The use of a non-adherent lipido-colloid dressings with silver in the management of wounds


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Silver has been used in wound care throughout the millennia for its antimicrobial properties. It was used by many cultures, predominantly in times of war, as an antimicrobial reservoir for food and water, from the ancient Phoenicians, Greeks, Romans and Egyptians, up to the Second World War (Alexander, 2009). The first mention of silver as a medicine comes from Hippocrates, who used silver particles in wounds for its beneficial therapeutic effects and anti-disease properties (Fong, 2005). Meanwhile, John Woodall recommended the use of silver nitrate in chronic wound management as early as 1617 (Klasen, 2000).

Although the antibacterial activity of the silver (Ag+) ion has been known since the studies conducted by Billroth in 1874 (Majno and Joris, 1979), it is Moyer who is recognised as the person who brought silver 'back to life' in wound care in 1965 for use in burn patients (White, 2001).

Silver was regulated by the US Food and Drug Administration in the 1920s as an antimicrobial for wound management (Hugo and Russell, 1982) and then, in the use of silver sulfadiazine by Fox in 1968 for use in burns patients as a broad-spectrum antibacterial agent, which led to a reduction in wound infection and sepsis, paving the way for this management to be included in many treatment protocols (Fox, 1967; Munster et al, 1970).

In wound management, the antimicrobial activity of silver is achieved as the silver ions bind to and hinder bacterial proteins and nucleic acids, and stimulate the generation of reactive oxygen species. The silver ions bind to bacterial walls, disrupting the walls and leading to cell death (Vermeulen et al, 2007). The ions also bind to bacterial enzymes, preventing them from functioning, and bind to the bacterial cell DNA, interfering with cell division and replication (Jude et al, 2007). The Silver Institute (2019) explains that silver interrupts the ability of bacteria to form the chemical bonds essential for its survival: "Silver ions can penetrate the cell walls of bacteria — without injuring mammalian cells — thus destroying the chemical and structural bonds essential for the bacteria's survival and growth." Silver has been more widely used in wound management as a broad spectrum antimicrobial in general wound management probably due to the spread of methicillin-resistant *Staphylococcus aureus* (MRSA) and the toxicity of other topical disinfectants (Vermeulen, 2007).

The controversy

Michaels et al (2009) published the VULCAN Study, which was a randomised controlled trial that included 213 patients with venous leg ulcers, which are commonly treated in the community without any selection criteria based on their clinical status (i.e. VLU presenting risk of infection or signs of bacterial colonisation).

The VULCAN study aim was to compare the wound healing time between the study group (treated with silver) and control group (standard of care). This pragmatic RCT was promoted by the National Health Service (NHS) in the UK, which was worried about the dramatic increase of use of silver dressings in the community. The conclusion suggested there was no statistically significant difference between the use of silver-containing dressings (of all types, including those impregnated with silver sulfadiazine) and the neutral control dressings in healing and recurrence, and the cost-effectiveness analysis found a higher cost associated with the silver

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dressings. The main issue with this trial is that it only analysed wound area reduction, but did not investigate wounds either clinically or microbiologically for presence of infection (Ayello et al, 2012). Furthermore, the trial was over 12 weeks — silver dressings are not intended for such an extended period, more so if infection is not present in the wound (Ayello et al, 2012).

The control of bioburden was never the main outcome of the trial, while the reason for use of antimicrobials is management of infection (Ayello et al, 2012). This international Consensus Document concludes that "it is unfortunate that the study findings have been generalised to suggest that silver dressings do not work and to justify withdrawal of their availability to clinicians".

Many studies have reached beneficial conclusions in regards to silver dressings' cost effectiveness and the same Consensus Document lists the following conclusions as regards to the utilisation of silver in wound management: reduced time to wound healing (Muangman et al, 2010; Koyuncu et al, 2010) shorter hospital stays (Paddock et al, 2007; Saba et al, 2009); reduced dressing change frequency (Caruso et al, 2006; Opasanon et al, 2010); reduced need for pain medication during dressing change (Caruso et al, 2006); and fewer MRSA bacteraemias resulting from MRSA-infected wounds (Newton, 2010).

Silver is indicated when a local negative impact of bacterial colonisation is suspected and/or confirmed (Lazareth et al, 2012) as it has a broad antimicrobial effect against both Gram-positive and Gram-negative bacteria, including *Pseudomonas aeruginosa*, MRSA and *vancomycinresistant enterococcus* (VRE), as well as some fungi, viruses and protozoa (Lansdown, 2002). It has not only been established as a broad spectrum antibacterial agent that has bactericidal ability against strains that are present in chronic wounds, but also shows low toxicity on fibroblasts (Tomaselli, 2006).

Furthermore, Silver et al (2006) stated that there is very low risk of resistance in relation to use of silver as a topical antimicrobial due to the properties of the antimicrobial involving several membrane- and nucleus-based sites.

Non-adherent lipido-colloid dressing with silver

Technology Lipido-Colloid (TLC), which was developed by Laboratoires URGO (France) comprises a matrix containing hydrocolloid and lipophilic substances; it has been shown to promote the proliferation of fibroblasts (Bernard, 2005), which contributes to the formation of new tissue (McGrath et al, 2014). In contact with exudate, hydrocolloid polymers are hydrated and constitute with the petrolatum part of the dressing, a lipidocolloid interface, which is designed to reduce adhesion to the wound surface, whether the wound is acute or chronic (Meaume et al, 2002).

The lipidocolloid interface is very cohesive and facilitates dressing removal; in addition, the open weave of the polyester is non-deformable and maintains the 500µm size when impregnated, thus reducing the chance of granulation tissue growing through and the consequent risk of trauma on removal (Meaume et al, 2002), leading to a painless removal (Meaume et al, 2004).

During a study by Bernard et al (2005), where TLC was compared to other contact layers, it was proven that this technology enhances fibroblast proliferation through local interactions with the cells by not only providing non-adherence, but also promoting a moist wound environment. The authors concluded that the favourable wound healing results obtained clinically on both acute and chronic wounds with TLC seemed to be due not only to the non-adherent and atraumatic characteristics of its composition, but also to local interactions with the cells in the wound environment (Bernard et al, 2005).

In another *in vitro* study conducted by the Bernard et al (2007), through the TLC's promotion of moist wound environment and non-adherence, it synthesises various extra-cellular matrix (ECM) macromolecules (particularly collagen and hyaluronic acid) as the technology showed stimulation and formation of the extracellular matrix of a static fibroblast cell culture by increasing collagen synthesis and hyaluronic acid synthesis. The study concluded that the TLC healing matrix increases hyaluronic acid and collagen production, which helps to generate the extra-cellular matrix, providing the dermis its definitive structure, flexibility and strength, thus guaranteeing optimal healing (Bernard et al, 2007).

Silver has been incorporated into the TLC healing matrix to provide its antimicrobial properties. Silver sulphate (3.5%) was combined with UrgoTul® (Urgo) to produce UrgoTul Ag/Silver® (Urgo), which is indicated for the treatment of non- to low-exuding acute wounds (burns, skin abrasions, traumatic injuries and second-degree burns) and chronic wounds showing signs of infection (White et al, 2015).

They can also be used on more heavily exuding wounds when used in combination with an absorbent dressing (White et al, 2015) or when it impregnates polyacrylate fibres (UrgoClean Ag®), an absorbent dressing impregnated with TLC-Ag matrix, which present additional desloughing properties (Dalac et al, 2016). According to the Laboratoires URGO Product File, TLC-Ag contains 0.35 mg/cm^2 of silver ion, brought by silver sulfate (0.50 mg/cm^2). Silver sulfate is a silver complex, their structural formula is Ag2 S04. In contact with the wound exudate, the silver sulfate breaks down (Ag2S04 -> 2 Ag+ + S042) and releases the Ag+ ion, while the CarboxyMethylCellulose particles swell to form a surface hydrocolloidal film. It is suggested that this controlled supply of Ag+ at the surface into the lipido-colloid gel guarantees a constant antibacterial activity, strictly in contact with the wound (Laboratoires URGO, 2009).

The evidence

An *in vitro* analysis was conducted by White et al (2015) to determine the antibacterial properties of the TLC Ag dressings on the survival of *Staphylococcus aureus*, *Pseudomonas aeruginosa*, *S pyogenes*, *C albicans* and *E coli* colonising acute and chronic wounds, along with strains resistant to antibiotics: MRSA, Multi-Resistant *Staphylococcus aureus* (MRB) and VRE, to determine the survival curves of the different microorganisms relative to the population observed with a control dressing without silver. The samples of dressings were inoculated with a bacterial suspension of 108 colony-forming units (CFUs) and then incubated. The number of surviving bacteria was calculated daily up until day 7. From day 1 and throughout the duration of the study, the reduction in the number of CFUs for all the bacterial strains studied was greater than 105, making it possible to conclude that the TLC-Ag contact layer demonstrates antibacterial efficacy on the microorganisms tested *[Figure 1]*.

A French multicentre, phase III, controlled, randomised trial in 24 investigating centres was conducted in two parallel groups where the first cohort was treated with the TLC-Ag interface dressing for 4 weeks followed by the neutral TLC dressing until the 8th week of treatment, while, the second control cohort was treated with the neutral TLC dressing throughout the 8-week follow-up period (Lazareth et al, 2008). The patients included in the trial were seen weekly until the 4th week of treatment (week 4), then every 2 weeks until week 8.

The efficacy of these two therapeutic strategies was judged on the basis of the primary study endpoint: reduction in the surface area of the ulcers treated at the end of the two treatment phases, at the 4th and 8th weeks of treatment with the study dressings. The ulcer surface areas were reported by the investigating physician on a planimetric record, weekly for the first 4 weeks of treatment then every 2 weeks until week 8. At the end of the trial, these surface areas were read digitally for statistical analysis of the results.

At the end of the first 4 weeks of treatment, the surface area of the ulcers (median value) had

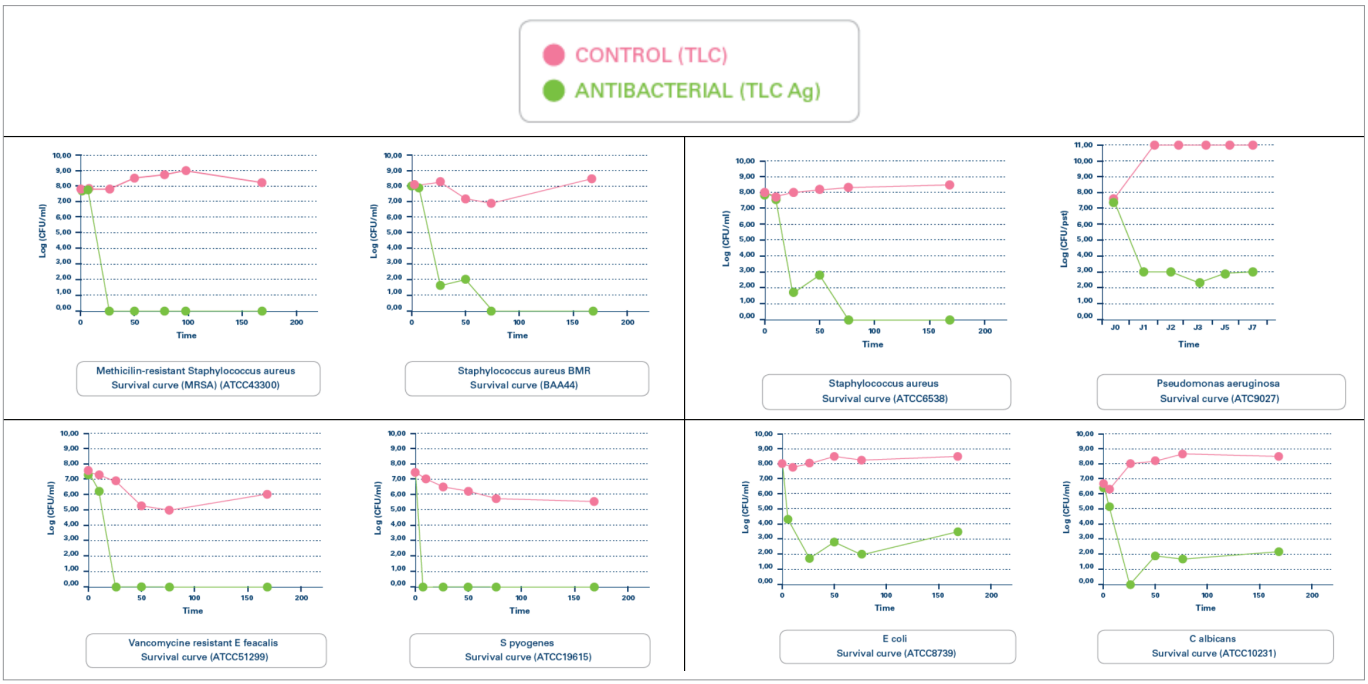

Figure 1. Results of in vitro *analyses of the bacterial survival curves showing the antimicrobial activity of the TLC-Ag contact layer in comparison with the same dressing without silver. Graphs portray the reduction in the number of CFU for all the bacterial strains studied.*

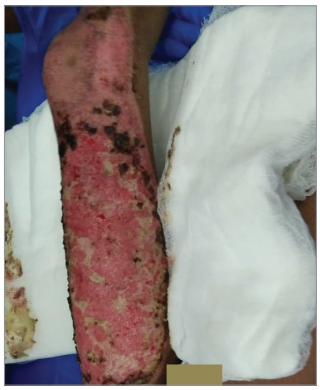

Figure 2. On presentation.

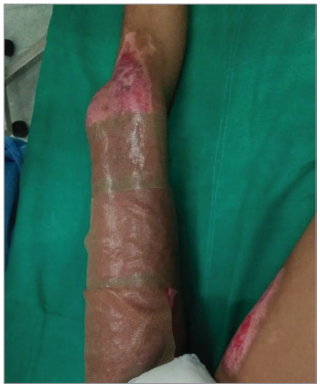

Figure 3. Application of UrgoTul Ag.

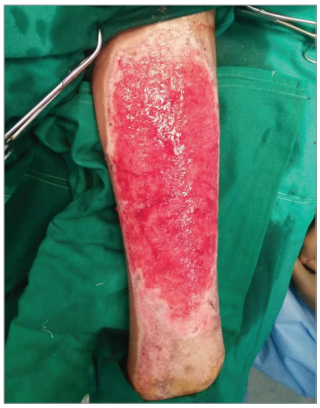

Figure 4. Wound after two dressing changes.

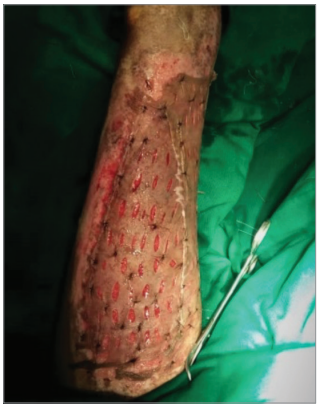

Figure 5. Split-thickness skin graft applied.

decreased by 4.2 cm^2 in the TLC-Ag group versus 1.1 cm^2 in the control group (*P*=0.0223). From the 4th week of treatment, after replacement of the TLC-Ag dressing by the neutral TLC dressing in the sequential group, the reduction in surface area continued in the group previously treated with the TLC-Ag dressing, in contrast with that observed in the control group. At the end of follow-up, the ulcer surface area (median value) had decreased by 5.9 cm^2 in the sequential group versus 0.8 cm^2 in the control group (*P*=0.002). At the end of the 8 weeks of treatment, the relative surface area reduction of the ulcers (median value) was significantly greater in the TLC Ag sequential group: 47.9% versus 5.6% in the neutral TLC group (*P*=0.036). The clinical score for wound colonisation (defined by the presence of clinical signs among five pre-specified signs at baseline) was significantly lower in the TLC-Ag group than in the neutral TLC group (1.43 versus 2.31, respectively (*P*=0.0001), while the number of patients presenting a surface area reduction of greater than or equal to 40% of the initial surface area was higher in the sequential TLC-Ag group: 54.9% of ulcers versus 35.4% in the neutral TLC group (*P*=0.051) with an odds ratio (multinominal logistic regression) of the chances to reach this endpoint of 2.7 (95%CI: 1.1–6.7. *P* =0.038) in favour of the silver group.

The number of local adverse events (LAEs) demonstrates the same distribution in both groups (11 LAEs in the TLC-Ag and neutral TLC groups). The acceptability was assessed at each dressing change by paramedical personnel throughout the duration of the trial. Since the study was sequential for one of the groups in the study (successive use of the TLC-Ag dressing for the first 4 weeks then of the neutral TLC dressing for the next 4 weeks), it was necessary to split the acceptability results into two periods: period 1 (day 0 to week 4) and period 2 (week 5 to week 8).

During the first period, no significant difference in terms of adherence to the wound, maceration, ease of application and conformability of the dressing to the wound, was observed, given the predictable similar behaviour of the two study dressings, which only differ in terms of the presence of silver ions in the TLC-Ag dressing. Laboratory tolerance assay of blood silver levels were conducted to analyse if silver ion passes into the blood stream (argyremia) following the use of the TLC-AG dressings at day 0, week 4 and week 8. It was shown that the TLC-Ag dressing did not induce any increase in blood silver levels in patients treated with the silver dressing.

Case

This case came courtesy of Dr. Uma Shankar at ABC Hospital, Trichy, India. An 8-year-old female presented with a 2-week-old burn on the left thigh on January 19, 2018 *[Figure 2]*, measuring 20 cm x 8 cm. The pain score was moderate to severe and the wound had moderate exudate. After cleansing with normal saline, the wound was dressed with Urgotul Ag *[Figure 3]*. The dressing was changed every 3 days. After two dressing changes, pain and exudate levels had subsided and the wound bed appeared healthy *[Figure 4]*. A split-thickness skin graft was also applied *[Figure 5]*.

Conclusion

Complications of wound infection are multifactorial, including direct delayed wound healing, increase of morbidity and mortality, and increase in cost, but wound infection also deteriorates the health-related quality of life of the patient due to pain, increase in exudate and malodour. The clinician needs to have in his/her toolbox a dressing that has been proven both scientifically and clinically. Urgotul Ag has shown its positive clinical outcomes and benefits both *in vivo* and *in vitro*, which suggests it is a viable option in providing wound care experts support in the challenge of wound infection in an efficient and effective manner. WME

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