol™, a 22-item questionnaire)	Chang et al. (2018)
	(2) Itching (scale from 0 (no itching) to 10 (severe itching))	Cristaudo et al. (2015)
	(3) Itch sensation (10-point scale: 0 = extreme itch to 10 = no itch)	Federici et al. (2012)
	(4) Severity of scratch marks (pruritus) on the lower legs (5-point scale: 0 = none to 4 = severe)	Izumi et al. (2017)
	(5) Itching (VAS)	Izumi et al. (2017)
	(6) Intensity of Pruritus via 10 cm Visual Analog Scale	Theunis et al. (2017)
	(7) Intensity of Pruritus via French version of the 5-D itch scale	Theunis et al. (2017)
(3) Stratum corneum hydration/ Dermal hydration	(1) Corneometer	Blaak et al. (2015), Danby et al. (2016), Behm et al. (2015a), Blaak et al. (2017), Chang et al. (2018), Cristaudo et al. (2015), Hahnel et al. (2017a, 2017b, 2017c), Kon et al. (2017), Korponyai et al. (2016), Martini et al. (2017), Narbutt et al. (2016), Theunis et al. (2017) and Weber et al. (2012a, 2012b, 2012c)
	(2) MoistureMeterSC	Brooks et al. (2017) and Gillis et al. (2016)
	(3) Bio-impedance skin analysis device (Hydr8)	Federici et al. (2015)
	(4) MoistureMeter D	Kon et al. (2017)
(4) Skin surface pH	(1) Skin pH Meter PH905	Blaak et al. (2015), Danby et al. (2016), Angelova-Fischer et al. (2018a, 2018b), Blaak et al. (2017), Hahnel et al. (2017a, 2017b, 2017c), Kon et al. (2017) and Narbutt et al. (2016)
	(2) Skin pH Electrode by SI Analytics GmbH, Mainz, Germany	Behm et al. (2015a, 2015b)
(5) Skin tears	(1) Incidence	Carville et al. (2014)
	(2) Number of skin tears	Carville et al. (2014)
	(3) Anatomical location of skin tears	Carville et al. (2014)
	(4) Classification of skin tears by STAR (Skin Tear Classification)	Carville et al. (2014)

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Table 6 (*Continued*).

Outcome domains (what?)	Outcome measurement instruments/techniques (how?)	References
(6) Transepidermal water loss	(1) Tewameter	Hahnel et al. (2017a, 2017b, 2017c), Angelova-Fischer et al. (2018a, 2018b), Chang et al. (2018), Cristaudo et al. (2015), Korponyai et al. (2016), Narbutt et al. (2016) and Weber et al. (2012a, 2012b)
	(2) AquaFlux AF200	Danby et al. (2016) and Theunis et al. (2017)
	(3) DermaLab	Blaak et al. (2015) and Blaak et al. (2017)
	(4) VapoMeter	Brooks et al. (2017) and Kon et al. (2017)
(7) Skin surface roughness	(1) VisioScanVC 98	Angelova-Fischer et al. (2018a)
	(2) Visual change in roughness severity (4-point scale: 1 = lack of any change to 4 = greatest severity changes)	Narbutt et al. (2016)
	(3) Tactile roughness with a 5-point clinical grading score (0 = absent (perfectly smooth and pliable) to 4 = extreme (gross irregularly and severe disturbance of skin markings and definite stiffening))	Weber et al. (2012a, 2012b, 2012c)
(8) Skin scaliness/desquamation	(1) VisioScanVC 98	Angelova-Fischer et al. (2018a)
	(2) Bio-impedance skin analysis device (Hydr8)	Federici et al. (2015)
	(3) D-Squame® adhesive tapes	Chang et al. (2018), Martini et al. (2017) and Theunis et al. (2017)
	(4) Visual change in severity of desquamation (4-point scale: 1 = lack of any change to 4 = greatest severity changes)	Narbutt et al. (2016)
(9) Stratum corneum cohesion	(1) SquamScan 850A	Angelova-Fischer et al. (2018a) and Blaak et al. (2015)
	(2) Protein quantification via SquamScan 850A	Danby et al. (2016)
	(3) Bio-Rad Protein Assay Kit I (Protein amount)	Blaak et al. (2015)
	(4) Infrared densitometer at wavelength of 850 nm (Absorption)	Blaak et al. (2015)
	(5) SC Protease activity via tape stripping	Danby et al. (2016)
	(6) Protein quantity (MMP-1 and filaggrin) via skin biopsy	Korponyai et al. (2016)
(10) Visual skin irritation	(1) Visual score (according to Frosch and Kligman 1979)	Angelova-Fischer et al. (2018b)
	(2) Visual change in skin irritation (4-point scale (1 = lack of any change to 4 = greatest severity changes))	Narbutt et al. (2016)
(11) Bacterial colonization/skin flora	(1) Culture-based microbiological methods (colony-forming units (CFU) per square centimetre of skin)	Blaak et al. (2015)
	(2) Skin microbial load via culture media on blood agar and MacConkey agar plates	Paulela et al. (2018)
(12) Stratum corneum recovery rate	(1) TEWL measurement 24 h after tape stripping	Blaak et al. (2015)
(13) Stratum corneum integrity	(1) Tape stripping method (D-Squame Standard) until TEWL increased by 3-fold=number of tape strips	Blaak et al. (2015)
(14) Quality of epidermal permeability barrier (EPB)	(1) Lipbarvis analysis: Number of intercellular lipid lamellae	Blaak et al. (2017)
(15) Number of lipids	(1) High performance thin layer chromatography	Blaak et al. (2017)
(16) Skin damage/skin breakdown	(1) Degree of skin breakdown via skin assessment: Intact skin or skin breakdown (mild, moderate, severe)	Brunner et al. (2012)
	(2) Time to skin breakdown (measurement of minutes and hours)	Brunner et al. (2012)
	(3) Prevalence of skin damage (any skin abnormalities/lesions; significant skin lesions)	Schoonhoven et al. (2015)
(17) Participant satisfaction	(1) Cosmetic acceptability questionnaire (12-item scale)	Chang et al. (2018)
	(2) 5-point-scale (1 = the lowest satisfaction to 5 = the highest satisfaction)	Narbutt et al. (2016)
(18) Safety: adverse events	(1) Not defined	Chang et al. (2018) and Theunis et al. (2017)
	(2) Treatment-related	Gin et al. (2017) Martini et al. (2017)
(19) Incontinence-associated dermatitis	(1) Brownś grading scale (0 = no erythema to 3 = severe erythema)	Conley et al. (2014)
	(2) IADS score (Assessment of erythema, rash, skin loss in 13 areas including perianal, perineal, perigenital skin and inner thighs)	Park and Kim (2014)
(20) Skin redness/erythema	(1) Mexameter MX18	Danby et al. (2016)
	(2) Erythema index by Photograph color calibration using image editing software	Kon et al. (2017)
(21) PCA (sodium pyrrolidone carboxylic acid) and Lactate	(1) Tape stripping sampling	Danby et al. (2016)
(22) Skin sebum content	(1) Sebumeter SM 810	Farwick et al. (2014) Narbutt et al. (2016)
(23) Cutaneous blood microcirculation	(1) Flowmeter Periflux PF4001	Farwick et al. (2014)
(24) Skin density/echogenicity	(1) Ultrasound scanner, Dermascan C	Farwick et al. (2014)
(25) Sagging	(1) Expert grading score	Farwick et al. (2014)
(26) Quality of life	(1) Skindex-16 (Japanese version) 16 items in three scales (symptoms, emotions, functioning)	Izumi et al. (2017)
(27) Pigmentation	(1) Melanin index by Photograph color calibration using image editing software (Photoshop CS5)	Kon et al. (2017)

(*Continued on next page*)

Table 6 (*Continued*).

Outcome domains (what?)	Outcome measurement instruments/techniques (how?)	References
(28) Sulcus cutis thickness	(1) Digital image analysis	Kon et al. (2017)
(29) Skin friction	(1) Frictiometer FR 700	Korponyai et al. (2016)
(30) Skin elasticity	(1) Cutometer MPA 580 (R0)	Korponyai et al. (2016)
(31) Thickness of epidermis and dermis and echogenicity of the papillary dermis	(1) DUB®-USB high-frequency, high-resolution, ultrasound system	Korponyai et al. (2016)
(32) Pressure ulcer (PU)	(1) Incidence of PU stage 2 or higher on application areas sacrum, hips and heels	Lupianez-Perez et al. (2015)
	(2) PU incidence	Park and Kim (2014) and Verdu et al. (2012)
(33) Effectiveness due to subject's opinion	(1) 100-mm visual analog scale (VAS) from 0 (not effective/not pleasant) to 100 (very effective/very nice)	Martini et al. (2017)
(34) Skin relief	(1) Silicon replicas with image analysis	Martini et al. (2017)
(35) Skin auto fluorescence	(1) AGE reader	Narbutt et al. (2016)

topical applications to prevent pressure ulcers. Based on high quality evidence only, the review authors concluded that most topical applications showed no benefit or harm (Moore and Webster, 2018).

5. Outcomes

The number of 35 different outcome domains and nearly 100 outcome measurement instruments was unexpectedly high. The situation in the field of basic care interventions in the aged is obviously similar to many other areas in the field of skin research (Schmitt et al., 2018). In order to improve the quality of clinical research and systematic reviews we recommend the identification of most relevant outcome domains first, followed by the selection of the best outcome measurement instruments for this domain. Such an initiative has been started for incontinence-associated dermatitis research (Van den Busche et al. 2017; Van den Busche et al. 2018) but is also needed for other areas relevant to nursing practice. Given the high prevalence of xerosis cutis in nursing care settings and in particular in the aged (30% to 90%), the high number of clinical studies and the substantial heterogeneity of outcomes this is one high priority area.

6. Limitations

Two major databases, one citation index and numerous reference lists were searched, but it is still possible that relevant studies were not identified. Although RCTs are the reference standard when investigating treatment effects, we also included a range of other study designs providing lower quality evidence. Only seven high quality RCTs (Federici et al., 2015; Hahnel et al. 2017a, 2017b; Martini et al., 2017, Pham et al. 2011, Quatresooz et al., 2009, Torra I Bou et al. 2005, Verdu and Soldevilla 2012) were included but the results of the weaker study designs were largely comparable. Our aim was to provide a comprehensive overview of the types of available studies, interventions and reported outcomes. Therefore, broad in- and exclusion criteria were used, because nurses and other individuals providing skin care need to do the clinical decisions on a daily basis irrespectively from the availability of high quality evidence.

In this review, we did not distinguish between evidence of effects and effectiveness. It can be assumed that observed effects in tightly controlled RCTs might not be reproducible in real world situations. The clinical relevance of chosen treatment durations (e.g. 2 weeks) and outcomes (e.g. transepidermal water loss) is also unclear. It can be assumed that properly designed pragmatic RCTs using clinical relevant outcomes are more important to inform clinical practice.

Another limitation was the use of a simplified methodological and evidence appraisal system (Oxford Center for Evidence Based Medicine, 2009). This approach is clearly limited compared to the state-of-the art methods for doing systematic reviews focusing on predefined outcomes according to the Cochrane Collaboration (Higgins and Green, 2011) but it does provide a framework to evaluate the overall quality of evidence.

7. Conclusions

Because of the substantial heterogeneity of study designs, interventions, skin care products and outcomes a meaningful evidence synthesis is challenging. Basic skin care strategies including low-irritating cleansers and humectant-containing leave-on products are helpful for treating dry skin and improving the skin barrier in the aged. Leave-on products with a low pH seem to have an additional positive effect on improving the skin barrier. The regular use of leave-on products also seems to prevent skin tear development. Standardized skin care approaches including the application of skin protection products help to prevent incontinence-associated dermatitis. Therefore we conclude, that the application of leave-on products containing basic and common ingredients such as petrolatum, paraffin or glycerin help to maintain skin integrity in this population. Overall, the quality of evidence is moderate to weak and in particular, the clinical relevance of differences between skin cleansing and caring products is unclear. There is an urgent need to improve the comparability of skin care product descriptions and classifications and outcomes in skin care trials.

Conflict of interest

None.

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Supplementary materials

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1	JOURNAL OF THE AMERICAN ACADEMY OF DERMATOLOGY	30,658	8.277	0.034840
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10	DERMATOLOGY	5,372	3.695	0.003850
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16	SKIN PHARMACOLOGY AND PHYSIOLOGY	1,829	3.314	0.001240
17	DERMATOLOGIC CLINICS	2,369	3.164	0.003370
18	Burns & Trauma	538	3.088	0.001320
19	JOURNAL OF DERMATOLOGY	5,229	3.072	0.007870

Rank	Full Journal Title	Total Cites	Journal Impact Factor	Eigenfactor Score
20	LASERS IN SURGERY AND MEDICINE	5,435	3.020	0.003720
21	International Wound Journal	3,446	2.825	0.005580
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23	EUROPEAN JOURNAL OF DERMATOLOGY	2,939	2.782	0.003030
24	Dermatology and Therapy	692	2.761	0.001720
25	MELANOMA RESEARCH	2,450	2.750	0.003740
26	Indian Journal of Dermatology Venereology & Leprology	2,122	2.712	0.002100
27	DERMATOLOGIC SURGERY	8,112	2.567	0.006930
28	WOUND REPAIR AND REGENERATION	5,833	2.471	0.005030
29	CLINICS IN DERMATOLOGY	3,846	2.458	0.003140
30	Journal of Tissue Viability	624	2.410	0.000910
31	PHOTODERMATOLOGY PHOTOIMMUNOLOGY & PHOTOMEDICINE	1,656	2.387	0.001230
32	ARCHIVES OF DERMATOLOGICAL RESEARCH	3,777	2.339	0.003460
33	Dermatologic Therapy	1,988	2.327	0.002140
34	JOURNAL OF DERMATOLOGICAL TREATMENT	2,425	2.156	0.003970
35	SKIN RESEARCH AND TECHNOLOGY	2,358	2.079	0.001980
36	INTERNATIONAL JOURNAL OF DERMATOLOGY	7,833	2.067	0.007720
37	BURNS	7,880	2.066	0.007350
38	CLINICAL AND EXPERIMENTAL DERMATOLOGY	4,863	1.977	0.003840
39	Clinical Cosmetic and Investigational Dermatology	1,161	1.970	0.002370
40	JOURNAL OF CUTANEOUS MEDICINE AND SURGERY	1,297	1.909	0.001900

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ORIGINAL ARTICLE

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The effect of a basic skin care product on the structural strength of the dermo-epidermal junction: An exploratory, randomised, controlled split-body trial

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Abstract

Skin ageing is associated with various structural alterations including a decreased strength of the dermo-epidermal adhesion increasing the risk for shear type injuries (skin tears). Topical applications of basic skin care products seem to reduce skin tear incidence. The suction blister method leads to the artificial and controlled separation of dermis and epidermis. Therefore, time to blister formation may be used as outcome measuring the strength of dermo-epidermal adhesion. We conducted an exploratory, randomised, controlled trial with a split-body design on forearms in healthy female subjects (n = 12; mean age 70.3 [SD 2.1] years). Forearms assigned to the intervention were treated twice daily with petrolatum for 8 weeks. Suction blisters were induced on forearms after 4 and 8 weeks and time to blister formation was measured. Stratum corneum and epidermal hydration were measured and epidermal thickness was assessed via optical coherence tomography. Time to blistering was longer and stratum corneum as well as epidermal hydration was consistently higher in intervention skin areas. We conclude that topical application of basic skin care products may improve mechanical adhesion of the dermo-epidermal junction and that the parameter "time to blistering" is a suitable outcome to measure dermo-epidermal adhesion strength in clinical research.

KEYWORDS

prevention, skin care, skin integrity, skin tears, suction blister

Key Messages

- Age-related structural changes of the skin, such as flattening of the dermo-epidermal junction, are associated with increased skin fragility which makes the skin prone to shear type injuries like skin tears
- This exploratory trial with a split-body design in healthy female participants was conducted to determine the effects of a basic skin care formulation on the mechanical adhesion strength of the dermo-epidermal junction using the suction blister method

- The suction blister method allows an artificial and controlled separation of dermis and epidermis
- Topical application of basic skin care products may improve the mechanical adhesion of the dermo-epidermal junction.
- The parameter "blistering time" reflects the mechanical integrity and is a suitable outcome to measure the strength dermo-epidermal adhesion

1 | INTRODUCTION

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.[1] The process of ageing involves numerous structural and functional changes including the skin. Due to its ageing-related loss of functional capacity, the skin becomes more susceptible to develop adverse skin conditions and dermatological diseases (eg, xerosis cutis and itch, fungal infections, skin cancer and dermatitis).[2-4]

Clinically very relevant age-related structural changes can be observed at the dermo-epidermal junction (DEJ).[5] The DEJ forms the interface between the lower layer of the epidermis and the top layer of the dermis and consists of a complex structural network of interacting proteins which mediate adhesion of these two very different tissue types.[6] Furthermore, it allows the exchange and transport of nutrients as well as various molecules between the non-perfused epidermis and the perfused dermis.[7] On the epidermal site of this network, the basal keratinocytes are interlinked to the basement membrane via hemidesmosomes and anchoring filaments. The interconnection of the basement membrane to the collagen meshwork of the dermis is mediated by anchoring fibrils.[8] In addition to these specific molecular characteristics of the DEJ, it has also a characteristic three-dimensional structure. It is described as finger-like projections of rete ridges (epidermal protrusion down into the dermis) and upwardly protruding dermal papillae from the dermis into epidermis.[9] This interdigitation is important in order to provide the skin with structural integrity as well as mechanical stability.[6] A consequence of intrinsic skin ageing, besides a gradual disorganisation of the anchoring system,[10] is a significant thinning and flattening of the DEJ,[8] caused by the retraction of rete ridges[11] as well as a reduction of dermal papillae.[12] These age-related structural changes beyond the 6th decade of life[13] leading to a flattened appearance of the DEJ and are associated with a reduced contact surface area and therefore less adhesion.[11] The more fragile dermo-epidermal interface in aged skin makes it more prone to bulla formation and trauma and less resistant to shearing forces, potentially leading to shear-type injuries such as skin tears.[6,13-16]

The prevalence of skin tears in aged care settings is 3% to 22%.[17-20] Empirical evidence indicates that basic skin care strategies may help to prevent skin tear development.[21] For example, Carville et al[22] showed that the application of a moisturiser twice a day reduced the skin tear incidence in residents living in aged care facilities by almost 50% compared to the control group. These study results led to the recommendation that topical leave-on products should be applied in long-term care as one component of a skin tear prevention program.[23] However, the underlying mode of action is unclear. Topically applied basic skin care products such as petrolatum, waxes and comparable lipophilic substances exhibit physical and chemical effects on and in the uppermost skin layers (eg, the stratum corneum [SC]). Petrolatum is one of the most effective moisturisers.[24] By forming an occlusive layer, the transepidermal water loss (TEWL) is reduced with a simultaneous increase of the stratum corneum hydration (SCH).[24-27] Furthermore, the application of petrolatum causes an increase of the epidermal thickness by swelling of the SC.[28] However, effects on the DEJ have not been described and it is unclear whether basic skin care products actually increase the strength of the DEJ.

Despite a wide range of invasive and non-invasive methods to measure structural and functional properties of the skin, approaches to quantify the dermo-epidermal adhesion strength directly are less established. One proposed approach to measure this parameter in vivo is the artificial induction of suction blisters (SBs).[10]

The first documented artificial mechanical separation of epidermis and dermis along the DEJ was described in 1887 by Unna.[29] Kiistala and Mustakallio[30,31] developed this method further by using suction cups and applying a constant negative pressure on the skin to create SBs. Through the application of constant negative pressure, interstitial fluid accumulates between the dermis and epidermis and hemidesmosomes detach from the basement membrane.[31,32] Initially, multiple tiny sub-epidermal vesicles arise which coalesce to form eventually a single cavity.[30] This process leads to a complete dermal-epidermal separation and results

in a macroscopically visible cavity filled with suction blister fluid. Today the SB technique is widely used in dermatological research for studying morphological, physiological, or pharmacological phenomena[33,34] and the creation of standardised wounds allows to study wound healing.[35,36] This method is also widely used in medical practice for epidermal grafting to treat various skin conditions.[37,38]

Based on the results of a systematic review about SBs in dermatology,[15] the parameter "blistering time" was proposed as a measure of the dermo-epidermal adhesion in skin research recently.[10] The blistering time can be defined as the time period from the start of suction until the appearance of visible vesicles. Among other factors, empirical evidence suggests associations between blistering time and age[15] or smoking status.[39,40] Therefore, the parameter "blistering time" reflects the strength of the dermo-epidermal adhesion and may be regarded as a clinically relevant parameter reflecting the mechanical integrity and resistance of the DEJ.[10,15] However, this proposed outcome has never been used in clinical research so far even though there is evidence supporting its usefulness.[10]

Based on the observation that basic topical leave-on products reduce the risk for skin tear development and that the parameter "time to blistering" is related to the dermo-epidermal adhesion strengths, the objective of this study was to investigate, whether there is an association between a basic skin care intervention and the adhesion strength of the DEJ.

2 | MATERIALS AND METHODS

2.1 | Trial design and setting

An exploratory, randomised controlled clinical trial (RCT) with a split-body design (left versus right volar forearm) was conducted in 2018 at the Clinical Research Centre for Hair and Skin Science at the Charité-Universitätsmedizin Berlin, Germany. The split-body design allows an intra-individual comparison of investigational sites and minimises inter-individual biological variation. The trial was approved by the local ethics committee of the Charité-Universitätsmedizin Berlin (EA1/060/18) and it was registered at clinicaltrials.gov (NCT03625167). No important changes were made after trial commencement.

2.2 | Participants

Healthy female volunteers were invited to participate when meeting the following inclusion criteria: (a) Age between 65 and 85 years, (b) Caucasian with phototype I to III according to Fitzpatrick classification, (c) body mass index (BMI) between 20 and 28 kg/m^2, (d) non-smoker of at least 1 year, (e) absence of skin diseases, scars or tattoos at the skin areas of interest. For this exploratory trial, females were included only to reduce biological variability. Written informed consent was obtained from all participants before inclusion.

Major exclusion criteria among others were (a) known or suspected defect of healing, (b) any skin affection which may interfere with the trial assessment (eg, urticaria, psoriasis or scars on investigational areas), (c) any acute or chronic pathology that may interfere with the trial conduct, (d) diabetes mellitus or history or establishment of diabetes or pre-diabetes, (e) use of topical or systemic treatment on the investigational areas within the past 4 weeks that would interfere with assessment, and/or investigational treatments (f) any known hyper-sensibility to one of the compounds of the investigational product.

2.3 | Interventions

All included subjects were instructed to apply petrolatum (Vaseline, white Ph.Eur., Fagron GmbH & Co. KG, Barsbüttel, Germany) to the randomly assigned interventional volar forearm. A member of the study team demonstrated the correct amount and application of the product at the baseline visit (pea-sized amount, equal to 0.6-0.7 g). During the trial, the skin care product was applied by the subjects at home. Adherence to the intervention was checked by weighing the petrolatum tubes at week 4 and week 8. Applications took place twice daily (morning and evening) for 4 and 8 weeks, respectively. This was performed after washing or showering to allow the product to stay on the skin during day or night. The other forearm remained untreated (control arm). During the trial, additional skin care products on the investigational skin areas were not allowed. Furthermore, the subjects were instructed not to have sun exposure or UV-light sessions, use any topical drugs or cosmetic products on both arms (except usual cleaning products) or have any physical treatments on the investigational areas.

2.4 | Outcomes

No distinctions were made between primary and secondary outcomes due to the exploratory nature of the trial. No changes to trial outcomes were made after trial commencement.

Outcomes for all investigational areas were the blistering time, SCH, epidermal hydration, and epidermal thickness on both forearms. The outcome "blistering time" was defined as (a) time to first vesicles (period of time until the appearance of the first macroscopically

visible vesicles) and (b) time to full blister (period of time until the appearance of a full blister covering the entire area to which the suction pressure was applied). A full blister can result by expansion of a single initial vesicle or by multiple coalescent vesicles. The blistering time was measured in minutes.

SCH was measured with the Corneometer CM 825 (Courage + Khazaka, Cologne, Germany). The measurement is based on the difference in the dielectric constant of water and other substances and measures the water content in the SC.[41] Values are expressed in arbitrary units (AU) and range from 0 to 120, with higher values indicating higher SCH. Absolute measurement errors of SCH measurements in terms of upper and lower limits of agreement are expected to be +4 AU and − 4 AU[42,43] and reliability coefficients exceed 0.9.[42,43] Therefore, comparisons of means within and between groups are justified.[44] Values above 40 AU may be considered as "normal" SCH, values <40 AU are regarded as sign for dry skin.[45]

Epidermal hydration was measured with MoistureMeterEpiD (Delfin Technologies Ltd, Kuopio, Finland). The measured dielectric constant values are proportional to the water content in the epidermal tissue and are expressed as percentage of tissue water (0%-100%; 0.5 mm measurement depth). Reliability of epidermal hydration measurements are also very high.[42]

The skin surface temperature of investigational areas was measured with the Skin-Thermometer ST 500 (Courage+Khazaka, Cologne, Germany) and expressed in °C. Empirical evidence suggests high reliability of skin surface temperature measurements.[46] All physiological skin measurements are expressed as means of duplicate measurements per investigational area.

Epidermal thickness was measured with optical coherence tomography (Thorlabs, Lübeck, Germany), according to the methods described by Trojahn et al.[47] Epidermal thickness was expressed in μm.

Before any measurements or the induction of suction blisters, the study volunteers had to acclimatise for 30 minutes at 40% to 60% relative humidity and at a temperature of 20 to 22°C with having both forearms uncovered. The non-invasive biophysical measurements on both volar forearms including SCH, epidermal hydration, and epidermal thickness were conducted at baseline visit as well as at week 2, 4, 6, and 8. At week 4 and 8, the skin surface temperature was measured additionally before induction of suction blisters.

2.5 | Suction blister induction

A vacuum pump (Hico-Rapidovac 761, Hirtz, Cologne, Germany) was used to produce a constant negative pressure at − 200 mmHg. The pump was connected to a main tube in order to transmit the negative pressure to the skin. The main tube was subdivided to obtain multiple ends to ensure that the same negative pressure was applied to all investigational areas at the same time. At the end of each tube, an upside-down-positioned disposable syringe with a diameter of 8 mm was attached. The tip of the syringe was attached airtight to the tube and the plunger was removed. The resulting 8 mm diameter cavity was placed on the test area to aspirate the skin. Due to the suction, the skin is pulled into the syringe and appears in a dome-like structure. After the blister fully developed, the syringes were removed, the blister fluid was punctured and a dressing was applied.

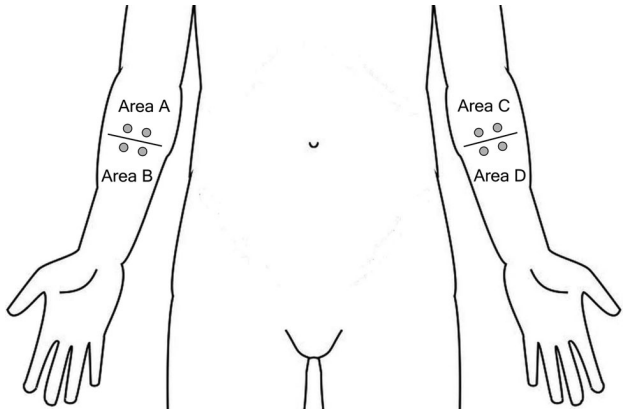

FIGURE 1 Schematic representation of investigational areas. Each of the indicated areas (A, B, C, and D) contain two suction blister induction sites (depicted as grey filled circles)

2.6 | Sample size

Due to the explorative character of this pilot trial, a formal sample size estimation was not performed. Following the recommendation by Julious,[48] it was planned to include n = 12 female subjects.

2.7 | Randomization and blinding

A two-step randomization was applied in this trial. The first step was a simple computer-generated randomization table with 1:1 allocation to the treatment volar forearm (right vs left). Sequentially numbered sealed opaque envelopes containing the assignment to the treatment volar forearm were prepared and used. After a participant was included and the baseline skin measurements were conducted, the study personnel opened the next numbered envelope in chronological order.

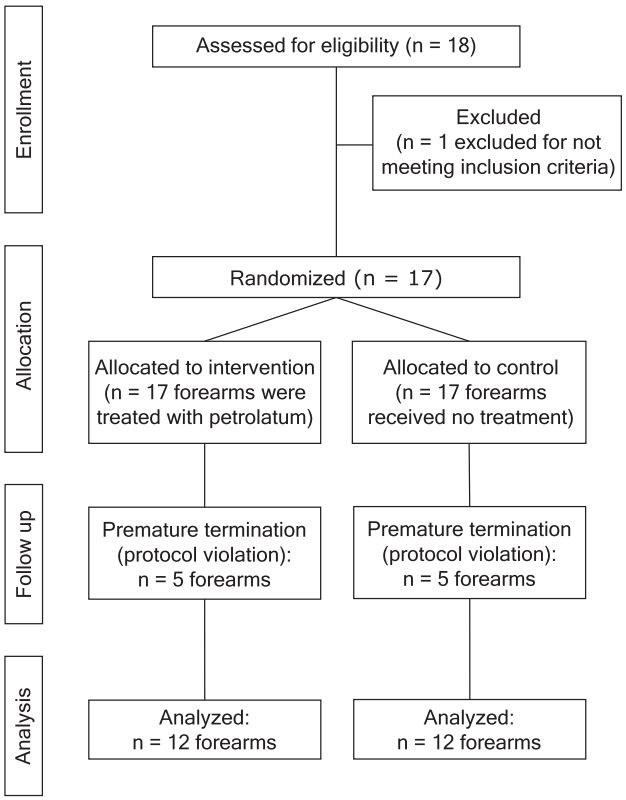

FIGURE 2 Flowchart outlining the participant flow during the trial

In the second step of randomization, for every participant a second sealed opaque envelope was prepared containing the order in which the suction blisters were induced on week 4 and week 8 (upper area A/C first vs lower area B/D first) (see Figure 1). The order was based on a computer-generated 1:1 randomization. The envelope was opened by the study assistant at week 4 before the first induction of SBs.

Both randomization lists were created by the data manager and the envelopes were prepared by another staff member, neither of whom was involved in any other of the study-related procedures.

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

2.8 | Statistical analysis

Demographic characteristics were described using mean and spread estimates. For the outcomes medians and the 25% to 75% interquartile ranges (IQR) were calculated for the total sample, for each group, and for group differences. Grouped boxplots were used to describe values of SCH, epidermal hydration, and epidermal thickness on intervention and control sites at week 0, 2, 4, 6, and 8. Because of the exploratory design, no statistical hypothesis testing was conducted. Statistical analysis was performed using IBM SPSS Statistics 25.

TABLE 1 Sample characteristics at baseline

Age (y) mean (SD); median (IQR)	**70.3 (2.1); 70.5 (69.0-72.5)**
BMI (kg/m^2) mean (SD); median (IQR)	26.0 (2.2); 26.5 (24.3-28.0)
Skin phototype	
II	3
III	9
Body temperature (°C) mean (SD); median (IQR)	36.3 (0.2); 36.3 (36.2-36.4)
Blood pressure (mmHg) mean (SD); median (IQR)	
Systolic	127 (16); 124 (117-140)
Diastolic	83 (9); 83 (76-92)

Abbreviation: IQR, interquartile ranges.

3 | RESULTS

3.1 | Participant flow

In total, 18 subjects were screened for eligibility and 17 healthy female subjects were included. One forearm of all included subjects was randomly allocated to the intervention and the other forearm served as control arm. It was planned to conduct the study in 12 subjects but until week 6 in five subjects major protocol violations have occurred. All of them applied additional skin care products to one or both of their forearms. Therefore, these subjects were replaced by another five subjects. A detailed description of the participant flow is shown in Figure 2.

3.2 | Recruitment

The recruitment period was from July 2018 to October 2018. The study stopped after the regular study termination of 12 subjects.

3.3 | Baseline data

Demographic characteristics are shown in Table 1.

3.4 | Outcomes and estimation

Table 2 shows the medians and IQRs for time to first vesicles as well as time to full blisters in minutes after

TABLE 2 Medians and IQR of time to first vesicles and time to full blisters in minutes (min)

	Time to first vesicles (min) (IQR)			Time to full blister [min] (IQR)		
	Intervention	Control	Difference	Intervention	Control	Difference
Week 4	43 (29-69)	39 (25-76)	3 (−8 to 10)	63 (53-94)	54 (45-71)[a]	6 (−9 to 15)
Week 8	47 (32-69)[a]	27 (24-60)[a]	7 (−2 to 17)	65 (49-75)[a]	62 (42-73)[a]	6 (−6 to 12)

Abbreviation: IQR, interquartile ranges.
[a]No development of second blister in one subject.

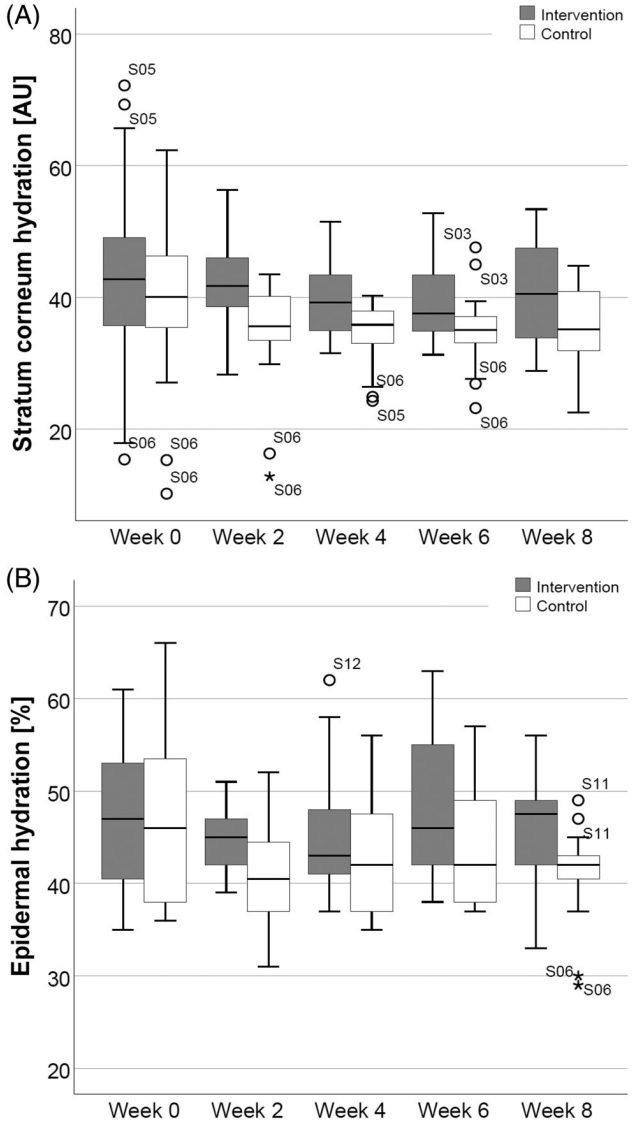

FIGURE 3 Boxplot representation of stratum corneum hydration (SCH) and epidermal hydration. SCH values expressed in arbitrary units (AU), A, and epidermal hydration values expressed as percentage of tissue water (%), B, all measurements performed as duplicates in all subjects on intervention and control arms at week 0, 2, 4, 6, and 8

4 and 8 weeks on interventional and control skin areas. The median time to blistering was 3 to 7 minutes longer on the intervention compared to the control arms. After week 4, the median time to fist vesicles was 3 minutes and after 8 weeks treatment 7 minutes longer on intervention sites. In both, week 4 and 8, the median time to full blister development was 6 minutes longer at intervention sites compared to control sites. At the beginning and during the induction, no drop or other changes in suction pressure were observed during the procedure at any induction sites of all subjects.

The boxplots in Figure 3A display the values of SCH for intervention and control measurements in all subjects at week 0, 2, 4, 6, and 8. At baseline, the median SCH was higher in the intervention compared to the control skin areas. During the course of the study, there seemed to be a decline in SCH in both groups, but the median differences persisted. The boxplots indicate relatively few outliers which are mainly restricted to subject S05 and S06. While subject S05 showed relatively high SCH values at intervention sites, subject S06 had low SCH values at intervention and control sites at the beginning of the study.

In contrast to measured SCH values, baseline epidermal hydration was similar in both arms and a difference developed over time. Measured epidermal hydration values for all time points, subjects, and sites are shown as boxplots in Figure 3B. Table 3 summarises the median SCH and epidermal hydration values as well as median differences between groups over the course of the trial.

Figure 4 represents measured values of epidermal thickness on week 0, 2, 4, 6, and 8 of intervention and control sites of all subjects. Measurement values of epidermal thickness ranged from 44 to 112 µm with median values of 67 to 76 µm across both groups and all time points. Median epidermal thickness values and median differences between groups at week 0, 4 and 8 are shown in Table 4. Measurements on both, intervention and control sites, showed some fluctuation over the course of the study without a group-related tendency. The majority of the few observed outliers were seen in subject S02.

TABLE 3 Medians and IQR of stratum corneum hydration expressed in AU and epidermal hydration expressed as percentage of local tissue water (%)

	Stratum corneum hydration (AU) (IQR)			Epidermal hydration (%) (IQR)		
	Intervention	Control	Difference	Intervention	Control	Difference
Week 0	43 (35-49)	40 (35-47)	4 (−1 to 9)	47 (39-54)	46 (38-54)	0 (−2 to 1)
Week 2	41 (40-46)	36 (34-40)	6 (4-11)	46 (42-48)	41 (37-46)	5 (2-7)
Week 4	39 (36-44)	36 (33-39)	5 (0-8)	43 (42-49)	41 (38-48)	3 (0-4)
Week 6	38 (35-43)	36 (33-37)	4 (1-7)	46 (42-58)	42 (38-50)	4 (2-6)
Week 8	41 (33-48)	35 (32-41)	5 (1-8)	47 (42-50)	42 (40-43)	6 (1-9)

Abbreviations: AU, arbitrary units; IQR, interquartile ranges.

TABLE 4 Median epidermal thickness and IQR expressed in micrometres (μm)

	Epidermal thickness (μm) (IQR)		
	Intervention	Control	Difference
Week 0	78 (65-86)	68 (63-80)	3 (−5 to 11)
Week 4	68 (60-84)	72 (63-79)	4 (−13 to 14)
Week 8	75 (62-79)	71 (65-77)	4 (−9 to 14)

Abbreviation: IQR, interquartile ranges.

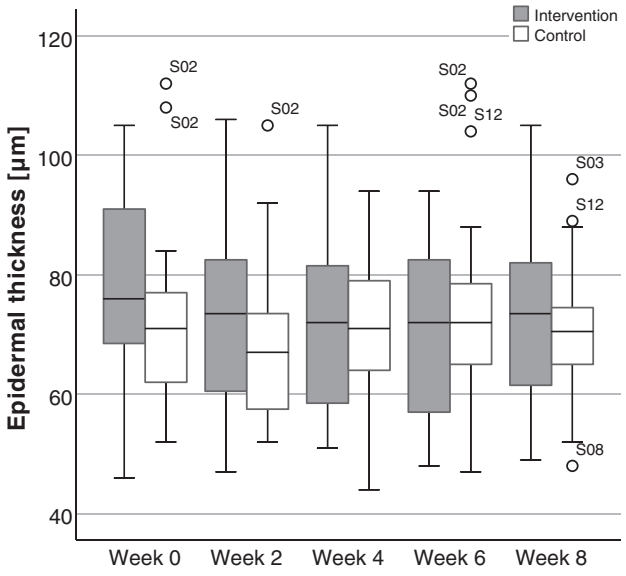

FIGURE 4 Boxplot representation of epidermal thickness. Epidermal thickness values expressed in micrometres (μm). Standardised thickness measurements based on duplicate optical coherence tomography images for all subjects on intervention and control arms at week 0, 2, 4, 6, and 8

3.5 | Harms

No harms or unintended effects were observed during the trial.

4 | DISCUSSION

The overall aim of the present trial was to investigate the effect of the daily application of a basic skin care intervention on the structural strength of the DEJ measured by the novel outcome time to blistering.

Baseline values of SCH were comparable to previous research in aged individuals.[49-54] Despite baseline differences, the forearms assigned to the intervention group consistently had higher SCH values compared to control forearms. There were no baseline differences regarding epidermal hydration but during treatment, it was higher on intervention arms compared to the control arm. Taken together, this supports the hydrating effect of petrolatum.[24-27]

Values of epidermal thickness were also comparable with previously reported results.[47] During the trial, no significant changes in epidermal thickness were seen in the intervention or control arms. Minor variations of epidermal thickness were observed in both groups. According to highly standardised measurements of the epidermal thickness, a range between 49 and 113 μm is reported for arms.[55] Our estimates are similar, ranging from 44 to 112 μm with only slight biological variations between measurement time points. Therefore, we assume that the hydrating effect of petrolatum on the epidermal thickness within the period of the trial was too low to cause a measurable epidermal thickness increase.

Suction blister time for both, the formation of first vesicles as well as the formation of complete blisters, took longer at the intervention than at control sites. The difference ranged from 3 to 7 minutes at all time points and skin areas. This finding suggests that the treatment increased the dermo-epidermal adhesion. The underlying mechanism of this finding is not fully understood so far but is in line with the reduction of skin tear incidence due to topical applications.[21,22] The treatment with petrolatum increased the SCH and epidermal hydration which

may also affect the DEJ. It is well known that in addition to hydrating effects basic topical treatments such as petrolatum change the entire epidermal structure, differentiation, and function.[27,56] Maybe these changes also increase the resistance against mechanical loads such as suction.

In addition, trial results indicate that the suction blister model is a suitable technique to investigate the effect of interventions or exposures on the strength of the dermo-epidermal adhesion. Because suction blister creation is time-consuming and invasive, it is unlikely that it can be widely applied. However, in skin research it is crucial to measure functional capacities and reserves[57,58] in addition to the many widely applied static non-invasive measures. Because this method has only a minimally invasive character and causes no or minimal pain or discomfort and collapsed SBs heal without scarring, we consider this approach as safe and reasonable. Despite existing evidence that this method seems to be a useful and direct approach to quantify the dermo-epidermal adhesion strength, it is surprisingly not used for this purpose in clinical research so far.[10] We see the potential of the parameter "blistering time" together with other well-established parameters for a better and more comprehensive understanding of the skin and its changes in structure/function over the life course. However, we are aware that the establishment of this outcome in clinical research requires a high degree of standardisation of the conduct and analysis to enable interpretation and comparability of different studies. The lack of a standardised guideline could also be a possible reason why this approach is not used in clinical research.

4.1 | Limitations

This exploratory trial had a small sample size and served to provide first empirical evidence about possible effects on the mechanical adhesion strength of the DEJ. Therefore, results should be regarded as descriptive and hypothesis generating. Due to the small sample size, we included only female subjects to reduce the group variance. SCH was measured in AU. This may limit comparisons with other skin hydration measures. Petrolatum was chosen because of its simple composition, safety, and well-known properties. However, compared to specific mixtures of hydrating ingredients the hydrating effect of petrolatum is lower.[59,60] Therefore, the use of other skin care products should be considered in future trials. Risk group-specific factors should be also taken into account, for example, elderly subjects with dry skin because they may benefit in particular from topical skin care products.

4.2 | Conclusions

Topical skin care products reduce the incidence of shear type injuries (skin tears) in aged populations, but the underlying mechanism is unclear. We hypothesise that topical applications of basic skin care products increase the hydration and change the structure and function of the entire epidermis and the DEJ. The parameter "time to blistering" is a suitable outcome to measure the dermo-epidermal adhesion strength in clinical skin research.

CONFLICT OF INTEREST

The authors declare no potential conflict of interest.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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14	WOUND REPAIR AND REGENERATION	5,625	2.952	0.006310
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17	JOURNAL DER DEUTSCHEN DERMATOLOGISCHEN GESELLSCHAFT	2,216	2.743	0.003870
18	LASERS IN SURGERY AND MEDICINE	5,052	2.726	0.003950
19	EXPERIMENTAL DERMATOLOGY	6,104	2.608	0.010760
20	Dermatitis	1,051	2.576	0.001930
21	DERMATOLOGIC SURGERY	7,308	2.471	0.008080
22	International Wound Journal	2,644	2.380	0.004900

CLINICAL TRIAL

BJD
British Journal of Dermatology

The effectiveness of two silicone dressings for sacral and heel pressure ulcer prevention compared with no dressings in high-risk intensive care unit patients: a randomized controlled parallel-group trial*

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Conflicts of interest
U.B.-P. has received honoraria from Cassiopea, Galderma, Johnson & Johnson, LEO and Pierre Fabre Dermocosmetique. J.K. has received honoraria from Mölnlycke Health Care, 3M and Stryker.

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Summary

Background There is a high incidence of pressure ulcers in high-risk settings such as intensive care. There is emerging evidence that the application of dressings to pressure ulcer predilection areas (sacrum and heels) improves prevention strategies.

Objectives To determine whether preventive dressings, applied to the sacrum and heels of high-risk patients in intensive care units, in addition to standard prevention, reduces the incidence of pressure ulcers.

Methods Between June 2015 and July 2018, a randomized, controlled, two-arm, superiority pragmatic study was performed with a concealed 1 : 1 allocation to the intervention and control group. Patients assigned to the intervention group had dressings applied to the sacrum and heels.

Results In total, 7575 patients were screened for eligibility and 475 patients were included and allocated to both groups. Finally, 212 patients in the intervention group and 210 in the control group were analysed. The mean age was 63·5 years and the majority of patients were male (65·4%). The cumulative pressure ulcer incidence category II and above was 2·8% in the intervention, and 10·5% in the control group ($P = 0·001$). Compared with the control group, the relative risk in the intervention group was 0·26 [95% confidence interval (CI) 0·11–0·62] and the absolute risk reduction was 0·08 (95% CI 0·03–0·13).

Conclusions The results indicate that the application of dressings, in addition to standard prevention, in high-risk intensive care unit patients is effective in preventing pressure ulcers at the heels and sacrum.

What's already known about this topic?

- Pressure ulcers are severe soft tissue injuries and wounds, which occur worldwide in all healthcare settings.
- Despite preventive interventions, pressure ulcers still develop.
- There is emerging evidence that dressings help to prevent pressure ulcers.

What does this study add?

- The incidence of pressure ulcers in intensive care units among high-risk patients remains high.
- The application of dressings to the sacrum and heels, in addition to standard preventive measures, reduces the relative and absolute risks for the development of pressure ulcers.
- The application of preventive dressings at the heels and sacrum seems to be feasible in intensive care settings.

Pressure ulcers (PUs) are severe forms of skin and tissue lesions caused by prolonged mechanical deformation of soft tissues between stiff internal structures such as bones or tendons and external support surfaces or medical devices. Adults in supine and semi-Fowler position mainly develop PUs at the heels and at the sacral area.[1] PU prevalence and incidence is high especially in high-risk settings including geriatric, long-term or intensive care.[2–4] PUs severely affect quality of life[5] and in the latest Global Burden of Skin Disease Study, PUs were assigned the highest disability index.[1] PU occurrence in healthcare settings is widely accepted as an unwanted adverse outcome in patient care.[6–8]

State-of-the-art PU prevention includes the identification of PU risk and the application of preventive measures. As mobility and activity limitations are the most important PU risk factors,[9] the cornerstone of PU prevention is repositioning, elevation and offloading of heels, early mobilization and the use of special support surfaces.[2]

There is emerging evidence that the application of dressings to PU predilection areas may help to prevent PUs.[2,10,11] Preventive dressings on intact skin might reduce friction between the skin and the support surfaces and therefore reduce shear forces within the skin and underlying soft tissues.[12,13] To increase hospital patient safety, the Clinical Quality and Risk Management of the Charité – Universitätsmedizin Berlin (Germany) decided to investigate whether these dressings are also effective in high-risk intensive care unit (ICU) patients at its facilities.

The primary objective of this study was to determine whether preventive multilayered soft silicone foam dressings applied to the heels and sacrum, in addition to standard prevention, reduced the cumulative PU incidence category II, III, IV and deep tissue injury (DTI) compared with standard prevention alone in ICU patients who were at high or very high PU risk.

Materials and methods

Trial design

A randomized, controlled, two-arm, superiority pragmatic study was performed with a 1 : 1 allocation to the intervention or control group. The study was approved by the local ethics committee at the Charité – Universitätsmedizin Berlin (approval number: EA1/190/14) and was registered at ClinicalTrials.gov (NCT02295735) on 20 November 2014. No important changes were made after study commencement.

Participants

ICU patients aged 18 years or older, within 6 h of admission to an ICU, at high or very high PU risk with an expected minimum length of stay of at least 3 days were considered eligible. The assessment of high or very high PU risk of the ICU patient was assessed by the research staff in close communication with the ICU staff and according to the classification of the hospital PU prevention standard.[14] According to the hospital standard, the risk assessment was based on mobility and care dependency. Informed consent was obtained from the patients or their legal representatives before or after inclusion as soon as the patients or the legal representatives were able to do so. ICU patients who were at the end of life or with existing PUs at any stage according to the National and European Pressure Ulcer Advisory Panels (NPUAP/EPUAP) 2014 classification system, or trauma at the heels and sacrum, or known allergies to the preventive dressings were excluded. ICU patients who were positioned on air-fluidized beds and patients who could not be repositioned owing to medical reasons (e.g. cardiovascular instability) were not considered eligible, because the patient could not be moved for dressing applications and skin inspections.

Settings and locations

The study was conducted in a tertiary care hospital from June 2015 to July 2018 at the Charité – Universitätsmedizin Berlin, Germany. Patients were recruited from seven ICUs including surgical, cardiovascular, gastroenterology, nephrology, anaesthesiology and neurology ICUs. The mean number of beds per ward was 14 (range 10–24). Study personnel walked rounds twice daily (including weekends and holidays) on all participating ICUs between 07·00 h and 19·00 h enabling a daily recruitment period of 18 h. In the case of a potentially eligible patient, a researcher from the study team checked the

inclusion and exclusion criteria using a screening form. If eligible, the patient was included and randomized.

Interventions

All included patients from ICUs who had high or very high PU risk received PU prevention according to the hospital standard. Besides PU risk scoring, the standard care included instructions for skin inspection within 6 h after admission and, depending on the risk, the following preventive measures: (i) patient information, (ii) daily skin inspection at least twice daily, (iii) mobilization, (iv) use of special support surfaces, (v) repositioning and (vi) heel flotation.[14]

For patients in the intervention group, dressings were applied on both heels (Mepilex® Border Heel, Mölnlycke Health Care, Gothenburg, Sweden) and on the sacral areas (Mepilex® Border Sacrum, Mölnlycke Health Care) according to manufacturer's instructions in addition to the standard care. Care was taken that the dressings were applied correctly and that no other skincare products were used between the skin and the dressings. The dressings were renewed every 3 days and the skin underneath the dressings was checked daily. In cases where dressings became soiled or dislodged, they were changed immediately. Dressings remained on the skin during the whole study period, including transfers to other wards or transfers for diagnostic or therapeutic purposes.

In both groups, included patients were followed up at least once daily by the study team in order to ensure study compliance, correct dressing use and fit, to assess the skin and to document the health condition and PU risk.

The follow-up visits stopped when one of the following occurred: (i) the patient was no longer at 'high' or 'very high' PU risk and no sacral or heel PU developed, (ii) a heel or sacral PU that developed within the study period had completely healed, (iii) an adverse event (AE) related to the preventive dressings occurred, (iv) the patient wished to withdraw, (v) a severe form of protocol violation occurred (e.g. nonwearing of the dressings for more than 24 h), (vi) the patient died or (vii) the patient was transferred to another setting outside the university hospital campus or was discharged.

Kick-off meetings at the participating ICUs, daily follow-up visits by the study team and monthly status reports on recruitment at the participating ICUs were provided to improve adherence to the study protocol. In addition, laminated patient cards were posted at or near beds. These cards included essential study information and contact details of the study team, and served as a reminder.

Outcomes

The primary outcome was the cumulative incidence of PU category II, III, IV, unstageable and DTI at heels or sacrum. PUs were categorized according to the NPUAP/EPUAP 2014 classification system.[2] The occurrence of a new PU of any category was assessed and documented daily during the study period.

Members of the study team, independently from the ward staff, conducted skin and tissue inspections daily and were aware of the group assignment. The study team members were instructed about the study design, procedures, data collection and documentation methods before carrying out the inspections. A 1-h skin inspection and PU classification instruction was provided, followed by an online examination (PuClas3)[15] for all researchers performing skin examinations.

Secondary outcomes were the incidence density (proportions of PUs per 1000 bed days) of PU category II and higher, the cumulative incidence and incidence density of PU category I (nonblanchable erythema) and higher. The total number of days free of PU categories I or II and higher at the heels and sacrum was also measured.

PU risk was measured according to the hospital standard and the Braden scale. The Braden scale is a standardized six-item PU risk assessment instrument with scores ranging from 6 (high PU risk) to 23 (no PU risk). The reliability of this score in the study setting has been previously confirmed.[16]

Other variables assessed at baseline were demographic characteristics (age, sex, smoking status), body mass index (BMI), main medical diagnoses at admission and prior to the ICU stay (coded according to the International Classification of Diseases 10), presence of diabetes mellitus or tetraplegia, the length of stay in the emergency department (ED) or on peripheral wards prior to the ICU stay. Data regarding urine and/or stool incontinence, type of support surfaces and positioning intervals were observed daily by direct observations. The skin phototype of participants was classified according the Fitzpatrick classification ranging from I (white skin, never tans) to VI (dark brown/black skin, tans deeply).[17,18]

In the intervention group, harms were classified into device deficiency (DD), AEs and adverse device effect. A DD was defined as inadequacy of a medical device with respect to its identity, quality, durability, reliability, safety or performance. An AE was defined as any untoward medical occurrence, unintended disease, injury or clinical sign related to the investigational dressings.

Sample size

A study of independent cases and controls with one control per case was planned. Available data from the hospital quality management system indicated that the average PU incidence at the ICUs was 0·06 per month. We expected a cumulative PU incidence for experimental participants to be 0·01 [relative risk (RR) 0·17]. In order to test this hypothesis, 211 experimental patients and 211 control patients were needed to reject the null hypothesis that the PU incidence in the intervention and control groups is equal with a probability (power) of 0·8. The type I error probability associated with this test of the null hypothesis is 0·05 (two-sided). We used the χ^2-test statistic to evaluate this null hypothesis. To prevent a possible loss of follow-up of 10%, we planned to include 464 patients.

An interim analysis was conducted after 50% of the sample ($n = 232$) had completed the study. We planned to stop the

study after the interim analysis, if the conditional power based on the observed data after 50% of recruitment was less than the 60% required to reject the null hypothesis.[19]

Randomization

A simple randomization with a 1 : 1 allocation as per computer-generated randomization table was used. The randomization table was created independently from the study team at the Department of Biometry and Clinical Epidemiology at the Charité – Universitätsmedizin Berlin. Sequentially numbered, opaque, sealed envelopes containing the group assignment were prepared and used. The data manager, who was not involved in any study procedures, prepared the envelopes. On the morning of the daily recruitment, approximately five to eight consecutive envelopes were taken for potential use during the day. After a patient was included and baseline data were collected, the study personnel opened the next numbered envelope and the patient was allocated to the intervention or control group. Based on the randomization logs there was no evidence of selection bias.

Blinding

Owing to the nature of the intervention, caregivers and the study team were not blinded. The data manager was blinded throughout the study.

Statistical methods

Depending on the levels of measurement (nominal, ordinal, continuous) variables were described using absolute and relative frequencies or arithmetic means, medians and spread parameters (minimum, maximum, interquartile ranges and SDs).

The primary outcome PU incidence category II, III, IV, DTI at the heels and/or sacrum was compared using the χ^2-test. This was the main analysis of this primary outcome. An α level of 5% (two-sided) was applied. Kaplan–Meier analysis was used to compare the times to development of a new PU between groups. A generalized linear model (GEE) analysis was conducted to adjust for different baseline covariates regarding the primary outcome. All statistical analyses were based on the intention-to-treat (ITT) principle. The ITT population included all participants who gave informed consent prior to or after randomization. Postrandomization exclusions occurred only for reasons of missing consent.

Secondary outcomes were analysed in a similar way. The χ^2-test or t-tests were applied to compare groups. In cases where the normality assumption was violated, the Mann–Whitney U-test was used rather than t-test. Results of these secondary outcomes were considered exploratory. All statistical analyses were performed using SPSS version 25 (IBM, Armonk, NY, U.S.A.).

Results

Participant flow

In total, 7575 ICU patients were screened for eligibility and 475 ICU patients (6·3%) were included. Overall, 238 patients were allocated to the intervention and 237 patients were assigned to the control group. In total, 23 patients (4·8%) personally declined participation after randomization. Additionally, 17 patients in the intervention group and 13 patients in the control group were excluded after randomization, e.g. because seeking informed consent was not possible owing to death and/or nonavailability of legal representatives. Finally, 422 patients (88·8%) were analysed, these were all patients who provided informed consent. A detailed description of the participant flow is shown in Figure 1.

Recruitment

The recruitment period was from 1 June 2015 to 26 July 2018. The study stopped after the required number of patients had been included.

Baseline data

Demographic and sample characteristics are shown in Table S1 (see Supporting Information). The mean (± SD) age of ICU patients was 63·5 years (± 15·4). The majority of the ICU patients were male (65·4%), the mean BMI was 26·5 kg m^{-2} (± 4·9) and most ICU patients had a Fitzpatrick skin phototype of II (75·1%). In total, 171 ICU patients (40·5%) were affected by diabetes mellitus and 10 patients (2·4%) had tetraplegia. Besides a slight imbalance regarding the proportions of sex, both groups were comparable.

Outcomes and estimation

Data relating to 422 ICU patients were analysed. Patients were followed up for an average of 12·6 days (± 12·7) (Table 1). The longest follow-up period was 130 days. The Mann–Whitney U-test showed that the follow-up periods were statistically significantly different between the intervention and control groups ($P = 0·006$).

Primary outcome

Numbers and proportions of all incident PU cases and categories are shown in Table 2. The cumulative incidence of PUs ranging from category II to DTI was 6·6% (28 of 422). The difference between groups was statistically significant ($P = 0·001$). The RR in the intervention group compared with the control group was 0·26 (95% CI 0·11–0·62). The absolute risk reduction was 0·08 (95% CI 0·03–0·13). Therefore, the number needed to treat was 12·3 (95% CI 29·9–7·8).

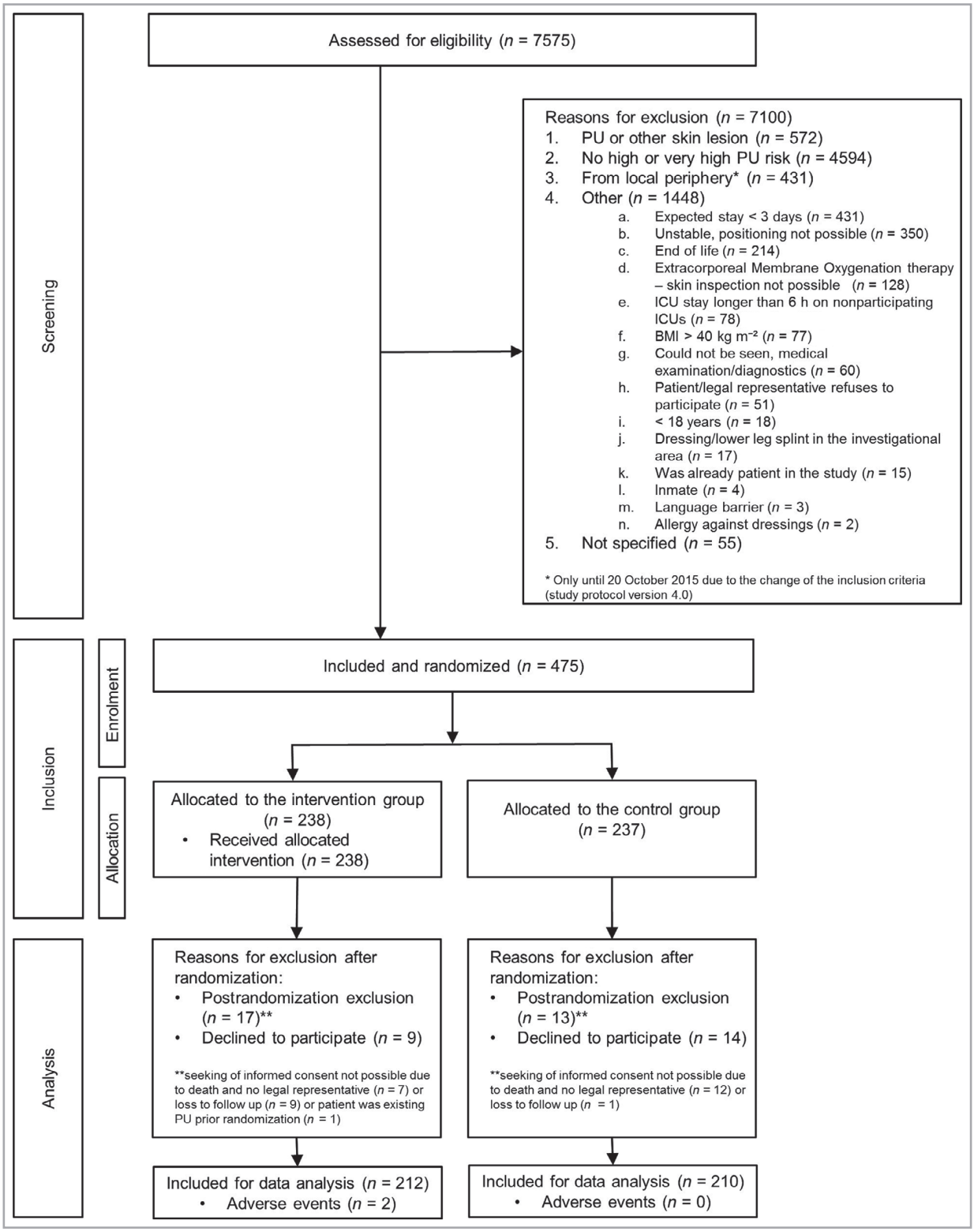

Fig 1. Flowchart outlining the flow of participants throughout the study.
PU, pressure ulcer; ICU, intensive care unit; BMI, body mass index.

Table 1 Follow-up period

	Intervention group (n = 212)	Control group (n = 210)	Total (n = 422)	Mann–Whitney U-test (P-values)
Follow-up period, days				
Mean (SD)	11·0 (10·3)	14·3 (14·6)	12·6 (12·7)	0·006
Median (IQR)	8 (4–14)	10 (6–17)	9 (5–16)	
Min–max, days	1–68	1–130	1–130	

IQR, interquartile range.

Table 2 Pressure ulcer (PU) location and incidence (cumulative)

	Intervention group (n = 212)	Control group (n = 210)	Total (n = 422)	Pearson χ^2-test, P-values
PU incidence, n (%)	6 (2·8)	28 (13·3)	34 (8·1)	< 0·001
PU sacrum, n (%)	6 (2·8)	23 (11·0)	29 (6·9)	–
Category I	0	4	4	–
Category II	4	10	14	–
Category III	0	1	1	–
Category IV	0	0	0	–
Category DTI	2	8	10	–
PU heel right, n (%)	0 (0·0)	2 (1·0)	2 (0·5)	–
Category I	0	1	1	–
Category II	0	1	1	–
Category III	0	0	0	–
Category IV	0	0	0	–
Category DTI	0	0	0	–
PU heel left, n (%)	0 (0·0)	3 (1·4)	3 (0·7)	–
Category I	0	1	1	–
Category II	0	1	1	–
Category III	0	0	0	–
Category IV	0	0	0	–
Category DTI	0	1	1	–
PU categories, n (%)				
PU category I	0 (0·0)	6 (2·9)	6 (1·4)	0·013
PU category II to DTI	6 (2·8)	22 (10·5)	28 (6·6)	0·001
PU category III to DTI	2 (0·9)	10 (4·8)	12 (2·8)	0·006
PU category IV to DTI	2 (0·9)	9 (4·3)	11 (2·6)	0·018
PU category DTI	2 (0·9)	9 (4·3)	11 (2·6)	0·018

DTI, deep tissue injury.

Secondary outcomes

The cumulative PU incidence of PUs ranging from category I to DTI was 8·1% (34 of 422) for the whole sample (Table 2). The most common location was the sacral area and most PUs were category II. The cumulative incidence was 2·8% (six of 212) in the intervention group and 13·3% (28 of 210) in the control group. This difference was statistically significant ($P < 0·001$). No PU classified as category IV was identified in either group.

The PU incidence rates are shown in Table 3. The differences between groups were statistically significant ($P = 0·001$) when category I PUs were included/excluded.

The mean (± SD) time to PU development (category II to DTI) for the whole sample was 12·1 days (± 12·2). In the intervention group, the mean time for PU development was 10·8 days (± 10·1) and 13·5 days (± 13·8) for the control group. The difference between the groups was statistically significant ($P = 0·025$).

The Kaplan–Meier plots for PU categories II to DTI are shown in Figure 2. The mean survival time was 60·7 days [SEM 4·1, 95% confidence interval (CI) 52·7–68·7] in the intervention group and 89·0 days (SEM 9·8, 95% CI 69·7–108·2) in the control group. The difference between the two groups was statistically significant ($P = 0·01$).

Results of the GEE analysis regarding the development of PUs ranging from category II to DTI in both groups are

Table 3 Pressure ulcer (PU) incidence density rate

	Intervention group (n = 212)	Control group (n = 210)	Total (n = 422)	Mann–Whitney U-test, P-values
Incidence density rate per 1000 bed days				
PU category II to DTI	7·8	30·5	19·1	0·001
PU category II to DTI	8·0	37·6	22·8	< 0·001

DTI, deep tissue injury.

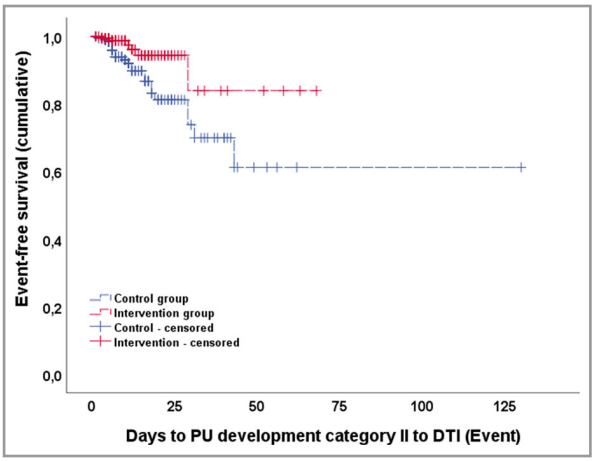

Fig 2. Event-free survival for pressure ulcer (PU) ranging from category II to deep tissue injury (DTI).

shown in Table 4. The model was adjusted for group allocation, follow-up time, age, diabetes mellitus and procedures prior to being transferred to the ICU (staying in the ED, staying in the operating room, staying for diagnostic reasons). ICU patients in the intervention group (β −1·312, odds ratio 0·269; P = 0·006) developed statistically fewer PUs ranging from category II to DTI compared with the control group. All other predictors were not statistically significant.

Harms

In total, two AEs occurred. One patient reported burning pain and warm sensation under the sacral dressing. No signs of inflammation or impaired skin integrity were seen. The dressing application was stopped immediately and the patient wished to withdraw. After the product application was stopped, the burning pain and warm sensation decreased. The outer layers of the skin of another patient peeled under the sacral dressing after application. No signs of inflammation were seen. The product application was not stopped and the patient terminated the study.

Discussion

There were limitations to this study. Performance and detection bias may have occurred because patients, caregivers and study personnel were not blinded to the study procedures and randomized allocation. A selection bias might also have occurred. However, because all eligible patients were screened during the recruitment period and randomized according to the planned order, a selection bias is considered unlikely. We used a simple 1 : 1 randomization as per computer-generated randomization tables. Study groups were similar regarding demographic and other characteristics, and observed imbalances regarding sex were minor. Owing to outliers, the maximum follow-up time was longer in the control group compared with the intervention group, but the medians were similar and an effect on the primary outcome is unlikely. Moreover, the a-priori-defined end-of-study criteria numbers (iii) (an AE related to the preventive dressings occurred) and (v) (protocol violation) were not in line with the ITT principle. However, neither of these criteria were applied in the

Table 4 Generalized linear model for the dependent variable ranging from pressure ulcer (PU) category II to deep tissue injury

			Hypothesis test				
Parameter	β	SEM	Wald χ^2-test	df	P-values	Odds ratio	95% CI
Group (0 = control; 1 = intervention)	−1·312	0·478	7·538	1	**0·006**	0·269	0·105–0·687
Follow-up time	0·022	0·012	3·482	1	0·062	1·022	0·999–1·046
Age	−0·007	0·014	0·287	1	0·592	0·993	0·966–1·020
Diabetes mellitus (0 = no; 1 = yes)	0·668	0·408	2·684	1	0·101	1·951	0·877–4·340
Stay in ED (0 = no; 1 = yes)	−0·823	0·524	2·464	1	0·117	0·439	0·157–1·227
Stay in operating room (0 = no; 1 = yes)	0·226	0·605	0·139	1	0·709	1·253	0·383–4·105
Stay for diagnostic reason (0 = no; 1 = yes)	0·198	0·411	0·232	1	0·603	1·219	0·545–2·729
Braden scale score	−0·025	0·137	0·033	1	0·856	0·975	0·745–1·276
Constant	−2·014	1·499	1·807	1	0·179	0·133	–

CI, confidence interval; ED, emergency department, β, regression coefficient, df, degrees of freedom.

trial. Furthermore, we did not collect information about PUs at body areas other than the heels and sacrum.

A major strength of this study was the pragmatic procedure. Pragmatic studies are able to measure realistic treatment effects in daily clinical routines compared with highly standardized randomized controlled trials (RCTs).[20] Demographic characteristics such as age and sex are comparable to previous studies in this setting.[21–24] The proportions of postrandomization exclusions were within the range of other RCTs in this setting.[13,25,26] The majority of PUs occurred at the sacral area, which is in alignment with other published research results.[23] However, patients in our sample were at higher PU risk compared with other studies.[4,13,23,27]

As ICU care organization and staff characteristics are setting-specific, generalizability to other ICUs in other regions or countries might be limited. However, the local hospital standard PU prevention corresponds to the international state-of-the-art approach[2] and the direction of the shown treatment effect is consistent with results of previous RCTs.[11,28]

Results of this pragmatic RCT indicate that the additional use of preventive dressings at the two most important PU predilection areas substantially reduces the development of new PUs at these areas. The absolute risk reduction of 8% was higher than expected, but might be explained by including only high-risk and very high-risk ICU patients. This effect estimate is based on category II PUs and above, which is a major strength of this study compared with other RCTs in this area.[29] As category I PUs are not wounds, the clinical relevance of this outcome is questionable and the measurement error of this outcome is high.[30] However, when category I PUs were included the absolute risk reduction was 10%, which is similar to the treatment effect of the primary outcome and also similar to the results of a cluster RCT in high-risk residents in aged care.[29] Additionally, the adjusted analysis for key prognostic factors showed that the allocation to the intervention group was the only significant factor, which strengthens our conclusions.

The principle underlying mode of action of the investigated dressings is lower friction between the outer dressing and the support surfaces, thus reducing shear within the skin and underlying soft tissues.[31,32] Other types of dressings are used for PU prevention and study results are mixed.[33,34] Therefore, compared with many other areas in PU prevention research, direct head-to-head comparisons are urgently needed to support clinical decision making.[35]

As the observed treatment effect is consistent with previous study results using the same dressing[13,23,29] and the AEs were minor, we conclude that the use of the investigated dressing in addition to standard care is effective in preventing PUs in high-risk ICU patients. Compared with other established preventive measures, such as the use of special support surfaces, repositioning, floating heels and mobilization,[2] this additional intervention can be easily implemented. Although the treatment effect was substantial, PUs in the intervention group still occurred. This indicates that PU prevention is still not optimal.

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Supporting Information

Additional Supporting Information may be found in the online version of this article at the publisher's website:

Table S1 Demographic and sample characteristics at baseline.

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2	JOURNAL OF THE AMERICAN ACADEMY OF DERMATOLOGY	26,450	6.898	0.035000
3	JOURNAL OF INVESTIGATIVE DERMATOLOGY	28,457	6.448	0.038800
4	BRITISH JOURNAL OF DERMATOLOGY	26,280	6.129	0.034830
5	Pigment Cell & Melanoma Research	4,430	6.115	0.007840
6	Advances in Wound Care	1,543	5.200	0.005240
7	JOURNAL OF THE EUROPEAN ACADEMY OF DERMATOLOGY AND VENEREOLOGY	9,711	4.287	0.019840
8	CONTACT DERMATITIS	5,484	4.275	0.003800
9	JOURNAL OF DERMATOLOGICAL SCIENCE	4,421	3.675	0.007260
10	DERMATOLOGIC CLINICS	1,988	3.214	0.002940
11	MELANOMA RESEARCH	2,356	3.135	0.004620
12	ACTA DERMATO-VENEREOLOGICA	5,818	3.127	0.009260
13	AMERICAN JOURNAL OF CLINICAL DERMATOLOGY	2,160	3.018	0.003200
14	WOUND REPAIR AND REGENERATION	5,625	2.952	0.006310
15	MYCOSES	3,378	2.793	0.004990
16	JOURNAL OF DERMATOLOGY	4,252	2.788	0.007490
17	JOURNAL DER DEUTSCHEN DERMATOLOGISCHEN GESELLSCHAFT	2,216	2.743	0.003870
18	LASERS IN SURGERY AND MEDICINE	5,052	2.726	0.003950
19	EXPERIMENTAL DERMATOLOGY	6,104	2.608	0.010760
20	Dermatitis	1,051	2.576	0.001930
21	DERMATOLOGIC SURGERY	7,308	2.471	0.008080
22	International Wound Journal	2,644	2.380	0.004900

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ORIGINAL ARTICLE

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Cost-effectiveness of multi-layered silicone foam dressings for prevention of sacral and heel pressure ulcers in high-risk intensive care unit patients: An economic analysis of a randomised controlled trial

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Abstract

Pressure ulcer incidence is high in intensive care units. This causes a serious financial burden to healthcare systems. We evaluated the cost-effectiveness of multi-layered silicone foam dressings for prevention of sacral and heel pressure ulcers in addition to standard prevention in high-risk intensive care units patients. A randomised controlled trial to assess the efficacy of multi-layered silicone foam dressings to prevent the development of pressure ulcers on heels and sacrum among 422 intensive care unit patients was conducted. Direct costs for preventive dressings in the intervention group and costs for treatment of incident pressure ulcers in both groups were measured using a bottom-up approach. A cost-effectiveness analysis by calculating the incremental cost-effectiveness ratio using different assumptions was performed. Additional dressing and labour costs of €150.81 (€116.45 heels; €34.36 sacrum) per patient occurred in the intervention group. Treatment costs were €569.49 in the control group and €134.88 in the intervention group. The incremental cost-effectiveness ratio was €1945.30 per PU avoided (€8144.72 on heels; €701.54 sacrum) in the intervention group. We conclude that application of preventive dressings is cost-effective for the sacral area, but only marginal on heels for critically ill patients.

KEYWORDS

cost-effectiveness, costs analysis, pressure ulcer, prevention, preventive dressings

1 | INTRODUCTION

Pressure ulcers (PUs) are defined as areas of localised injuries to the skin and/or underlying tissues, usually over bony prominences, as a result of persistent local pressure or pressure in combination with shear forces.[1] Hospital-acquired pressure ulcers (HAPUs) are associated with serious consequences including medical complications, prolonged hospital stays and death.[2] Especially critical ill patients in intensive care units (ICUs) are at high risk of developing HAPUs. This can be explained by their underlying multiple comorbidities, unstable hemodynamics, immobility and increased use of special medications.[3] Therefore, in this high-risk setting the PU incidence and prevalence are particularly high.[4-6] PUs are considered mostly preventable and are widely used as an indicator of the quality of nursing in hospital care.[7]

Besides their substantial impact on the patient's well-being with regard to physical, social as well as psychological aspects, PUs cause a serious financial burden for all involved parties.[8,9] The costs of prevention and treatment of PUs were recently summarised by Demarré and colleagues. Reported costs of prevention ranged from €2.65 to €87.57 per patient per day and the costs of treatment ranged from €1.71 to €470.49 per patient per day across different care settings.[9] A recent article reported average direct treatment costs of USD 12 for category I PUs to USD 66 834 for category IV PUs in ICU patients.[10] Another recent article suggests that a HAPU could cost USD 10 708 per patient on average.[11] These findings provide clear justification for the value of prevention. Previous research specifically on the economics of preventing PUs has illustrated that a standard prevention protocol is not only cost-effective, but may be cost saving across multiple care settings including intensive care.[12,13] Recent studies have also found that including prophylactic dressings in a prevention protocol provides added value.[14,15]

Regular repositioning, early mobilisation and the use of pressure redistributing support surfaces are cornerstones of PU prevention.[1] There is emerging evidence that the application of preventive dressings to PU predilection sites in addition to standard prevention helps to prevent the development of PUs in ICU patients[16-21] and patients on other wards assessed to be at "high" or "very high risk" for developing PUs.[22] From June 2015 to July 2018, a pragmatic randomised controlled trial (RCT) was conducted at the Charité–Universitätsmedizin Berlin. Results of this trial found an absolute risk reduction of 0.08 (95% confidence interval [CI] 0.03-0.13) and a relative risk reduction of 0.74 (95% CI 0.38-0.89) of category II PUs and higher.[23]

Key Messages

- Pressure ulcer incidence in intensive care units is high und causes a serious financial burden to healthcare systems
- There is little knowledge about the cost-effectiveness of multi-layered silicone foam dressings for pressure ulcer prevention in intensive care unit patients
- A randomised controlled trial among 422 intensive care unit patients was performed to assess the efficacy of multi-layered silicone foam dressings for prevention of pressure ulcers on heels and sacrum
- The application of the dressings to sacrum and heels, in addition to standard preventive measures, reduced the pressure ulcer incidence in these high-risk patients
- Applying preventive dressings on the sacral area in addition to standard pressure ulcer prevention in high-risk intensive care unit patients is clinically effective and cost-effective

The objective of this article is to evaluate the cost-effectiveness of using multi-layered silicone foam dressings for PU prevention based on this RCT. We hypothesized that prophylactic dressings would be cost-effective on both sacrum and heels in intensive care.

2 | MATERIALS AND METHODS

A cost-effectiveness analysis based on the pragmatic RCT[23] was conducted from the hospital perspective. The time horizon of the analysis was based on the average duration of patient admission to an ICU. An incremental cost-effectiveness ratio (ICER) was calculated directly from information in the trial, and expressed in terms of cost per PU avoided; decision modelling was not needed. Analytical uncertainty was quantified through univariate sensitivity analysis.

2.1 | Design

A randomised, controlled, two arms, superiority pragmatic trial was performed with a 1:1 allocation to the intervention or control group. Patients in both groups received the hospital PU prevention standard care including PU risk

assessment, skin inspection within 6 hours after admission and, depending on the respective risk categories, the implementation of preventive measures, including (a) patient information, (b) daily skin inspection, (c) mobilisation, (d) use of special support surfaces, (e) repositioning and (f) floating heels.[24] Patients assigned to the intervention group additionally had a multi-layered silicone foam dressing applied to both heels (Mepilex Border Heel, Mölnlycke Health Care, Sweden) and to the sacrum (Mepilex Border Sacrum, Mölnlycke Health Care, Sweden).

All included patients were followed up at least once daily in the ICU by members of the study team to ensure compliance, doing skin inspections, documenting health conditions and assessing the PU risk and to verify if any new PU had developed. In the intervention group, additional attention was paid to the correct application and fit of the dressings and that no other skin care products were used between the skin and the dressings. The daily skin assessment in the intervention group was performed by partially peeling off the dressings to visualise the underlying skin, afterwards the dressing was reapplied. The dressings were changed regularly every 3 days and additionally in case of becoming soiled or dislodged.

Any newly developed PU on heels or sacral area that had occurred during the study was documented and followed up daily during the remaining study period, including used resources (consumable resources and labour costs) for PU treatment.

2.2 | Study population

To be considered eligible for study participation, potential participants had to be older than 18 years, at high or very high PU risk according to the hospital PU prevention standard[24] and had to have an expected length of stay of at least 3 days. The assessment of high or very high PU risk of the ICU patient was assessed by the study personnel according to the classification of the hospital PU prevention standard.[24] Participants were included in the trial within a maximum of 6 hours after admission to a surgical or internal ICU. Patients at the end of life, with existing PUs or trauma at the heels and sacrum or known allergies to the used dressings were excluded. ICU patients positioned on air-fluidised beds and patients who could not be repositioned due to medical reasons were not included.

2.3 | Outcome measures

The primary outcome was the cumulative incidence of PUs of category II, III, IV, unstageable and deep tissue injury (DTI) at heels or sacrum developed in the ICU in both groups. PUs were categorised according to the NPUAP/EPUAP 2014 classification system.[4]

2.4 | Resources and costs

A bottom-up approach was used to calculate the costs of prevention and treatment of PUs by documenting the actual use of resources during the trial. Resources for the calculation of costs included preventive dressings, nursing time (wound assessment, documentation, wound care, preventive dressing application/change), dressings for wound care in case of newly developed PUs on heels and/or sacrum, consultation by wound managers (WMs) and medical consumables (eg, gloves, cotton gaze). The costs of these resources were considered only for the time of ICU stay and after the transfer to peripheral wards within the hospital. Further treatment costs associated with the PUs after the patients had been discharged from the hospital were not included in the analysis.

Costs for the standard PU prevention care were not listed separately because this was provided in both groups equally, so we assume that the costs for the standard care were similar in both groups.

2.5 | Costs for prevention

Calculated costs of PU prevention in the intervention group were based on the sum of the costs for the applied preventive dressings and labour costs for application or change. Therefore, we counted the actual number of used dressings on heels and sacrum and multiplied the number by the unit price of the dressings. Labour costs were calculated by multiplying the time needed for the application or change of the dressings by the hourly pay rate of the nurses. In Germany, the hourly pay rate for registered nurses (RN) with a collective labour agreement in public services varies according to their years of professional experience. Experience-dependent payment ranges from 1 to 15 years. We used for our analysis the hourly pay rate of a RN with 6 to 9 years of work experience in the federal state of Berlin, Germany. We used the average prices for dressing materials and hourly pay rates for nurses from June 2015 to July 2018.

2.6 | Costs for PU treatment

The cost associated with newly developed PUs on heels and sacrum is the sum of multiplying the resources for PU treatment by their respective unit prices and by

multiplying the needed labour time for wound care, wound assessments and documentation and external WM consultation by the hourly pay rate of RNs or WMs.

2.7 | ICER analysis

We performed a cost-effectiveness analysis by calculating the ICER. ICERs express how much more than an existing treatment a new more effective treatment would cost for additional benefits.[25] In general, a higher value of the ICER indicates a less cost-effective treatment. The ICER was measured in terms of cost spent on inpatient care and prevention materials relative to the PU incidence on a per patient basis using the following formula:

$$\text{ICER} = \frac{\text{Costs intervention group per patient} - \text{Costs control group per patient}}{\text{Pressure ulcer incidence intervention group} - \text{Pressure ulcer incidence control group}}$$

The ICER is expressed in Euros (€) per PU avoided per patient.

2.8 | Sensitivity analysis

To explore the uncertainty of our cost estimates and to identify the impact of key variables on the cost-effectiveness, we performed multiple univariate sensitivity analyses. This was performed by varying the number of used preventive dressings, the price of the dressings, the nursing time needed for dressing application or changes as well as the average costs for intervention. Variables included in the analysis range between ±15% and results were presented in tornado diagrams. In addition, we also varied the effects of the intervention to explore the resulting costs. For this purpose, we varied the incidence of PUs in the intervention group also within a range of ±15%. The described analyses were applied to the entirety of used resources and costs as well as in two separate analyses for sacrum and heel dressings.

3 | RESULTS

3.1 | Baseline data

In total, 422 ICU patients were analysed. Except for a slight difference regarding the distribution of sex, the intervention and control group were comparable with regard to mean age and proportions of patients with high and very high PU risk at baseline.

3.2 | Resources and costs for PU prevention

Applied additional resources and assigned costs are shown in Table 1. In total, 1050 sacral and 2260 heel dressings were used. The total material costs for the used dressings were €28 463.82 (heel dressings: €22 292.52; sacrum dressings: €6171.13). Based on our own estimation and published data[26] we assumed that the time per dressing application or change was 2 minutes when the patient was turned over and held by nurses as part of regular repositioning, skin inspections or other medical examinations. The total labour costs for application or change were €3508.60 (heel dressings: €2395.60; sacrum dressings: €1113.00). Thus, the total additional direct costs of PU prevention in the intervention group were €31 972.42 with an average cost of €150.81 per patient (Table 1).

3.3 | Resources and costs of PU treatment

The resources and direct treatment costs for PUs that had developed within the trial are shown in Table 2. These costs were categorised into material costs (dressings, gloves and further medical consumables) and labour costs (external wound consultations, wound assessment and documentation, wound care).

The total costs for PU treatment in the intervention group (n = 6 PUs) were €134.88 (€106.77 material; €28.11 labour costs) with an average cost of €22.48 per patient. In the control group (n = 22 PUs) the total costs for treatment were €569.49 (€445.96 material; €123.53 labour costs) with an average of €25.89 per patient. The total direct treatment costs in the control group were 4.2 times higher than in the intervention group, and the average treatment costs per PU case were €3.41 higher in the control group.

TABLE 1 Additional resources and direct costs of prevention in the intervention group

	Intervention group (n = 212)		
Unit	**Number**	**Unit price (€)**	**Subtotal (€)**
Sacral dressing 18 × 18[a]	1017	5.81	5912.52
Sacral dressing 23 × 23[a]	33	7.84	258.78
Heel dressing[a]	2260	9.86	22 292.52
Nursing time sacral dressing[b] (2 min per change)	1050	1.06	1113.00
Nursing time heel dressing[b] (2 min per change)	2260	1.06	2395.60
Total	€31 972.42		

[a]Unit price obtained from Mölnlycke Healthcare AB.
[b]Unit price obtained from personnel department of Charité – Universitätsmedizin Berlin. €31.83 were the average employers' costs (2015–2018) per hour for a registered nurse in an intensive care unit with 6 to 9 years of nursing experience.

TABLE 2 The total direct costs of pressure ulcer (PU) treatment in the intervention and control group

	Intervention group (n = 6)			Control group (n = 22)		
	Quantity	**Price per unit (€)**	**Subtotal (€)**	**Quantity**	**Price per unit (€)**	**Subtotal (€)**
External wound consultation[a] (5 min)	—	—	—	5	2.64	13.19
Wound assessment/documentation[b] (2 min)	7	1.06	7.43	23	1.06	24.40
Wound care[b] (3 min)	13	1.59	20.69	54	1.59	85.93
Foam dressings[c]	13	7.00	91.00	46	7.00	322.02
Hydrocolloid dressings[c]	—	—	—	7	6.99	48.96
Absorbent dressings[c]	—	—	—	1	5.85	5.85
Skin protectant[c]	2	2.16	4.32	10	2.16	21.62
Sodium chloride irrigation[c]	13	0.26	3.38	54	0.26	14.04
Gloves[c]	52	0.03	1.56	216	0.03	6.48
Other materials[c]	13	0.50	6.50	54	0.50	27.00
Total direct costs for PU treatment per group	€134.88			€569.49		

[a]Unit price obtained from personnel department of Charité – Universitätsmedizin Berlin. €31.66 were the average employers' costs (2015-2018) per hour for a registered nurse (wound care manager) with 6 to 9 years of nursing experience.
[b]Unit price obtained from personnel department of Charité – Universitätsmedizin Berlin. €31.83 were the average employers' costs (2015-2018) per hour for a registered nurse in an intensive care unit with 6 to 9 years of nursing experience.
[c]Unit price obtained from the hospital purchase department of Charité – Universitätsmedizin Berlin.

Table 3 shows the treatment costs for different PUs per day and per PU case according to their location and category. The daily treatment costs range from €0.33 (heel; category II) to €4.32 (sacrum; category III).

Based on our study documentation we calculated an average length of stay in the hospital after PU development of 12 days. Based on this duration we calculated the costs per PU case.

The primary outcome analysis showed that the cumulative incidence of PU categories II to DTI was 6.6% (28/422). 10.5% (22/210) of the patients in the control group developed a PU of the category II to DTI on heels or sacrum compared with 2.8% of patients (6/212) in the intervention group (P = .001) (Table 4).

3.4 | Base case

In the base case, the ICER for additional preventive dressings compared with hospital PU standard care alone was €1945.30 per PU avoided (Figure 1A). The analysis of

TABLE 3 Treatment costs per day per pressure ulcer (PU) case by category, localisation and group

	Intervention		Control	
	Sacrum (€)	Heel	Sacrum (€)	Heel (€)
Category II				
Cost per day	2.97	—	3.34	0.33
Cost per hospital PU case[a]	35.69	—	40.08	3.95
Category III				
Cost per day	—	—	4.32	—
Cost per hospital PU case[a]	—	—	51.80	—
DTI				
Cost per day	1.06	—	1.44	0.66
Cost per hospital PU case[a]	12.73	—	17.30	7.90
Average treatment cost per PU per day	1.93	—	3.03	0.50
Average treatment cost per PU case[a]	24.21	—	36.39	5.93

Abbreviation: DTI, deep tissue injury.
[a]Costs per hospital PU case are based on the calculated average stay in the hospital of 12 days after the development of a PU in an intensive care unit.

TABLE 4 Numbers of incident pressure ulcers (PUs) in the intervention and control groups by category and localization

	Intervention (n = 6)			Control (n = 28)		
Category	Sacral	Heel right	Heel left	Sacral	Heel right	Heel left
I	—	—	—	4	1	1
II	4	—	—	10	1	1
III	—	—	—	1	—	—
IV	—	—	—	—	—	—
DTI	2	—	—	8	—	1

Abbreviation: DTI, deep tissue injury.

the ICERs for preventive dressings separated by heels and sacrum show a base case ICER of €8144.72 per heel (Figure 1B) and €701.54 per sacrum (Figure 1C) PU avoided.

3.5 | Sensitivity analysis

Results of the sensitivity analyses are shown in tornado diagrams (Figure 1). We identified the dressing costs in general and the number of used heel dressings as the parameters that mostly influenced the ICER. Compared with these findings the variation of nursing time had a noticeably weaker impact on the results. Variation of the incidence in the intervention group by ±15% also showed that the incidence has a higher impact on the ICER than the nursing time and number of used sacrum dressings but has lesser impact than the dressing costs and number of used heel dressings (Figure 1A).

4 | DISCUSSION

Based on the results of a pragmatic RCT this economic analysis indicates that approximately €2000 are needed to prevent one sacral and/or heel PU category II or higher in high-risk ICU patients. Compared with other costs this might be considered as a good value from the patient and health system perspective. From the hospital perspective, this might be considered expensive. However, the ICER was substantially lower for preventing sacral PUs compared with heel PUs. The main reason was that only few heel PUs developed but a high number of sacral PUs in the underlying RCT. The ICER might be completely different in a setting where more heel PUs occur.

Compared with other expensive preventive measures an ICER of approximately €700 for preventing one sacral PU category II or higher can be considered good. Because incident PUs and associated costs were only documented for the length of stay on the ICU and the within hospital stay, the actual treatment costs are higher. Direct and

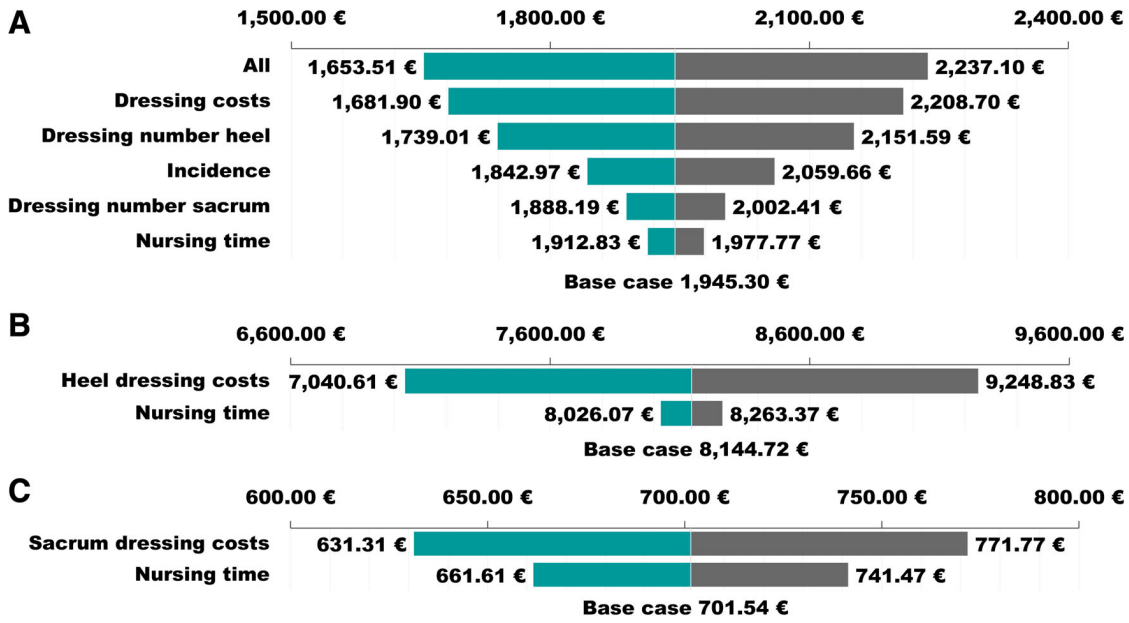

FIGURE 1 Incremental cost-effectiveness ratio (ICER) tornado diagram of multiple univariate sensitivity analysis. The influence of each variable on the ICER is presented from top to bottom. A, ICERs for additional use of heel and sacrum dressings. B, ICERs for additional use of heel dressings only. C, ICERs for additional use of sacrum dressings only

indirect costs including rehabilitation services, wound care in the community or the loss of productivity after hospital discharge were not considered in this analysis. Results further indicate that the main costs were due to the preventive dressings. Therefore, prolonging the wear times might be one strategy to improve the cost-effectiveness from the hospital perspective.

There is clear evidence that the additional application of preventive dressings to the sacral area and heels of ICU patients reduces the development of new PUs at these areas.[17,19,23,27] There is a lack of economic evaluations to assess the cost-effectiveness of these dressings in comparison to standard care alone. A cost-benefit analysis of an RCT with a similar setting showed that the use of preventive dressings results in cost savings in the acute care hospital.[26]

To the best of our knowledge, there is no economic analysis that investigates the cost-effectiveness of preventive dressings for prevention of sacral and heel PUs in addition to standard prevention in high-risk ICU patients by calculating ICERs.

It is also important to keep in mind that single interventions such as the use of preventive dressings is only one part in the complex process of PU prevention. Other important aspects are PU risk determination and early PU detection to allocate preventive interventions.[1] Improved risk assessment strategies combined with targeted preventive intervention might further increase cost-effectiveness but currently the link between risk assessment, intervention planning and conduct in clinical practice is weak.[28-30]

5 | LIMITATIONS

The follow-up visits stopped when patients were discharged from the hospital. For that reason, we could not measure the duration until complete healing. The majority of incident PUs within this study did not heal during the hospital stay. Therefore, additional costs following the patients' discharge from hospital were not taken into account but would significantly increase the total costs of PU treatment thus reducing the ICER. Furthermore, the study population consisted mostly of critically ill patients or patients with major trauma, therefore some of these patients died soon after the development of a PU owing to their underlying illness. These circumstances make it difficult to calculate the time until the healing of a PU. For these reasons, we focused only on the costs during the hospital stay and not until PU healing.

Even though we meticulously collected data for PU treatment, it is likely that we missed resources and/or underestimated costs. However, results of the sensitivity analyses indicate that the variation of our estimates is minor. This economic analysis is based on a pragmatic RCT that might be considered as an optimal approach for an economic analysis. We could also show that the included sample was representative for a high-risk ICU

population.[23] However, the observed effect sizes and consequently the ICERs might not be comparable to other ICUs.

In this study, we used a bottom-up trial-based approach to calculate resources and costs. Other health economic evaluation approaches are model-based (eg, Markov-models) or hybrids between trials-based and modelling techniques.[31] Every approach has advantages and disadvantages.[32]

6 | CONCLUSION

Applying preventive dressings on the sacral area in addition to standard PU prevention in high-risk ICU patients is clinically effective and cost-effective. Due to the low incidence of heel PUs, the application of preventive dressings on the heels was much more expensive and less cost-effective. Preventive dressings do not replace established measures but rather represent an effective addition for PU prevention. In terms of economic efficiency, only high-risk patients should receive additional preventive dressings.

This cost-effectiveness analysis was conducted from the hospital perspective. Nevertheless, the totality of all the affected parties should be considered, whether in financial or social terms. Therefore, further research is needed to determine the far-reaching consequences of PUs for the patient as well as the community.

Future PU prevention studies should combine different complementary preventive approaches to assess the effectiveness and costs of the total complex care process.

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CONFLICT OF INTEREST

W. V. P. is a principal consultant for Monument Analytics,and on the scientific advisory board of Mölnlycke Health Care AB. J. K. received consultancy fees from Mölnlycke Health Care AB. All other authors declare no conflicts of interest.

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ETHICS STATEMENT

The underlying trial was approved by the local ethics committee at the Charité – Universitätsmedizin Berlin (approval number: EA1/190/14) and was registered at clinicaltrials.gov (NCT02295735) on the 20th of November in 2014. No important changes were made after trial commencement.

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Mein Lebenslauf wird aus datenschutzrechtlichen Gründen in der elektronischen Version meiner Arbeit nicht veröffentlicht.

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