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# The effectiveness of silver-releasing dressings in the management of non-healing chronic wounds: a meta-analysis

Shu-Fen Lo, Chee-Jen Chang, Wen-Yu Hu, Mark Hayter and Yu-Ting Chang

**Aim.** The purpose of this study was to examine the efficacy of silver-releasing dressings in the management of non-healing chronic wounds.

**Background.** Non-healing chronic wounds often have a negative physical impact on patients and place a financial burden on healthcare systems. Silver dressings are wound products designed to control infection and provide a wound environment conducive to healing. However, validation of the clinical efficacy of these dressings is lacking.

**Design.** Systematic review and meta-analysis.

**Methods.** A systematic search of the major electronic databases PubMed, CINAHL, Cochrane, MEDLINE, British Nursing Index, EBSCO, OCLC and Proquest between 1950–June 2007 was conducted. Hand searches of selected periodicals, textbooks and checking reference lists and contacting experts was also performed.

**Results.** Eight studies were selected from a potentially relevant 1957 references screened. Analysis incorporated data from 1399 participants in the eight randomised control trials. We found that silver dressings significantly improved wound healing ($CI_{95}$: 0·16–0·39, $p < 0·001$), reduced odour ($CI_{95}$: 0·24–0·52, $p < 0·001$) and pain-related symptoms ($CI_{95}$: 0·18–0·47, $p < 0·001$), decreased wound exudates ($CI_{95}$: 0·17–0·44, $p < 0·001$) and had a prolonged dressing wear time ($CI_{95}$: 0·19–0·48, $p = 0·028$) when compared with alternative wound management approaches. An analysis of sensitivity in these studies by subgroup analysis generally supported these associations. Furthermore, studies indicated an improvement in quality of life ($CI_{95}$: 0·04–0·33, $p = 0·013$) using silver dressings in wound management with no associated severe adverse events.

**Conclusion.** This meta-analysis confirms the effectiveness of silver dressings in wound healing and improving patients' quality of life. However, it also highlights the need for additional well-designed randomised controlled trials to evaluate the effectiveness of silver-related dressings further.

**Relevance to clinical practice.** The results of this study provide objective data on the effectiveness of silver-related dressing when applied to non-healing chronic wounds.

**Key words:** clinical effectiveness, meta-analysis, nurses, nursing, review, wound care

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## Introduction

Non-healing chronic wounds are a serious health issue: they cause great pain and suffering to patients impacting on their quality of life and place a significant financial burden on health systems.

A recent innovative concept in chronic wound care is represented by the 'wound bed preparation' model proposed by Sibbald *et al.* (2001) who identifies four main strategies to good wound bed preparation; specifically, tissue management, infection and inflammation control, moisture balance and edge of wound care (Sibbald *et al.* 2001, Moffatt 2004, Fletcher 2005). When the wound bio-burden exceeds a host-manageable level, a wound may become infected. Chronic infection is clearly detrimental to wound healing (Tomaselli 2006). Non-healing chronic wounds, e.g. pressure ulcer, venous ulcer, arterial ulcer and diabetic ulceration, are usually contaminated with several species and the progression to local infection occurs in stages, often leading to critical colonisation (Ayello & Cuddigan 2004, Giulio & Barrett 2005). When this occurs and host response is reduced, the normal wound healing process is interrupted because of a prolonged inflammatory response, molecular and cellular abnormalities in the wound bed and granulation tissue breakdown resulting in a non-healing and deteriorating wound (Giulio & Barrett 2005, Gray *et al.* 2006). Appropriate management of infected and critically colonised wounds is essential to encourage wound healing progression (Bowler 2003). Treatment of infected wounds should focus on the removal of dead or necrotic tissues and the management of wound exudates (Schultz *et al.* 2003, Ayello & Cuddigan 2004). Unfortunately, not only there are difficulties in diagnosing critical colonisation or infection, but traditional topical antimicrobials can be toxic to granulation tissues or increase the chance of resistant organisms. It is possible, however, to reduce the wound bio-burden and avoid systemic infection by silver-releasing wound dressings (Gray *et al.* 2006, White & Cutting 2006).

Silver, in its common ionic (active) form ($Ag^+$), is particularly attractive as an antibacterial agent because it can be readily incorporated into dressing materials. When the materials contact an aqueous environment, the silver complex contained in them is dissociated (Ovington 2004, White & Cutting 2006). The mechanism of action for $Ag^+$ is that it binds to bacterial cell DNA and enzymes and proteins in the cell wall. Once the silver cation attaches to these sites, it alters their structure, resulting in structural and functional changes in the bacterial cell (Ovington 2004). It is suggested by numerous authors that silver dressings should be used when critical colonisation within a wound occurs (Ovington 2004, White & Cutting 2006). However, the evidence base for this assertion is not particularly strong. If nurses are to provide evidence-based care to their patients a clear, evidence-based, body of knowledge should underpin their practice. In wound care, this means continually reviewing the evidence related to wound management (Leandro 2005, Melnyk & Fineout-Overholt 2005). This study conducts a meta-analysis of the current evidence base for the efficacy of silver dressings in the treatment of chronically infected wounds. Meta-analysis studies contribute to many aspects of clinical research, not only by enabling an increased statistical power of comparison but also in obtaining clear and reliable results that can be used as a basis for clinical guidelines (Leandro 2005). To date, two meta-analyses have included studies of silver-based dressings and topical agents on leg ulcers (Chambers *et al.* 2007, Vermeulen *et al.* 2007). However, information on economic evaluation, duration of dressing wear time and the frequency of dressing change was not specified enough for clinical application. Furthermore, this analysis also sought to analyse the evidence of patient preference and symptom control.

## Aim of the study

This study's purpose was to examine the efficacy and safety of silver-releasing dressings in the management of non-healing chronic wounds by conducting a meta-analysis of randomised control trials (RCT). Therefore, the research questions addressed in the current meta-analysis were:

- What are the mean effect sizes of silver-releasing dressing as a whole?
- What is the magnitude efficacy and safety of silver-releasing dressings?

## Methodology

### Search strategy for identification of studies

The search for eligible studies was comprehensive and involved multiple strategies. Relevant studies were identified by searching the electronic searches of the core bibliographic databases: PubMed, CINAHL via Ovid online, Cochrane Database, MEDLINE via Ovid online, EBSCO host, Proquest, British Nursing Index and OCLC. The search terms used to locate relevant studies are summarised in Table 1. Moreover, we also carried out hand searching of selected periodicals, reviewed reference lists of published papers, searched wound management websites and contacted wound dressing manufacturers. A search for unpublished literature was conducted through dissertation and conference abstracts. The time parameters of the search were from 1950s–June

**Table 1** Search strategy for review

| Electronic databases searched | | Data searched |
|---|---|---|
| PubMed | 1950s–June 2007 | December 2006–June 2007 |
| CINAHL via Ovid online | 1982–June 2007 | December 2006–June 2007 |
| Cochrane Database | 1991–June 2007 | December 2006–June 2007 |
| MEDLINE via Ovid online | 1951–June 2007 | December 2006–June 2007 |
| EBSCO host | October 2006 | December 2006–June 2007 |
| Proquest | 1950–June 2007 | December 2006–June 2007 |
| British Nursing Index | 1994–June 2007 | March 2007 |
| OCLC | 1967–January 2007 | January 2007 |

Textbooks on critical colonisation issues or reference lists
- Wounds-related electronic journals or websites
  - Worldwide wounds
  - European Wound Management Association (EWMA)
  - World Union of Wound Healing Societies (WUWHS)
  - The World Council of Enterostomal Therapists (WCET)
  - Wounds UK
- The contacted manufacturers
  - Coloplast
  - Conca Tec
  - Smith and Nephew
  - Johnson and Johnson
  - Urgotul
  - Silver Ion/Argentum Medical

| Search terms used | Potentially relevant hits |
|---|---|
| #1 infection (MeSH) or | (1,10,752) |
| #2 sepsis (MeSH) or | (9167) |
| #3 colonised or | (149) |
| #4 colonisation or | (3201) |
| #5 antimicrobial or | (9894) |
| #6 silver (MeSH) or | (2702) |
| #7 Ag or | (908) |
| #8 ionic silver or | (1) |
| #9 wounds (MeSH) or | (6671) |
| #10 diabetic ulcers (MeSH) or | (142) |
| #11 venous ulcer (MeSH) or | (286) |
| #12 pressure ulcer (MeSH) or | (609) |
| #13 #1 or # 2 or #3 or #4 or #5 | (1,32,162) |
| #14 #6 or #7 or #8 | (3600) |
| #15 #9 or #10 or #11 or #12 | (7696) |
| #16 #13 and #14 and #15 | (1957) |

2007. The literature search was carried out on 30 June 2007 and papers were included in the review if retrieved by 5 July 2007 (Table 1).

## Selection criteria

Screening of relevant studies for inclusion was conducted independently by S-FL and Y-TC Chang who used titles, publication years and abstracts. The criteria for considering studies for the review were as follows. Studies were assessed for inclusion based on inclusion criteria determined a *priori* (Fig. 1). Studies excluded after full paper review are presented in Table 2.

### *Type of studies*

We performed a meta-analysis of primary studies, which concerned the effectiveness of interventions applied to management of non-healing chronic wounds. Owing to language and resource constraints, studies included were limited to published or unpublished papers in English or Chinese. RCT studies were included (single-group pre- and postcontrolled trials or experimental studies were excluded).

### *Type of participants*

Study participants all had wounds that exhibited delayed healing or had wounds that were clinically diagnosed with critical colonisation or infection (acute wounds such as burns were excluded).

### *Type of intervention*

To be included, studies should focus on silver dressing compared with non-silver dressings or silver dressing compared with traditional wound management, such as gauze.

### *Type of outcome measurement*

Based on the protocol for this review the reported outcomes were classified as physical, psychological or economic.

### *Assessment of study quality*

In this review, the title, abstract and key words of each identified record were screened for relevancy (step 1 screening) by the primary reviewers. Full-text articles were obtained for all remaining records. Non-English articles were obtained and translated as required. The same two reviewers independently assessed each full-text article. The quality and strength of the studies were evaluated using the CONSORT statement and the checklist developed by Melnyk and Fineout-Overholt (2005) was used to critically appraise RCT. A total of 15 study elements were critically appraised to determine a study quality score. The highest possible study quality score was 30; each item had a possible score of 0–2 (score of 0 = not done; 1 for unclear, 2 for done), with possible scores ranging from 0–30. Papers with a quality score over 60% ($>18$) of the total possible score were included in this analysis (step 2 screening; Table 3). Inter-rater agreement was calculated at each screening step with the use of Cohen's kappa statistic.

  

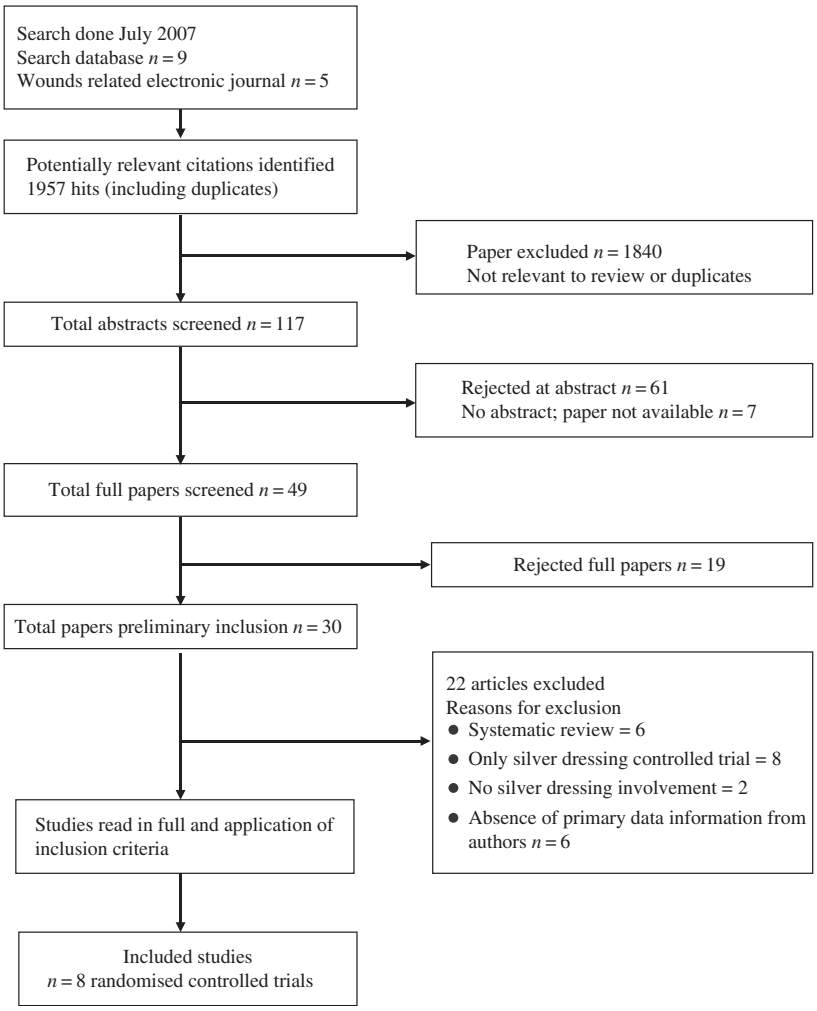


**Figure 1** Summary of study selection and exclusion.

**Table 2** Excluded studies

| Study | Reason |
|---|---|
| Chambers *et al.* (2007) | Systematic review and meta-analysis in leg ulcers |
| Bergin and Wraight (2006) | Systematic review in diabetic foot ulcer |
| Sibbald *et al.* (2005) | Lacking in rigour |
| O'Meara *et al.* (2001) | Lacking in rigour |
| Bolton (2006) | Lacking in rigour |
| Rayman *et al.* (2005) | Non-comparative study |
| Lazareth *et al.* (2007) | Non-comparative study |
| Sibbald *et al.* (2001) | Non-comparative study |
| Schuman *et al.* (2007) | Non-comparative study |
| Karlsmark *et al.* (2003) | Non-comparative study |
| Ziegler *et al.* (2006) | Non-comparative study |
| Vanscheidt *et al.* (2003) | Non-comparative study |
| Joergensen *et al.* (2007) | Non-comparative study |
| Verdu *et al.* (2007) | Non-comparative study |
| Rucigaj (2007) | Non-comparative study |
| Sigal-Grinberg *et al.* (2007) | No useable data was reported |
| Verdu Soriano *et al.* (2004) | Definition of outcomes unclear. No further data could be obtained |
| Rogers and Alvarez (2004) | Definition of outcomes unclear. No further data could be obtained |
| Serra *et al.* (2005) | Definition of outcomes unclear. No further data could be obtained |

**Table 3** Summary of included studies

| Authors/ QS | Study design | Participant | Inclusion criteria | Intervention | Main outcome measured | Results |
|---|---|---|---|---|---|---|
| Jude *et al.* (2007)<br>QS = 28/30 | RCT; open label; stratified randomised<br>Setting: no clear report | A total of 134 patients from 18 centres in four countries (Germany, Sweden, UK and France)<br>I:67 vs. C:67<br>F:35 vs. M:99<br>average age 58·9 years<br>Drop-out rate: 15·6% loss to FU | 1. Type I or II diabetes mellitus with Wanger Grade 1 or 2 diabetic foot ulcers<br>2. Wound area $\geqq$ 1 $cm^2$<br>3. Use or non-use of systemic antibiotic<br>4. Risk of infection or infection | Eight weeks duration at admission, 4 weeks ± 2 days and 8 weeks ± 2 days wound evaluation<br>I: Silver hydrofibre dressing<br>C: Calcium alginate dressing<br>Financially supported by a commercial company | Wound area: $W \times L$ ($cm^2$)<br>Wound depth: a sterile swab could be inserted into the wound<br>Percentage of the wound bed tissues composition | 1. Reduction of wound area: no significant differences between the two groups ($p$ = 0·975)<br>2. Reduction of ulcer depth: I group had a significant decrease more than the C group ($p$ = 0·042)<br>3. Wound bed tissues composition: no significant differences between the two groups ($p$ = 0·058)<br>4. AE: no significant differences between the two groups |
| Verdu *et al.* (2004)<br>QS = 25/30 | RCT; open label; simple randomised<br>Setting: no clear report | A total of 125 patients from 10 centres in Spain<br>I: 67 vs. C:58<br>Gender and age not reported<br>Drop-out rate: 10·0% loss to FU | 1. 18 years or above<br>2. Lesion with granulation and/or devitalised tissues<br>3. Chronic wound with no clinical signs of local infection | Six weeks duration at admission, unclear wound evaluation<br>I: Silver charcoal dressing<br>C: Hydropolymer adhesive dressing<br>Financially supported by a commercial company | Lesion type and location<br>Bacterial status (four categories) | 1. Contaminated wounds: no significant differences between the two groups<br>2. Colonised wounds: no significant differences between the two groups<br>3. Wound with high level of bacteria: no significant differences between the two groups<br>4. Infected wound: I group had a significant decrease more than the C group ($p$ < 0·001)<br>5. AE: no significant differences between the two groups |

 

**Table 3** (Continued)

| Authors/ QS | Study design | Participant | Inclusion criteria | Intervention | Main outcome measured | Results |
|---|---|---|---|---|---|---|
| Munter *et al.* (2006) QS = 27/30 | RCT; open label; block randomised<br>Setting: specialist wound care centre | A total of 619 patients from 80 centres in nine countries (Canada Germany, Belgium, Switzerland, UK, Denmark, Brazil, Slovenia and Italy)<br>I: 326 vs. C:293<br>F:381 vs. M:238<br>average age 69·8 years<br>Drop-out rate: not unclear report | 1. 18 years or above<br>2. Wounds delayed healing<br>3. Moderate- to high levels of exudates<br>4. Ulcer depth $< 0{\cdot}5$ cm<br>5. Risk of infection or infection<br>6. Malodour<br>7. All types of wounds | Four weeks duration at admission and weekly evaluation of wound<br>I: Silver hydrophilic foam dressing<br>C: Local best practice (included gauze, hydrocolloid, foam/alginate and other active dressings)<br>Financially supported by a commercial company | Wound area: $W \times L$ ($cm^2$) $\times D$ (mm)<br>Odour (four-point scale)<br>Wound bed tissues composition (four tissue types)<br>Exudate (four-point scale)<br>Wound progress (six-point scale)<br>EQ-5D (three-point scale)<br>Pain (10-point numerical box scale)<br>Time spent (four categories)<br>Wear time (days) | 1. Reduction of wound area: I group had a significant decrease more than the C group ($p = 0{\cdot}0019$)<br>2. Malodour: I group had a significant improvement more than the C group ($p < 0{\cdot}0001$)<br>3. Slough: I group had a significant improvement more than the C group ($p = 0{\cdot}0038$)<br>4. Exudate level: I group had a significant reduction more than the C group ($p = 0{\cdot}0055$)<br>5. Wound progress: I group had a significant improvement more than the C group ($p = 0{\cdot}0001$)<br>6. EQ-5D: no significant differences between the two groups<br>7. Pain: I group had a significant improvement more than the C group ($p < 0{\cdot}0001$)<br>8. Time spent: I group had a significant decrease more than the C group ($p = 0{\cdot}0003$)<br>9. Wear time: I group had a significant decrease more than the C group ($p < 0{\cdot}0001$)<br>10. AE: not reported |



 

**Table 3** (Continued)

| Authors/ QS | Study design | Participant | Inclusion criteria | Intervention | Main outcome measured | Results |
|---|---|---|---|---|---|---|
| Jørgensen *et al.* (2006) QS = 27/30 | RCT; open label; block randomised Setting: no clear reported | A total of 129 patients from in 15 centres in seven countries (UK, Germany, Canada, USA, Demark, Italy and Netherlands) I: 65 vs. C:64 F:82 vs. M:47 age between 40–99 years Drop-out rate: not unclear report | 1. Moderate- to high levels of exudates 2. Wounds delayed healing diagnosis with chronic venous or mixed venous/arterial leg ulcer 3. Critical colonisation | Four weeks duration at admission and weekly evaluation of wound I: Silver hydrophilic foam dressing C: Foam without silver dressing Financially supported by a commercial company | 1. Wound area: $W \times L$ ($cm^2$) 2. Odour (four-point scale) 3. EQ-5D (three-point scale) 4. Exudate (four-point scale) 5. Maceration were subjectively evaluated by researchers 6. Wear time (days) | 1. Reduction of wound area: I group had a significant decrease more than the C group ($p = 0{\cdot}034$) 2. Odour: I group had a significant improvement more than the C group ($p = 0{\cdot}0013$) 3. EQ-5D: no significant differences between the two groups 4. Exudate level: I group had a significant improvement more than the C group ($p = 0{\cdot}002$) 5. Maceration: I group had a significant decrease more than the C group ($p = 0{\cdot}008$) 6. Wear time: I group had a significant decrease more than the C group ($p = 0{\cdot}023$) 7. AE: Four in I group and three in C group, no mention of statistical difference |
| Romanelli and Price (2005) QS = 22/30 | RCT; open label; parallel and block randomised Setting: no clear report | A total of 109 patients from multi-centre in UK I:52 vs. C:57 Age and gender not reported Drop-out rate: 11·0% loss to FU | 1. Chronic venous ulcer 2. Mixed venous/ arterial leg ulcers 3. Ankle/brachial index $\geqq 0{\cdot}65$ 4. With critical colonisation 5. Moderately to highly exudate 6. Ulcer between 2 cm and 49 $cm^2$ | Four weeks duration and daily evaluation of wound by study personnel I: Silver foam dressing C: Foam dressing Financially supported by a commercial company | 1. Odour (four-point scale) 2. Exudate level 3. Comfort during wear (four-point scale) 4. Pain (11-point scale) 5. Wound area: $W \times L$ ($cm^2$) | 1. Odour: I group had a significant improvement more than the C group ($p = 0{\cdot}02$) 2. Exudate level: I group had a significant improvement more than the C group ($p < 0{\cdot}01$) 3. Comfort during wear: no significant differences between the two groups 4. Pain: no significant differences between the two groups 5. Reduction of wound area: I group had a significant improvement more than the C group ($p = 0{\cdot}03$) 6. AE: not reported |

 

**Table 3** (Continued)

| Authors/ QS | Study design | Participant | Inclusion criteria | Intervention | Main outcome measured | Results |
|---|---|---|---|---|---|---|
| Sigal-Grinberg *et al.* (2007) (oral presentation; unpublished data) QS = 21/30 | RCT; parallel and block randomised Setting: no clear report | A total of 102 patients from in multi-center in France I: 51 vs. C:51 F:63 vs. M:36 average age 74·9 years Drop-out rate: not unclear report | 1. Perilesional erythema 2. Pain between two dressing changes 3. Malodours 4. Abundant exudates 5. Oedema | Eight weeks duration and weekly evaluation of wound I: Silver hydroalginate dressing C: Calcium alginate dressing Financial support not reported | Wound area: $W \times L$ ($cm^2$) Clinical score | 1. Reduction of wound area: I group had a significant and quick improvement more than the C group ($p = 0{\cdot}024$) 2. Clinical score: I group had a significant improvement more than the C group ($p = 0{\cdot}024$) 3. AE: not reported |
| Russell (2005) QS = 25/30 | RCT; open label; parallel and block randomised Setting: chronic wound clinic | A total of 82 patients from 12 centres in UK I: 43 vs. C:39 F:36 vs. M:46 average age 73 years Drop-out rate: not unclear report | 1. Medium- to high-level exudates (A Grade II–III pressure ulcer or diabetic foot ulcers) 2. 18 years of age or above 3. Full foul odour 4. Clinically infected ulcer 5. Wound with risk of infection | Four weeks duration and weekly evaluation of wound by wound care practitioners I: Silver hydrophilic foam dressing C: Local best practice (included gauze, hydrocolloid, foam/alginate and other active dressings) Financially supported by a commercial company | 1. Wound area: $W \times L$ ($cm^2$) 2. Exudate handling (four-point scale) 3. Ease of dressing application and removal (four-point scale) 4. Wear time (days) 5. Peri-ulcer skin condition 6. Reduction of erythematous periulcer skin 7. Reduction in systemic antibiotic treatment 8. Malodour | 1. Reduction of wound area: I group was 42%; C group was 28% 2. Exudate handling: I group was significantly more better than the C group ($p = 0{\cdot}0032$) 3. Ease of dressing application: I group was significantly more better than the C group ($p = 0{\cdot}0003$) 4. Ease of dressing removal: I group was significantly more better than the C group ($p < 0{\cdot}0001$) 5. Mean wear time: I group was 4·2 days; C group was 3·4 days 6. Peri-ulcer skin normal condition: I group was 40%; C group was 31% 7. Reduction erythematous: I group was 62%; C group was 12% 8. Reduction in systemic antibiotic treatment: I group was 63%; C group was 4% 9. Malodour: disappeared in I group; no reduction in C group 10. AE: One in I group and unclear in C group, no mention of statistical difference |

 

**Table 3** (Continued)

| Authors/ QS | Study design | Participant | Inclusion criteria | Intervention | Main outcome measured | Results |
|---|---|---|---|---|---|---|
| Meaume *et al.* (2005) QS = 28/30 | RCT; open label; parallel and block randomised Setting: no clear report | A total of 99 patients from 13 centres in France I: 51 vs. C:48 F:63 vs. M:36 average age 74·9 years Drop-out rate: 19·2% loss to FU | Leg ulcer between 2–20 cm 2. Ankle/brachial index (ABI) > 0·7 3. A Grade III–IV pressure ulcer 4. Local infection 5. Over 50% defective wound bed | Four weeks duration and daily evaluation of wound by two clinicians I: Silver hydroalginate dressing C: Calcium alginate dressing Financially supported by a commercial company | Wound area: $W \times L$ ($cm^2$) Wound severity score | 1. Reduction of wound area: no significant differences between the two groups ($p$ = 0·117) 2. Healing rate: I group had a significantly quick rate more than the C group ($p$ = 0·024) 3. Wound severity score: no significant differences between the two groups ($p$ = 0·063) 4. Percentage decrease in wound severity score: I group had a significant improvement more than the C group ($p$ = 0·034) 5. AE: Three in I group and one in C group, no mention of statistical difference |

QS, Quality of Score; I, intervention group; C, control group; RCT: randomised control trial; F: female; M: male; W: width; L: length; D: depth; AE, study-related adverse events; FU, follow-up.

Information about methodological quality and potential risks of bias were used to guide sensitivity analyses and explore sources of heterogeneity.

### Data extraction

A data extraction form was developed for the analysis and pilot tested prior to use. For all the trials baseline data, study design, statistical analysis and ethics, participant characteristic, outcome measure and adverse events were extracted. Double data collection was used to prevent errors during transcription of study results. In the meantime, data from each study were collated in tabular summaries to help identify outcomes that could be combined (meta-analysis) and characteristics of studies that should be considered when investigating variation in effect (heterogeneity).

### Data analysis

A measure of the effect of an intervention is generated by comparing outcomes in the experimental compared with the control group: relative ratio/rate ratio (RR), odds ratios (OR), absolute risk reduction (ARR) or number needed to treat (NNT) from individual studies for binary data of effect measures. Mean difference, weighted mean difference (WMD), standardised mean difference (SMD) and 95% confidence intervals (95% CI) for continuous data of effect measures (NHS Centre for Reviews and Dissemination 2001).

The heterogeneity test plays an important role in the assessment of the consistency of effects across studies. A non-significant result suggests that no statistically significant heterogeneity is present. The Cochran's $Q$-test and 95% CI was performed to evaluate heterogeneity within the identified studies. Significant heterogeneity was considered to be present when the $p$-value was $< 0{\cdot}05$. In meta-regression, a way of exploring the reasons for the heterogeneity of results and adjustment for confounding effects is seen. In the absence of heterogeneity ($p > 0{\cdot}10$) a fixed effect model was applied. On the contrary, in the presence of heterogeneity ($p < 0{\cdot}10$), a random effects model was used; however, random effects model may be suitable if the number of studies is small (approximately less than 10; Abrams & Jones 2001, Sutton *et al.* 2001). Publication bias was examined with the use of funnel plots and with Egger tests (Petticrew & Roberts 2006). An analysis of sensitivity in the studies was performed by subgroup analyses according to similar dressings and similar patient groups. All statistical tests were two-sided. All analyses were conducted using Comprehensive Meta-Analysis, Version 2.


 

## Results

### Search results

Figure 1 shows the steps and criteria for search strategy and the number of trials evaluated at each stage of the systematic review. Primary searched studies resulted in potentially relevant citations and identified 1957 hits (step 1). The agreement between the two primary reviewers at this step of screening was substantial (estimated kappa = 0·79). Of these, 30 studies were reviewed and eight RCT were included. Twenty-two were excluded from the meta-analysis for the reasons outlined in Fig. 1. Agreement between the two reviewers at the second step of screening was almost perfect (estimated kappa = 0·93). Thereafter, two systematic and meta-analysis studies (Chambers *et al.* 2007, Vermeulen *et al.* 2007) on sliver dressing for chronic wound were reviewed and principle investigators contacted by e-mail to request additional information on meta-analysis. However, data were not available. Therefore, the final sample consisted of eight RCT studies published in English between 2004–2007. Of the eight studies, seven were published journal articles and one was unpublished conference article. All eight papers scored between 20–28 on the critical appraisal tool.

### Assessment of methodological quality

Of the eight included studies, four were of high methodological quality. Two trials showed no evidence of sample size estimation (Romanelli & Price 2005, Munter *et al.* 2006) and an intention-to-treat analysis (Romanelli & Price 2005, Sigal-Grinberg *et al.* 2007). Four of the studies reported drop-out rates that varied from 10·0–19·2% and the remaining trials did not mention drop-out rates (Russell 2005, Jørgensen *et al.* 2006, Munter *et al.* 2006, Sigal-Grinberg *et al.* 2007). The sum of drop-outs from the group I was 25 and from the group C 24. There was no significant difference found in any of the studies (Table 3).

### Study characteristics

Of the 1399 combined patients in the eight RCT, 721 were allocated for silver-relating dressings (group I) and 668 for without silver dressings (group C). Five studies were from single countries: UK (2), France (2), Spain (1) and multiple countries (UK, Germany, Canada, USA, Demark, Italy, Netherlands, Belgium, Switzerland, Brazil and Slovenia). Exactly, 597 participants in the studies were females and 466 were males. There were also 336 patients whose gender was not given. Average age ranged from 58·9–74·9 years. Two trials (Romanelli & Price 2005, Sigal-Grinberg *et al.* 2007) did not give details of patient ages. In addition, 48·73% ($n$ = 579) of the studies reported including subjects with venous leg ulcer, 9·93% ($n$ = 118) with mixed venous/arterial ulcer, 16·83% ($n$ = 200) with pressure ulcer, 15·40% ($n$ = 183) with diabetic foot ulcer and 9·09% with another type of non-healing chronic wound. Two trials (Russell 2005, Jørgensen *et al.* 2006) did not give details of wound type (Table 3).

All the trials compared silver-releasing dressing with a non-silver-releasing dressing (foam dressing, alginate dressing and hydro-polymer adhesive dressing). Silver dressings included hydrophilic polyurethane foam (Romanelli & Price 2005, Russell 2005, Jørgensen *et al.* 2006, Munter *et al.* 2006), hydroalginate dressing (Meaume *et al.* 2005, Sigal-Grinberg *et al.* 2007), activated charcoal dressing (Verdu Soriano *et al.* 2004) and hydrofibre (Jude *et al.* 2007). The duration of intervention varied from four to eight weeks, all five studies included data after four weeks, one study six weeks and two studies included data after eight weeks of intervention. The majority of studies ($n$ = 4) conducted a weekly evaluation of wound bed progresses. The studies used the following physiological outcome variables: wound area ($n$ = 6), odour ($n$ = 3), maceration ($n$ = 3), exudates ($n$ = 3), wound bed tissues composition ($n$ = 2) and pain ($n$ = 2).

### Pooled efficacy and safety

*Physiological outcomes*

To examine the overall efficacy and safety of silver-relating dressings, six results were retrieved from eight studies (in some cases, more than one result was retrieved from a study).The results of our meta-analysis shows a significant effect of group I in wound area reduction compared with group C with the effect size 0·28 ($CI_{95}$: 0·16–0·39, $p < 0·001$; $t$-test). Heterogeneity tests were obtained for six studies showing no significant difference between studies ($p$ = 0·497; chi-square test).

Wound odour was described in three trials, which presented a significant effect of group I in wound odour improvement compared with group C with the effect size 0·38 ($CI_{95}$: 0·24–0·52, $p < 0·001$; $t$-test). There was no significant between-study heterogeneity ($p$ = 0·302; chi-square test).

For wound exudate, three trials showed a significant effect of group I in the wound exudate level reduction compared with group C with the effect size 0·31 ($CI_{95}$: 0·17–0·44, $p < 0·001$; $t$-test). There was no statistical heterogeneity ($p$ = 0·126; chi-square test).

A reduction in wound pain was described in two trials, which displayed a significant effect of group I more than group C with the effect size 0·33 ($CI_{95}$: 0·18–0·47,

$p < 0{\cdot}001$; *t*-test). There was no significant between-study heterogeneity ($p = 0{\cdot}758$; chi-square test).

*Psychological and economic outcomes*

The results of our meta-analysis shows a significant effect of group I in the EQ-5D (Standardised instrument for use as a measure of health outcome) compared with group C with the effect size 0·18 ($CI_{95}$: 0·04–0·33, $p = 0{\cdot}013$; *t*-test). Heterogeneity test was obtained for two studies that showed no significant difference between studies ($p = 0{\cdot}349$; chi-square test). For dressing wear time, two trials showed a significant effect of group I compared with group C with the effect size 0·33 ($CI_{95}$: 0·19–0·48, $p = 0{\cdot}028$; *t*-test). There was no significant between-study heterogeneity ($p = 0{\cdot}645$; chi-square test).

*Adverse events*

Four of the studies included information about adverse events. No severe adverse events were registered in any of the studies. Three trials did not mention adverse events (Romanelli & Price 2005, Munter *et al.* 2006, Sigal-Grinberg *et al.* 2007). The deterioration of peri-ulcer skin and burning sensation were the main local adverse events reported (Table 3).

*Sensitivity testing*

Sensitivity testing was conducted in relation to the type of dressing used and:

- wound area reduction
- wound odour
- wound exudates
- reduction in wound pain
- quality of life.

In all cases there was no statistically significant heterogeneity.

### Publication bias

We minimised the potential for publication bias by conducting a thorough literature search that included gray literature and contacting experts. We also generated funnel plots and Egger's tests for the primary outcome (reduction in wound area), which included six studies demonstrating symmetry indicating no publication bias. In addition, we used Egger's linear regression test to detect publication bias (Whitehead 2002). The intercept was 0·72, with 95% CI (–2·20, 3·64) – concurring with the visual inspection of the funnel plot.

## Limitations of the study

This review has some limitations. First, the review was exclusively drawn from publications in English or Chinese. This has the potential for affecting the results of a meta-analysis (NHS Centre of Reviews and Dissemination 2001). Second, variability in the type of dressings and patient groups might affect the efficacy and safety of silver-releasing dressings. However, our post-hoc subgroup analysis did not verify this effect. Another limitation of this review was the exclusion of non-healing wounds over four to six weeks duration, such as burns, traumatic or postoperative wounds. This decision was because of the different bio-mechanisms between the two wound types (Ayello & Cuddigan 2004). Furthermore, this decision was also guided by the fact that non-healing chronic wounds are much more common and contribute to the greatest health issues, not only in terms of direct cost to healthcare services, but also in terms of pain, economic loss and impaired quality of life experience by patients. Finally, all included trials differed in several dimensions, including characteristics of the participants and wound type, inclusion and exclusion criteria, type of dressing product, evaluation of outcome and status with regard to industry funding. In addition, no studies included research questions or hypotheses, leading to a possibility of reporting bias. Some studies may have lacked the power to adequately detect beneficial outcome. All studies were conducted in western healthcare environments. It is unknown whether patients with non-healing chronic wound from other regions of the world would respond similarly to the same interventions. Finally, we found that all of the open label trials showed a significant positive outcome. It is possible that this type of research design could lead to the problem of higher estimation of silver dressing efficacy through 'Novelty' or 'Hawthorne' effects.

## Discussion

This systematic review adds to one previous review of silver-related dressings in chronic wounds by Vermeulen *et al.* (2007), which included three RCT assessing the effectiveness of silver in the treatment of contaminated and infected acute or chronic wounds. However, the authors highlighted that there was insufficient evidence to recommend the use of silver dressings for treatment of infected or contaminated chronic wounds. The results of this meta-analysis support the hypothesis that silver-dressings can improve wound bed composition in non-healing, chronically infected wounds. We found not only significant effectiveness of physical outcomes, reduction in wound area, reductions in malodour, decreases in wound exudates and wound pain, but also improvement in the participant's quality of life and prolonged dressing wear time. The variety of outcome measures included in the studies within this meta-analysis strengthens the evidence base for their use – providing evidence of not only physical improve-

  

ments but of an impact upon psychological and economic indicators too. Moreover, as 1399 subjects were involved in this meta-analysis, the results obtained can be expected to have more clinical significance than individual studies alone.

### Relevance to clinical practice

Although providing a clear addition to the evidence base for practice this review also demonstrates the need for further investigation. First, several well-designed RCT are needed to clear up the continued uncertainty about the therapeutic effects of different type of silver-relating dressing on non-healing chronic wounds in various clinical settings and patient populations. Second, it is also important to describe the silver-relating dressing delivery mode, indications, contraindications, frequency and duration of treatment in future studies. Third, the application of the findings of this review is restricted to settings and patients similar to those in the primary studies. Most of the included studies did not mention trial setting and the majority were conducted in Europe, therefore, primary research is needed to examine the efficacy and safety of silver-relating dressings in healthcare circumstances in the East. Finally, although evidence of effectiveness is an appropriate standard from which to base reimbursement policies only two trials demonstrated a positive effect upon wear time, thus, further studies are need to evaluate the cost-effectiveness of silver-releasing dressings to inform health policy within wound care practice.

## Conclusion

In conclusion, this meta-analysis of RCT confirmed that silver-releasing dressings can improve wound bed composition, enhance quality of life and save medical cost. However, we found that majority of the participants were older than 60 years of age and had several advanced chronic diseases. Understanding the differences in silver dressing efficacy among different populations is important when selecting patients for this treatment. Notwithstanding, this meta-analysis showed that silver dressings were associated with few adverse events and the authors of the papers reviewed reported no significance differences for these between groups I and C. However, it may be the case that with industry-funded trials adverse events may be under-reported; therefore, an adverse events assessment should be conducted when practitioners use this intervention.

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## Contributions

Study conception and design: SL, LC; data collection and analysis: SL, WH, YC and drafting and critical revision of manuscript: SL, MH, WH, LC.

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