The controversial and diverse conclusions of clinical studies on the use of silver in the management of patients with venous leg ulcers


Authors:
Dr Hussam Itani and Abdulkareem Iblasi

Topical antimicrobial agents include antibiotics and antiseptics. Although antibiotics are vigorous antimicrobial agents with high specificity, the persistent emergence of antibiotic-resistant strains of pathogens and the slow breakthrough in developing novel antibiotics have led to the need to find alternative treatments. Antiseptics are thought to prevent the growth of pathogenic microorganisms without damaging living tissue. In the past, honey, potassium permanganate, hypochlorite, lactic acid and hydrogen peroxide were widely used in managing wounds. In recent years, silver-based dressings have been heavily marketed for managing infection in chronic wounds. This review attempts to provide an insight into the use of silver-based dressings by describing their mechanisms of action, reviewing supporting evidence and outlining perceived limitations.

***Dr Hussam Itani** is Regional Advisor, Wound Healing and Tissue Repair Wound Care Specialist in Canada and the UAE; **Abdulkareem Iblasi** is Clinical Nurse Manager, Wound Management Unit, King Saud Medical City, Riyadh, Saudi Arabia; PhD (C) Chulalongkorn University, Thailand*

Venous leg ulcers (VLUs) are associated with chronic venous insufficiency and are reported to affect 1–3% of the adult population worldwide (Mekkes et al, 2003). The 12-month recurrence rates for VLUs are estimated at 18–28% (Margolis et al, 2002). Individuals with VLUs commonly present with moderate-to-high exudate, pain and malodour, which often have a substantial impact on patients' quality of life (Gonzalez-Consuegra and Verdu, 2011). Several studies demonstrate that patients with VLUs suffer for several years without improvement and that 50–60% of these ulcers fail to heal within 20–24 weeks, despite the use of appropriate treatments, including compression therapy (Lipsky and Hoey, 2009; Watson et al, 2011).

Margolis et al (2004) suggested that deep vein involvement, large ulcer size (>10 cm^2), and long duration (open for 12 months or more) are indicators of a poor prognosis for healing and high chance of recurrence. David et al (2007) also proposed that non-healing VLUs often have a prolonged inflammatory phase of healing, which is usually related to heavy bio-burden, which is marker of the metabolic load of multiplying bacteria in wounds (Warriner et al, 2005). Recent microbiological studies suggest that 80–100% of VLUs may be critically colonised with bacteria and tend to be infected, confirming the direct relationship between infection and delayed healing in VLUs (Moore et al, 2010). Davis (1996) first described critical colonisation as the multiplication of bacteria without causing invasion. No agreed definition of 'critical colonisation' (CC) currently exists (Leaper 2006), yet it is used in clinical studies to define the delay in wound healing by microbial factors without overt clinical signs of infection (Cutting, 2003). Use of microbiological tests has been demonstrated to more reliably identify CC than clinical assessment (White and Cutting 2008).

Prevention and management of infection in patients with wounds is a debatable issue, particularly in light of the growing number of resistant microorganisms, lack of consensus on the definition of wound infection, inappropriate antibiotic use, allergy and toxicity risks of topical antimicrobials (Leaper, 2006; Atiyeh et al, 2007). Silver, which is known for its broad spectrum of antibacterial properties (Marx and Barillo 2014), is recommended by the International Consensus (2012) to control bio-burden or localised infection in chronic wounds, including VLUs. The literature describes a remarkable increase in the use of different forms of silver-containing dressings (SD) for chronic wounds, such as VLUs (Leaper, 2006; Lo et al, 2008; 2009; Carter et al, 2010; Toy et al, 2011). This research also reports their effectiveness in managing infection

and increasing healing rates. However, two recent Cochrane reviews on the efficacy of SDs provided contradictory conclusions with regards to improving healing rates of VLUs (Vermeulen et al, 2007; O'Meara et al, 2014). This review will discuss the controversial and diverse conclusions of clinical studies on the use of silver in the management of patients with VLUs.

History of silver in medicine

Silver is known for its preservative antimicrobial properties (Alexander, 2009). Hippocrates (460BC–370BC) believed in its beneficial healing and anti-disease properties, while ancient Phoenicians (1550BC–300BC) used to store water, wine and vinegar in silver vessels to prevent spoiling (Alexander, 2009). In 1880, Crede used silver nitrate (SN) to prevent neonatal eye infections (Burrell, 2003), whereas in 1890, Crusius used SN to treat burn wounds (Lansdown, 2004). Use of SN as an antimicrobial for minimising postoperative infection in surgical wounds continued until it lost favour following the introduction of antibiotics in the 1940s (Alexander, 2009).

Silver in wound care

In the 1960s, the use of silver re-emerged for use in wound healing (Burrell, 2003). Silver compounds (SCs), such as 1% silver sulfadiazine cream (SSD) and 0.5% SN solution, became widely used as topical antimicrobial agents to treat burns and manage postoperative wound infection (Moyer et al, 1965; Fox, 1983). The silver within these compounds is reported to provide the primary bactericidal effect, while the sulfadiazine and nitrate have bacteriostatic properties, according to Klasen (2000). Bactericidal action is the ability of an antimicrobial substance to kill microorganisms, while bacteriostatic action is its ability to inhibit the action of the proliferation of microorganisms by disrupting their cell membranes (Marx and Barillo, 2014).

Although SCs have been the standard topical antimicrobial therapy for burns for many years (Atiyeh et al, 2007), adverse effects, such as argyria, leukopenia, hyponatremia, hypochloremia, and hepatic and renal toxicity, have been documented in patients, however, the number of these reports is small (Klasen, 2000; Lansdown, 2002). Thus, the use of newer preparations of silvers combined with dressings such as foams, hydrogels, hydrocolloids, alginates and meshes for wounds healing by secondary intention have been developed with the aim of eliminating adverse effects (Leaper, 2006; Adhya et al, 2014).

Silver dressings, mechanism of action and bactericidal effect

Current SDs differ in terms of their chemical formulations (elemental or metallic silver), amount of silver within the dressing, and prolonged ion release time (Marx and Barillo, 2014). However, the common claim among them is the antimicrobial action of the silver ion; while some dressings release this into the wound bed to act on the micro-organisms, some of them do not release silver and they kill the micro-organisms that are in direct contact with the silver dressings (White et al, 2006; Marx and Barillo, 2014). The silver impregnated into dressings is inert and cannot kill bacteria. However, when exposed to an aqueous environment, such as wound exudate, it becomes ionised (Lansdown, 2002). Ionised silver is highly reactive as it binds to the bacterial cell-surface receptors, yeasts and fungi, and initiates its antimicrobial effect (White and Cutting, 2006).

Four mechanisms are suggested to be responsible for the antimicrobial effects of ionised silver. These include its ability to: damage bacterial cell walls and membranes, inhibit respiratory enzymes, bind to microbial DNA and RNA to prevent transcription and division, and destroy bacterial cells by releasing silver free radicals into the cell to bind and precipitate proteins with thiol and cysteine groups that lead to the cell death (Legler et al, 2001; Cutting et al, 2007; Marx and Barillo, 2014). Warriner and Burrel (2005) proposed that it is unlikely for an organism to develop resistance to silver because of these multiple antimicrobial actions against bacterial cell systems.

Based on the existing *in vitro*, *in vivo* and clinical evidence supporting the effectiveness of SDs in managing infection, clinical guidelines recommend its use to reduce wound bio-burden, treat local infection and prevent systemic spread of infection, and suggest their use for short periods before re-evaluation of the wound status (Leaper, 2012).

Studies examining the efficacy of silver dressings in healing VLUs

A recent Cochrane review by O'Meara et al (2014) identified five randomised controlled trials (RCTs) studying the effectiveness of SDs on the healing rates of VLUs. Jorgensen et al (2005) investigated the effect of treating patients with VLUs and mixed venous/arterial ulcers (ABPI>0.65) that had delayed healing and were considered to be CC, with a silver-releasing foam (Contreet® Foam, Coloplast A/S, Denmark) against a hydrocellular foam dressing (Allevyn®, Smith & Nephew, UK) in a multicentre RCT over 4 weeks.

One hundred and twenty-nine participants were selected based on the inclusion/exclusion criteria and randomised into a study group (SG) (Contreet Foam) (*n*=65) and a control group (CG) (Allevyn) (*n*=64) using computer-generated randomisation. No clear information was provided on how CC was diagnosed, or regarding group allocation or blinding of participants and outcome assessors. This increases the risk of selection bias, performance bias, and detection bias and questions the reliability of the study. There were no imbalances between groups at baseline.

The results showed that the median relative reduction in wound size was statistically significant in the SG versus the CG (45% vs 25%, respectively; *P*= 0.034). However, there was no difference with regards to complete wound healing during the trial 5/65 (8%) and 5/64 (8%) ulcers healed in the SG and CG, respectively, although the *P* value was not reported. The authors failed to provide a full outcome data report and reference to sample size/power calculations, which could have led to a biased and underpowered study. Nevertheless, the significant decrease in odour, better exudate management, reduction in leakage and maceration in the SG compared to the CG, provides evidence on the superior performance of SD in the healing rate of VLUs.

In the same year, a multicentre RCT by Meaume et al (2005) reported contradictory findings. The authors compared VLU rates over a 4-week period with a silver-releasing calcium alginate dressing (Silvercel®, Systagenix, UK) and a calcium alginate dressing (Algosteril®, Smith & Nephew Ltd, UK) in 71 patients considered to have CC wounds. Patients were selected based on the inclusion/exclusion criteria and were randomised into SG (Silvercel) (*n*=38) and CG (Algostril) (*n*=33) using a computer-generated randomisation programme. CC was confirmed if a patient had at least two of the following signs: pain, erythema, oedema, heat and moderate-to-high levels of exudate. No information regarding methods of random sequence generation, allocation concealment, blinding of participants and blinding outcome assessors was reported, which increases the risk of selection bias, allocation bias, performance bias and detection bias.

A larger proportion of SG participants withdrew (23%; 9/38) compared to CG (18%; 6/33), which increases the risk of attrition bias. Although there is no universally accepted standard regarding acceptable losses to follow-up in an RCT, more losses in one group compared to another may cause asymmetric distribution of the population and lead to attrition bias (Polit and Beck, 2012).

The median baseline ulcer area and duration were comparatively greater in the SG. Therefore, the use of clinical signs of infection to identify CC, the larger ulcer area and duration reported at baseline among the SG and the loss of 20% of SG participants during the study may have impacted the results, increasing doubt around validity of the outcome. The results demonstrated no statistical difference in complete wound healing (SG 1/38 vs CG 1/33, 95% CI – 0.06 to 0.05) and wound size reduction (SG 23.7% vs CG 24.0%, 95% CI – 17.08 to 16.48).

Munter et al (2006) conducted a large multicentre RCT (*n*=415) on the effectiveness of SDs on VLUs and mixed venous/arterial ulcers with delayed healing over 4 weeks. The study compared silver-releasing foam dressings (Contreet Foam) with local best practice, which included foam/alginate dressings (53%), hydrocolloid dressings (12%), gauze (3%), other silver dressings (17%), other antimicrobial dressings (9%) and other active dressings (6%). Using a computer-generated list in sealed envelopes, patients were randomly allocated based on the inclusion and exclusion criteria into SG (*n*=218) (VLUs 150/218; venous/arterial 68/218) and CG (*n*= 197) (VLUs 147/197; venous/arterial 50/197). No data on microbiological assessment or participant and outcome assessor blinding were discussed, which might lead to performance bias and detection bias. However, at baseline, it is apparent the median ulcer size of participants in the SG was 60% higher than those in the CG.

The results showed a statistically significant reduction in the median ulcer area (SG 45.5% vs CG 28.8%; *P*=0.0001) while no noticeable difference in complete healing by end of week four was noted between groups (25/218 vs 21/197, SG and CG, respectively, 95% CI- 0.04 to 0.05). Despite the significant difference in the ulcer sizes at base line, potentially favouring the CG the statistical analysis gained strength from the large sample, which supports validity of the outcome.

In 2008, Lazareth et al carried out a multicentre RCT (*n*=102), examining the effect of a contact-layer silver dressing (Restore Silver®, Hollister Wound Care, USA) versus the same contact-layer dressing without silver (Restore®, Hollister Wound Care, USA) on patients with VLUs with delayed healing, for example, CC. CC was defined as the presence between 3–5 clinical signs of heavy bacterial

load (pain, erythema, oedema, malodour, and heavy exudate). Using a random list balanced by blocks of four patients, each centre received at least four sealed envelopes with a number corresponding to the chronological order of patients' inclusion.

Participants were allocated into SG (*n*=52) and CG (*n*=50). No statement was given on participant and outcome assessor blinding, which might lead to performance bias and detection bias. VLU characteristics were comparable across groups at baseline. However, the withdrawal rate in the CG (28%; 14/50) was significantly higher than the rate in the SG (6%; 3/52), which is considered to be a high risk of attrition bias. The results showed a statistically significant reduction in the median percentage of the ulcer area at 4 weeks (SG 28.1% vs CG 8.6%; *P*=0.04) and at 8 weeks (SG 36.6% vs CG 6.2%; *P*=0.01). While the results of complete wound healing at 8 weeks favoured the CG, this was not statistically significant (SG 2/52 vs CG 5/50).

Despite the significant increase in healing rate of VLUs in the SG, the high risk of attrition bias owing to the high withdrawal rate from the CG and the use of clinical signs of infection as criteria to identify CC might call into question the reliability of generalising the findings to the general population.

More recently, Michaels et al (2009) conducted a prospective multicentre RCT on the clinical and cost effectiveness of SDs versus non-silver low-adherence dressings to treat patients with VLU (VULCAN trial). The authors randomised 213 patients using a computer programme to a SG (*n*=107) who received antimicrobial silver dressings versus a CG (*n*=106). The SD was selected by clinicians from a pre -approved list (Aquacel® Ag; Convatec, Acticoat™, Acticoat™7, Acticoat™Absorbent; Smith & Nephew, Contreet Foam; Coloplast and Urgotul® SSD; Urgo), while the control dressing was specified as any non-antimicrobial dressing from any manufacturer (most were knitted viscose dressings). The main outcome measured was the rate of complete healing at 12 weeks. There were no imbalances between groups at baseline. No information on signs of ulcer infection or CC was reported.

The authors concluded that there was no statistically significant difference between the use of SG and CG dressings for the proportion of ulcers healed and time to healing. The median time to healing in the SG was 67 days (95% CI – 54 to 80) versus 58 days in the CG (95% CI – 43 to 73) (*P*>0.05), while the percentage of participants with complete ulcer healing at 12 weeks in the SG was 62/107 (58%) versus 59/106 (56%) in the CG (*P*>0.05). Based on the results, the authors suggested there was no general and regular indication for the use of SD to promote the healing of VLUs.

Despite the high quality of the VULCAN study design, its main limitations are the use of various types of SD with varying concentrations and different release rates of silver ions, long-term use of SDs (12 weeks), use of SDs to heal VLUs rather than to control bio-burden; and having no laboratory or clinical assessment of bio-burden made. These aspects contradicted recommendations of prior studies on the use of SDs in the management of infection in chronic wounds (Dowsett, 2004; Leaper, 2006; Chopra, 2007). However, reviewers have considered these conclusions to be potentially misleading, possibly even negatively impacting clinical practice (Gottrup and Apelqvist, 2010; Leaper and Drake, 2011).

O'Meara et al (2014) concluded that despite the identified risks of bias issues the overall quality of the trials discussed was not low. Nevertheless, issues such as use of improper tools to identify CC (Meaume et al, 2005; Lazareth et al, 2008), failing to report wounds' microbiology status (Jorgensen et al, 2005; Munter et al, 2006; Michaels et al, 2009), and discrepancies between group baseline parameters (ulcer sizes) that were not taken into account during outcome analysis (Meaume et al, 2005; Munter et al, 2006), as well as losses of patients to follow-up by 20% or more in one group (Jorgensen et al, 2005; Lazareth et al, 2008), and generalisability of trial results to populations (Michaels et al, 2009), remains a source of bias with a potentially undesirable impact on the outcome validity.

Conclusion

The evidence concerning the efficacy of SDs in the treatment of VLUs is confusing and revealed that such interventions have not been appropriately validated. This discrepancy is based on the use of complete healing as an endpoint, which is imposed upon by regulatory bodies, such as the Food and Drug Administration of the USA in clinical trials (Stromberg et al, 1994; Enoch and Price, 2004).

As a consequence, many studies rely on partial wound-healing outcomes as end points to determine improvements in VLU healing. However, the use of SDs was never recommended to directly promote wound healing, but rather to control or reduce bio-

burden in hard-to-heal VLUs which, if not addressed, does lead to delayed healing and increase the overall cost of treatment (Jemec et al, 2014). Furthermore, there is a need for properly powered clinical trials according to international standards to guide the use of SDs in the management of VLUs in clinical practice in the future. WME

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