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Review Article

Effectiveness of Different Topical Treatments in the Healing of Pressure Injuries: A Network Meta-analysis

Luis Furuya-Kanamori MEd, PhD^a, Rachel M. Walker PhD, RN^{b,c,*},
 Brigid M. Gillespie PhD, RN, FACORN^{b,d}, Justin Clark BA^e,
 Suhail A.R. Doi PhD, FRCP(Edin)^a, Lukman Thalib MSc, PhD^f

^a Department of Population Medicine, College of Medicine, Qatar University, Doha, Qatar

^b School of Nursing and Midwifery, Griffith University, Gold Coast, Australia

^c Division of Surgery, Princess Alexandra Hospital, Metro South Health, Brisbane, Australia

^d Gold Coast University Hospital, Gold Coast Health, Gold Coast, Australia

^e Centre for Research in Evidence Based Practice, Bond University, Gold Coast, Australia

^f Department of Public Health, College of Health Sciences, Qatar University, Doha, Qatar

A B S T R A C T

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Objectives: Pressure injuries (PIs) are one of the most common types of complex wounds and impose a huge economic burden on the healthcare system and the patients. A plethora of topical treatments is widely available for PI treatment, yet there is a paucity of evidence with regard to the most effective treatment. The objective of this study was to compare the effect of various topical treatments and identify the best treatment choice(s) for PI healing.

Design: Systematic review and network meta-analysis.

Setting and participants: All published randomized controlled trials that compared the effectiveness of 2 or more of the following dressing groups: basic, foam, active, hydroactive, and other wound dressings.

Measures: The outcome was the relative risk (RR) of complete healing following treatment and the generalized pairwise modeling framework was used to generate mixed treatment effects against hydroactive wound dressing, currently the standard of treatment for PIs. All treatments were then ranked by their point estimates.

Results: 40 studies (1757 participants) comparing 5 dressing groups were included in the analysis. All dressings groups ranked better than basic (ie, saline gauze or similar inert dressing). The foam [RR 1.18; 95% confidence interval (CI) 0.95–1.48] and active wound dressing (RR 1.16; 95% CI 0.92–1.47) ranked better than hydroactive wound dressing in terms of healing of PIs when the latter was used as the reference group.

Conclusions/Implications: There was substantial uncertainty around the point estimates; however, evidence from our analysis supports the use of hydroactive wound dressings to replace basic dressings. Foam and active wound dressing groups seem promising and therefore need further investigation. High-quality, rigorously conducted research about the clinical effectiveness of the topical treatments in these 2 groups developed in consultation with health professionals, patients, and their carers is needed to identify if indeed foam and active wound dressings provide advantages over hydroactive dressings.

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L. Furuya-Kanamori and R. M. Walker are joint first authors.

S. A. R. Doi and L. Thalib are joint senior authors.

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* Address correspondence to Rachel M. Walker, PhD, RN, Nursing Practice Development Unit, Building 15, Level 2, Princess Alexandra Hospital (PAH), Ipswich Road, Woolloongabba QLD 4102, Australia.

E-mail address: r.walker@griffith.edu.au (R.M. Walker).

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Pressure injuries (PIs),¹ also known as pressure ulcers or bed-sores, are wounds involving the skin and sometimes the tissue on bony parts of the body, often occurring over bony prominences such as the sacrum and heel.² They are caused by a combination of pressure, shear, and friction that leads to microcirculatory occlusion, resulting in stimulation of inflammatory processes.² This in turn can lead to cell death, ulceration, and tissue necrosis.³ PIs can have a significant impact on those affected, as they can cause pain and infection that can increase patient's hospital length of stay and significantly decrease

their health-related quality of life.⁴ People at high risk of developing PIs include those with limited mobility such as older people, people with short- or long-term medical conditions, and those with spinal injuries.⁵ Lack of mobility, reduced sensory perception, poor nutrition, and hydration as well as lack of blood flow can all increase the risk of developing PIs.⁵ Development of PI can be rapid and lead to irreversible tissue damage in vulnerable patients after as little as 30 minutes of uninterrupted pressure.⁶

Globally, PIs are one of the most common types of complex wounds. An estimated 2.5 million people are affected annually in the US alone.⁷ A large European pilot study estimated the hospital PI point prevalence to be 10.5%.⁸ National PI data collected in the UK's National Health Service (NHS) reported a prevalence of 4.2% across community and acute care settings in September 2017,⁹ although the study could have underestimated the actual prevalence of PIs in the United Kingdom because of the low sensitivity of the tool used to identify the cases.^{10,11} Prevalence of PIs can vary according to setting and can be as high as 26% in some settings such as long-term, acute-care, and rehabilitation settings.¹²

Managing PIs can be expensive. Annual health care costs associated with PIs in the United Kingdom in 2012–2013 were estimated to be in the range GBP 4.5 to 5.1 billion.¹³ In the USA in 2014 alone, treatment for PIs were estimated at USD 9.1 to 11.6 billion annually with 2.5 million people affected and approximately 60,000 deaths resulting from PIs.¹⁴ The total costs to the Australian health care system for treating PIs have been estimated at AUD 1.8 billion annually or 9% of public hospital expenditure.¹⁵ Although dated, these cost estimates provide an insight about the substantial financial burden PIs represent within contemporary health contexts.

In terms of the treatment of PIs, there are 2 major strategies that are currently being employed: (1) the use of pressure-relieving support surfaces (eg, alternating pressure air mattresses) and (2) management of ulcers using topical treatments such as wound dressings.^{16,17} Other general strategies for treating and healing PIs include optimizing circulation/perfusion, improving nutrition and the treatment of clinical infection.^{2,16} Topical treatments are widely used to treat PIs, there are a plethora of options to choose from including alginate, hydrocolloid, protease-modulating dressings, topical agents, and other therapies. Despite this, there is paucity of evidence to facilitate decision making regarding the type of topical treatments that are the most clinically effective. This is despite many published meta-analyses examining effects of dressings, negative-pressure wound therapy, and topical agents on healing of PIs in mainly adult populations in care settings.^{18–22}

A key issue has been the statistical methods used in previous reviews of topical treatments such as hydrogel,¹⁹ alginate,¹⁸ and foam²² as well as other therapies such as negative-pressure wound therapy²⁰ which only allowed pairwise comparisons. Results from these reviews consistently reported low to very low certainty of evidence from included studies because of high risk of bias (lack of allocation concealment and blind assessment) and imprecision (small studies and incomplete reporting). More significantly, they were unable to provide clear advice on effectiveness of the topical treatment in healing PIs. While we were undertaking this project, an attempt to address this limitation via a network meta-analysis was published.²¹ However, the authors of the study were still unable to determine which topical treatments were the most likely to heal PIs because sparseness of their network led to inconclusive results.²³ Our approach differs from the latter in several ways, including in the classification of topical treatments, extent of coverage of studies, and methodology used, which brings much more clarity to this issue and does away with the issue of sparseness.

Methods

Findings of this systematic review and meta-analysis are presented according to PRISMA reporting guidelines.²⁴

Search Strategy

The original search strategy was designed in PubMed and converted for use in the following databases using the Systematic Reviews Accelerators Polyglot Search Translation module,²⁵ with no limitations on year or language: CINAHL, Embase, Web of Science, Scopus, and the Cochrane Central Register of Controlled Trials (CENTRAL). The initial search was conducted on September 15, 2016, and updated on December 1, 2017. Search terms related to pressure injuries, pressure ulcers, topical treatment types, and outcome measurements (ie, healing) were included. The full search strategy is shown in [Supplementary Material S1](#). In order to achieve a comprehensive evaluation of the published evidence, the systematic search was supplemented with a forward and backward citation search as well as retrieving the first 20 similar articles from PubMed for each of the papers included from the searches. We sought additional papers from the reference lists of relevant meta-analyses and review papers.^{16,19–21,26,27}

Titles and abstracts of all papers that were extracted by the search engine were uploaded to the Rayyan platform (<http://rayyan.qcri.org/>) which is a web application developed by [Qatar Computing Research Institute \(Data Analytics\)](#).²⁸ Five authors (LFK, RW, BG, SD, and LT) independently screened the titles and abstracts on the Rayyan platform. Any disagreements were resolved through author consensus. Additionally, LFK and RW examined the full-text papers for eligibility against the review protocol. Disagreements were resolved through consensus and by involvement of a third author (BG).

Selection Criteria

Eligible studies were published and unpublished randomized controlled trials (RCTs) that enrolled patients with stage 2 to 4 PIs and compared the effectiveness of 2 or more of the following 13 narrow topical treatment categories: antimicrobial, basic (ie, gauze with normal saline), collagenase, collagen, combined treatment (ie, when multiple active components were included), film, foam (ie, Lyofoam, polyurethane), growth factors, hydrocolloid, hydrogel, moisture retentive (ie, calcium alginate), negative pressure, and radiant heat. These dressings were selected because they were either (1) identified in the literature as wound care products used for the treatment of PIs; (2) available to clinicians for use in routine practice; (3) recommended by international clinical guidelines²; or (4) under investigation as an experimental or alternative dressing for the treatment of PIs. Dressings were grouped according to their dominant element. The network using these 13 narrowly defined topical treatment categories initially selected was noted to be sparse. The key issue with this is that networks that are not well connected may provide unreliable estimates and rank treatment options incorrectly and/or may lead to inconsistent ranking of the dressing when the reference category changes.

For these reasons, a parallel analysis using a broader classification based on mechanisms of action provided by Horn²⁹ was conducted. This classification defined 5 dressing groups as follows: basic wound dressing (ie, inert materials like saline gauze), hydroactive wound dressing (ie, hydrocolloid, hydrogel, moisture-retentive dressings), foam dressing, active wound dressing (ie, collagen, growth factors), and other wound dressing (ie, antimicrobial, collagenase, film, negative pressure, radiant heat) to achieve a network that was not sparse. These 2 classifications are given in [Table 1](#).

Table 1
Classification of the Dressings

Topical Treatment Categories		Wound Dressing Groups	Description
BAS	Basic (eg, saline gauze, placebo)	BWD	Inactive dressings can pick up secretions from the wound, but do not create a specific microenvironment that promotes wound healing.
HCD	Hydrocolloid (eg, DuoDerm, Comfeel Plus, Tegaderm)	HWD	Hydroactive wound dressings accelerate wound healing by altering the microclimate of the wound and imitating the physiological process to form a moist wound environment.
HGD	Hydrogel (eg, Askina Transorbent, BioFilm hydrogel, Acemannan hydrogel)		
MRD	Moisture retentive (eg, UrgoSorb, Aquacel)	FOA	Foam dressings absorb wound exudate, insulate the wound and provide a moist wound healing environment.
FOA	Foam (eg, Epi-Lock dressing, Allevyn hydrocellular foam, Spyrosorb)		
COL	Collagen (eg, Promogran, Medifil Collagen Particles)	AWD	Active dressings have a defined mechanism of action through which they intervene in the pathophysiological processes in the wound by substitution and suppression or alteration of factors.
GRF	Growth factor (eg, Dermagraft, Transforming growth factor beta-3, Recombinant platelet-derived growth factor-BB)		
AMD	Antimicrobial (eg, Cadexomer iodine, povidine soaked wet gauze, Dakin solution)	OWD	Wound dressings with other mechanisms of action
CLD	Collagenase (eg, Iruxol mono ointment)		
FIL	Film (eg, 3M Tegaderm Absorbent Clear Acrylic Dressing)		
NPD	Negative pressure (eg, V.A.C. therapy system)		
RHD	Radiant heat (eg, Augustine Medical warm-up)		
COM	Combined—multiple active components		
		Classified in a dressing group depending on the type of combination of the active ingredients.	

Topical treatment categories: AMD, antimicrobial; BAS, basic; CLD, collagenase; COL, collagen; COM, combined treatment; FIL, film; FOA, foam; GRF, growth factor; HCD, hydrocolloid; HGD, hydrogel; MRD, moisture retentive; NPD, negative pressure; RHD, radiant heat. Wound dressing groups: AWD, active; BWD, basic; FOA, foam; HWD, hydroactive; OWD, other wound dressing.

Studies were also excluded if they assessed effectiveness more than 1 year post-treatment or included other types of wounds (eg, chronic wound and venous leg ulcers). Because we used a pairwise modeling approach (described below), if studies compared an odd number of eligible treatments, we selected a pair (or multiple pairs) of treatments for inclusion in meta-analysis. In such cases, we prioritized the inclusion of treatments with the lowest dose and that are currently in widespread use for PI healing over novel treatments.

Data Extraction

Data extraction was performed by L.F.K. and R.W. We extracted the year and country of study; study population topical treatment names, types, and schedules; sample size; number of people “healed” and “not healed” after treatment; and follow-up time. If a study compared the same intervention in both arms, it was assumed that the effect of such an intervention canceled itself from both arms (eg, a RCT compared hydrocolloid + hydrogel against hydrocolloid + collagen, it was considered as hydrogel compared to collagen), and dressings were classified according to the remaining active ingredients.

Quality Assessment

Quality of included studies was assessed using the Cochrane Collaboration's tool for assessing risk of bias in randomized trials.³⁰ This scale assessed studies for risk of bias using items related to random sequence generation, allocation concealment, selective reporting, blinding, incomplete data, and attrition rate (Supplementary Material S2).

Statistical Analysis

We aimed to examine healing rate; that is the proportion of treated individuals whose PIs healed completely based on the cure criteria, where reported in each study. The outcome calculated for each study was the relative risk (RR) of cure following topical treatment. We used an automated generalized pairwise modeling (GPM) framework³¹ to generate mixed treatment effects against basic dressings, currently

the simplest standard treatment. This framework requires no additional assumptions other than that of transitivity, and uses an automated process to extend the previously reported Bucher method³² for single 3-treatment loops. The method involves: (1) pooling effect sizes for direct comparisons between each combination of 2 treatments using meta-analysis; (2) performing indirect comparisons by automated generation of all possible closed loops of 3 treatments such that one is common to 2 studies; and (3) pooling all direct and indirect effects using meta-analysis to give a final effect size comparing each treatment to the common comparator. To pool estimates, we used the inverse variance heterogeneity model, which uses a quasi-likelihood based variance structure without distributional assumptions and has been shown to perform better when compared to the random effects method.³³ For comparison, all analyses were re-run using the random effects model within a multivariate frequentist framework.³⁴

We assessed statistical heterogeneity across pooled direct effects using Cochran's Q and the H index. The H index is the square root of H^2 , the estimated residual variance from the regression of the standardized treatment effect estimates against the inverse standard error in each direct meta-analysis. H was computed as follows:

$$H = \sqrt{\frac{\max[\max(1, n-1), Q]}{\max(1, n-1)}}$$

where n is the number of study estimates and Q represents the chi-squared from Cochran's Q .

Transitivity across the network was assessed by examining inconsistency across the network using the weighted pooled H index ($\bar{H}$), which was computed from Cochran's Q as follows:

$$\bar{H} = \sqrt{\frac{\sum_{j=1}^k \max[\max(1, n-1), Q]}{(\sum_{j=1}^k n) - k + s}}$$

where n is the number of estimates pooled across each comparison and s is the number comparisons (out of k) where $n = 1$. The minimum value H or $\bar{H}$ can take is 1. $\bar{H} < 3$ was taken to be minimal inconsistency based on our simulations in homogenous direct meta-analyses.

Fig. 1. PRISMA flow diagram of study selection for quantitative synthesis.

Sensitivity analyses were performed based on restricting the network to studies that examined efficacy within 6 to 12 weeks and to assess the impact of the risk of bias on the results (using a quality effects model³⁵).

Publication bias was assessed using “comparison-adjusted” funnel plots, that plots the difference of each study’s observed $\ln(RR)$ versus the comparison’s mean $\ln(RR)$ obtained from meta-analysis on the horizontal axis. In the absence of small-study effects, studies are expected to form an inverted funnel centered at zero.³⁶

All analyses involved in the generalized pairwise modeling (GPM) framework were conducted using MetaXL version 5.3 (EpiGear; Brisbane, Australia) developed by one of us (S.D.). Funnel and network plots were created in Stata, version 14.1 (College Station, TX).

Role of Funding Sources

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Results

Identified Studies

Database searches, forward and backward citation search, and retrieving the first 20 similar articles from PubMed identified 2496 studies that were initially screened by title and abstract, from which 172 potentially relevant papers were selected. Of these, 44 met the inclusion criteria for the systematic review and were included in the network meta-analysis (Figure 1).

Characteristics of Included Studies

The 44 included studies were published between 1983 and 2015. Studies were conducted in Asia (2 countries [Korea and Iran], 2 studies), North America (1 country [USA]; 21 studies), and Europe (10 countries [Denmark, Finland, France, Germany, Italy, Netherlands, Poland, Spain, Sweden, and UK]; 21 studies).

Twenty studies had a comparison to basic dressing, and 31 studies to a hydroactive dressing; representing the 2 most common topical treatments. The remaining studies had a variety of topical treatment

types. Complete healing was assessed at a median follow-up of 8 weeks (IQR 6.5–13 weeks) with a range of 1.5–52 weeks (Table 2).

Included Topical Treatments

A total of 13 topical treatment categories and 5 dressing wound groups were included in the network meta-analyses. Topical treatments within the same category were deemed exchangeable (Table 2). Figure 2 depicts the network plot showing the comparison groups for each study.

Quantitative Synthesis

Based on 44 studies examining treatment of PIs, when basic dressing was used as the reference treatment category, all topical treatment categories were found to have a better rank than basic dressing being negative pressure, film, and combined treatment the ones with the biggest effect size. Combined treatment (RR 1.88; 95% CI 1.08–3.25) was found to be the only dressing category to have statistically significant improvement in healing when compared to basic dressings (Figure 3A). When hydrocolloid was used as the reference category in the analysis, the ranking of the dressing categories dramatically changed (Figure 3B). It is clear from the results that the network with 13 dressing categories was sparse, the point estimates were not reliable, and the ranking of the treatments was not stable. This analysis was not informative, and therefore we proceeded with the next analysis.

When the analysis was carried out using the 5 wound dressing groups as defined by Horn,²⁹ 40 studies were included; 4 studies^{44,45,49,60} were excluded because they compared wound dressings within the same group. The basic wound dressings was used as the reference group, all dressings groups were better in rank than basic dressings. In ascending order of efficacy based on the point estimate, the ranking was other, hydroactive, active, and foam dressings and only the latter being statistically significantly better (Figure 4A). The ranking of dressing groups remained unchanged when the hydroactive dressings was used as the reference (Figure 4B and Supplementary Material S3), revealing a stable (nonsparse) network with reliable results.

Analysis using a conventional approach (ie, multivariate frequentist framework) did not alter the ranking nor the pooled

Table 2
Characteristics of the Included Studies

First Author and Year of Publication	Study Location	Follow-up Duration	Topical Treatments	Topical Treatment Category	Wound Dressing Group	Number of Participants (Healed/Treated)	Criteria for Complete Healing
Alm (1989) ³⁷	Sweden	6 wk	Hydrocolloid	HCD	HWD	17/31	Area of the PI equal to zero
			Saline gauze	BAS	BWD	4/25	
Anguilo-Sanchez (2001) ³⁸	Spain	7 wk	Alginate and hydrocolloid	COM	HWD	20/35	Not reported
			Saline gauze	BAS	BWD	10/35	
Ashby (2012) ³⁹	UK	26 wk	Hydrocolloid, alginate	COM	HWD	0/6	Epithelialization and cessation of treatment to achieve healing
			Negative-pressure dressing	NPD	OWD	1/6	
Bale (1997) ⁴⁰	UK	4 wk	Polyurethane foams	FOA	FOA	7/29	Not reported
			Hydrocolloid	HCD	HWD	5/31	
Banks (1994a) ⁴¹	UK	6 wk	Semipermeable polyurethane dressing	FOA	FOA	11/13	Not reported
			Hydrocolloid	HCD	HWD	10/16	
Banks (1994b) ⁴²	UK	12 wk	Polyurethane dressing	FOA	FOA	12/20	Not reported
			Hydrocolloid	HCD	HWD	10/20	
Belmin (2002) ^{43,*}	France	8 wk	Hydrocolloid	BAS	BWD	31/53	Surface area reduction $\geq 40\%$
			Calcium alginate and hydrocolloid	MRD	HWD	43/57	
Brod (1990) ^{44,†}	USA	8 wk	Poly(HEMA) dissolved in polyethylene glycol	HGD	HWD	14/27	Not reported
			Hydrocolloid	HCD	HWD	10/16	
Brown-Etris (1996) ^{45,†}	USA	10 wk	Hydrogel	HGD	HWD	39/77	Not reported
			Hydrocolloid	HCD	HWD	37/77	
Brown-Etris (2008) ⁴⁶	USA	8 wk	Hydrocolloid	HCD	HWD	22/37	Closed PI wounds
			Transparent absorbent acrylic	FIL	OWD	21/35	
Burgos (2000) ⁴⁷	Spain	12 wk	Hydrocolloid	HCD	HWD	3/19	PI with final surface area of zero
			Collagenase ointment	CLD	OWD	3/18	
Colwell (1993) ⁴⁸	USA	12 wk	Hydrocolloid wafer dressing	HCD	HWD	11/33	PI completely covered with epithelial tissue
			Saline gauze	BAS	BWD	1/37	
Darkovich (1990) ^{49,†}	USA	8.5 wk	Hydrocolloid	HCD	HWD	9/36	PI wound closure
			Biofilm hydrogel	HGD	HWD	12/35	
Ford (2002) ⁵⁰	USA	6 wk	Vacuum-assisted closure	NPD	OWD	2/20	Not reported
			Healthpoint system	COM	HWD	2/15	
Gorse (1987) ⁵¹	USA	11 wk	Hydrocolloid	HCD	HWD	54/76	Not reported
			Wet-to-dry dressing with Dakin solution	AMD	OWD	26/52	
Graumlich (2003) ⁵²	USA	8 wk	Hydrocolloid	HCD	HWD	15/30	Not reported
			Collagen	COL	AWD	18/35	
Hirshberg (2001) ^{53,‡}	USA	16 wk	TGF- $\beta 3$ 1 $\mu\text{g}/\text{cm}^2$	GRF	AWD	0/4	Not reported
			TGF- $\beta 3$ 2.5 $\mu\text{g}/\text{cm}^2$ (excluded arm)	—	—	—	
			Placebo gel	BAS	BWD	0/5	
Hollisaz (2004) ^{54,§}	Iran	8 wk	Hydrocolloid	HCD	HWD	12/18	Intact dermis and epidermis, no abrasion or ulceration
			Saline gauze	BAS	BWD	3/19	
			Phenytoin cream (excluded arm)	—	—	—	
Kim (1996) ⁵⁵	Korea	7.6 wk	Hydrocolloid	HCD	HWD	21/26	When no further dressing was required
			Wet-to-dry dressing with povidone iodine	AMD	OWD	14/18	
Kraft (1993) ⁵⁶	USA	24 wk	Saline gauze	BAS	BWS	3/14	Not reported
			Epi-Lock dressing	FOA	HWS	10/24	
Kuflik (2001) ^{57,}	USA	6 wk	ResurfixR	COM	AWD	2/5	Not reported
			Petrolatum jelly	BAS	BWD	0/3	
Landi (2003) ⁵⁸	Italy	6 wk	Topical nerve growth factor	GRF	AWD	8/18	Not reported
			Balanced salt solution	BAS	BWD	1/18	
Matzen (1999) ⁵⁹	Denmark	12 wk	Saline gauze	BAS	BWD	0/15	Not reported
			Hydrocolloid	HCD	HWD	5/17	
Moberg (1983) ^{60,†}	Sweden	8 wk	Saline, enzyme debriding, or nonadhesive dressing	COM	OWD	1/18	Not reported
			Cadexomer iodine	AMD	OWD	6/16	
Muller (2001) ⁶¹	Netherlands	14 wk	Collagenase ointment	CLD	OWD	11/12	Total epithelialization of PIs
			Hydrocolloid	HCD	HWD	7/11	
Mustoe (1994) ^{62,¶}	USA	26 wk	rPDGF-BB 100 $\mu\text{g}/\text{mL}$	GRF	AWD	2/15	Area of opening being equal to zero
			rPDGF-BB 300 $\mu\text{g}/\text{mL}$ (excluded arm)	-	-	-	
			Placebo—Growth factor excluded	BAS	BWD	1/14	
Neill (1989) ⁶³	USA	8 wk	Hydrocolloid	HCD	HWD	13/42	Not reported
			Saline gauze	BAS	BWD	10/45	
Nisi (2005) ⁶⁴	Italy	26 wk	Povidone iodine plus paraffin	AMD	OWD	28/40	Not reported
			Protease modulating matrix	COL	AWD	36/40	
Oleske (1986) ⁶⁵	USA	1.5 wk	Polyurethane self-adhesive foam dressing	FOA	HWD	0/5	Not reported
			Saline gauze	BAS	BWD	0/5	

(continued on next page)

Table 2 (continued)

First Author and Year of Publication	Study Location	Follow-up Duration	Topical Treatments	Topical Treatment Category	Wound Dressing Group	Number of Participants (Healed/Treated)	Criteria for Complete Healing
Payne (2001) ^{66,***}	USA	52 wk	GM-CSF Placebo bFGF (excluded arm) Sequential GM-CSF and bFGF (excluded arm)	GRF BAS — —	AWD BWD — —	12/15 10/15 — —	Wound closure $\geq 85\%$
Payne (2004) ⁶⁷	USA	24 wk	Saline gauze Dermagraft	BAS GRF	HWD AWD	2/16 2/18	Full epithelialization and the absence of drainage
Payne (2009) ⁶⁸	USA	4 wk	Self-adhesive polyurethane foam dressing Saline gauze	FOA BAS	HWD BWD	10/20 6/16	Not reported
Piatkowski (2012) ^{69,††}	Germany	3 wk	Polyurethane foam dressing + collagen Polyurethane foam dressing	COL BAS	AWD BWD	5/5 4/5	Not reported
Price (2000) ⁷⁰	UK	6 wk	Alginate Radiant heat dressing	MRD RHD	HWD OWD	2/25 3/25	Not reported
Ramos-Torrecillas (2015) ^{71,‡‡}	Spain	5 wk	Saline gauze PRGF 2 doses of PRGF (excluded arm) PRGF + hyaluronic acid (excluded arm)	BAS GRF — —	HWD AWD — —	0/25 3/34 — —	Total closure of the PI
Rees (1999) ^{72,§§}	USA	16 wk	Saline gauze Becaplermin gel 100 µg/g only Becaplermin gel 100 µg/g alternated with placebo (excluded arm) Becaplermin gel 300 µg/g alternated with placebo [excluded arm]	BAS GRF — —	BWD AWD — —	0/31 7/31 — —	100% healed PIs
Scevola (2010) ⁷³	Italy	14 wk	Allogenic platelet gel Standard treatment	GRF COM	AWD HWD	0/8 0/8	Not reported
Sebern (1986) ⁷⁴	USA	8 wk	Moisture vapor permeable dressing Wet-to-dry gauze	FIL BAS	OWD BWD	14/22 0/12	Not reported
Seeley (1999) ⁷⁵	USA	8 wk	Hydrocolloid Hydrocellular foam	HCD FOA	HWD FOA	8/19 8/20	Closed PI
Sipponen (2008) ⁷⁶	Finland	26 wk	Sodium carboxymethylcellulose hydrocolloid polymer Resin salve of the Norway spruce	MRD AMD	HWD OWD	4/9 12/13	Not reported
Sopata (2002) ⁷⁷	Poland	8 wk	Lyofom Hydrogel	FOA HGD	FOA HWD	15/18 15/20	Closed PI wounds
Thomas (1998) ⁷⁸	UK	10 wk	Acemannan hydrogel Saline gauze	HGD BAS	HWD BWD	10/16 9/14	Not reported
Thomas (2005) ⁷⁹	UK	12 wk	Hydrocolloid Radiant heat dressing	HCD RHD	HWD OWD	7/20 8/21	Not reported
Xakellis (1992) ⁸⁰	USA	10 wk	Hydrocolloid Saline gauze	HCD BAS	HWD BWD	16/18 18/21	PI had epithelial covering

bFGF, basic fibroblast growth factor; GM-CSF, granulocyte macrophage colony-stimulating factor; pHEMA, poly(2-hydroxyethyl methacrylate); PRGF, plasma rich in growth factor; rhPDGF-BB, recombinant human platelet-derived growth factor-BB; TGF-β3, transforming growth factor, beta 3.

Topical treatment categories: AMD, antimicrobial; BAS, basic; CLD, collagenase; COL, collagen; COM, combined treatment; FIL, film; FOA, foam; GRF, growth factor; HCD, hydrocolloid; HGD, hydrogel; MRD, moisture retentive; NPd, negative pressure; RHD, radiant heat. Dressing wound groups: AWD, active; BWD, basic; FOA, foam; HWD, hydroactive; OWD, other wound dressing.

*Belmin (2002): Both intervention arms received hydrocolloid; the effect of hydrocolloid cancels and the comparison will be saline (BAS) versus calcium alginate (MRD).

†Brod (1990), Brown-Etris (1996), Darkovich (1990), and Moberg (1983) were excluded from the analysis using the 5 dressing groups.

‡Hirshberg (2001): Contains 3 intervention arms (2 active [GRF] and 1 control [BAS]); the active arm with the lowest dose and the control were included in the analysis.

§Hollisaz (2004): Contains 3 intervention arms, phenytoin cream was excluded from the analysis as it does not fit in any of the prespecified dressing categories.

||Kuflik (2001): Both intervention arms contain petrolatum, the effect of petrolatum jelly cancels and the comparison will be saline (BAS) versus combine treatment (COM).

*Mustoe (1994): Contains 3 intervention arms (2 active [GRF] and 1 control [BAS]); the active arm with the lowest dose and the control were included in the analysis.

**Payne (2001): Contains 4 intervention arms (3 active [GRF] and 1 control [BAS]); the active arm with the GM-CSF and the control were included in the analysis.

††Piatkowski (2012): Both intervention arms received foam dressing; the effect of foam dressing cancels and the comparison will be saline (BAS) versus collagen (COL).

‡‡Ramos-Torrecilla (2015): Contains 4 intervention arms (3 active [GRF] and 1 control [BAS]); the active arm with the lowest dose and the control were included in the analysis.

§§Rees (1999): Contains 4 intervention arms (3 active [GRF] and 1 control [BAS]); the active arm with the lowest dose and the control were included in the analysis.

estimates significantly, but differed in terms of error estimation (confidence intervals) (Supplementary Material S4).

Sensitivity Analysis and Assessment of Bias

Sensitivity analysis restricting the network to studies that assessed healing between 6 and 12 weeks after treatment ($n = 28$), showed that the results remain robust to these changes in the selection criteria,

revealing that foam, active wound dressing, and hydroactive wound dressing are the only treatment options (Supplementary Material S5).

The most common deficiencies in safe-guarding against bias were: participants and personnel not blind to study group allocation (6 studies) or not clearly stated (354 studies); allocation concealment not properly conducted (4 studies) or not stated (32 studies); and outcome assessors not blind to study group allocation (6 studies), or not stated (26 studies) (Supplementary Material S2). Results after

Fig. 2. Network plot showing the (A) 13 topical treatment categories and (B) 5 wound dressing groups. The circle size is proportional to the number of arms whereas the width of the lines is proportional to the number of pairs. (Topical treatment categories: AMD, antimicrobial; BAS, basic; CLD, collagenase; COL, collagen; COM, combined treatment; FIL, film; FOA, foam; GRF, growth factor; HCD, hydrocolloid; HGD, hydrogel; MRD, moisture retentive; NPD, negative pressure; RHD, radiant heat. Dressing wound groups: AWD, active; BWD, basic; FWA, foam; HWD, hydroactive; OWD, other wound dressing.)

application of the quality effects model³⁵ were not different to the main results (Supplementary Material S6).

Comparison-adjusted funnel plots (Supplementary Material S7) demonstrated little evidence of asymmetry. There was minimal inconsistency across treatment networks, with $H = 1.20$. There was little inconsistency across direct and indirect effects ($H < 3.0$) for each of the treatment comparison pairs, including when the network was restricted in sensitivity analyses.

Discussion

The results of the network meta-analysis that included 40 RCTs involving 1757 participants, comparing 5 dressing groups revealed that foam and active dressings are the most effective treatments for healing PIs. Although the effect size of all dressing groups was higher than basic wound dressings, the uncertainty was also high, which means that these results need confirmation.

A major issue in the recent network meta-analysis may have been the approach the researchers used to group PI topical treatments, leading to a sparse network,²³ and we avoided this by creating groups of tentatively similar mechanisms of action. Another key strength of the current study is the use of the GPM framework, which does not require assumptions that are not stated explicitly or cannot be verified when the method is applied. In comparison, the multivariate frequentist framework commonly used in other network meta-analyses²¹ assumes that if there is no common comparator in the network, this then has to be handled by augmenting the data set using

fictional arms with high variance. This requires a decision as to what constitutes a sufficiently high variance and therefore may not always be impartial.⁸¹ Additionally, the GPM framework has fewer assumption (ie, transitivity and independence of treatment effects between studies) than the multivariate frequentist framework that also requires distributional assumptions as well as augmented data sets (using fictional study arms of high variance) when studies lack the reference treatment.³⁴

The absence of robust research in this area and the extensive heterogeneity of dressings makes it difficult for researchers to provide clear advice to clinicians and decision makers about safe and effective PI treatment options for patients. Although the findings from our analysis contribute to decision making related to choice of therapy and topical treatments, they should be considered carefully. Given the huge variety of treatment options now available within the health industry, clinicians should also consider contextual factors such as wound characteristics, patient preference, and cost. However, the results of this study do indicate that basic dressings should be abandoned in favor of the better options in terms of wound healing.

Despite the methodological strengths of our study, we acknowledge some limitations. First, the topical treatments included in the designated categories may have been developed by different manufacturers, had slightly different compositions, and had variation in duration of interventions between studies. Additionally, the assumption of exchangeability within category was an empirical judgment and should be considered a limitation of this network meta-analysis. Second, the network meta-analysis only focused on complete

Fig. 3. Network forest plot based on 44 studies ranking comparisons based on their relative risk for wound healing using (A) basic and (B) hydrocolloid as the reference topical treatment category. When the reference treatment category changes, the ranking changes as well because of sparseness in the network, making these results unreliable. (Topical treatment categories: AMD, antimicrobial; BAS, basic; CLD, collagenase; COL, collagen; COM, combined treatment; FIL, film; FOA, foam; GRF, growth factor; HCD, hydrocolloid; HGD, hydrogel; MRD, moisture retentive; NPD, negative pressure; RHD, radiant heat.)

Fig. 4. Network forest plots based on 40 studies ranking comparisons based on their relative risk for wound healing using (A) basic and (B) hydroactive as the reference dressing group. This network is nonsparse and stable; thus, rankings remain reliable when the reference dressing group changes. (Dressing wound groups: AWD, active; BWD, basic; FOA, foam; HWD, hydroactive; OWD, other wound dressing.)

wound healing. Other outcomes such as time to complete healing, reduction in ulcer size, adverse events, cost, and patient quality of life should also be considered in future analyses.

Conclusion

Findings from this systematic review and network meta-analysis demonstrate evidence for the discontinuation of use of basic dressings. Hydroactive dressings are the mainstay practice, but our analysis suggests that the use of foam or active wound dressings may be more effective strategies for healing PIs. This should not be considered conclusive and more high-quality, rigorous research about the effectiveness of the dressings within these 2 groups is needed to confirm if these are indeed better than the current standard of hydroactive dressings.

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Supplementary Data

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