Silver dressings in wound healing: what is the evidence?

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Abstract

Silver has a long history of medicinal use based on its antimicrobial effects. Microbial burden can delay wound healing and makes silver an attractive local antiseptic for wounds affected this way, especially as antibiotics have limitations. Whilst there is good evidence in preclinical studies of the effects of silver on microbes and on processes that delay wound healing, evidence for the benefits of silver products on human wound healing is still far from robust. At this stage, silver products should be confined to adequately assessed wounds that are failing to heal with cheaper products, especially where microbial burden appears to be delaying healing.

There are a range of silver products currently available, with differing formulations and delivery of silver, and differing product bases. Current evidence does not clearly demonstrate that one product is more effective that another, and choice of an initial product will be based on wound and patient characteristics, product availability and practitioner familiarity and preferences.

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Introduction

Silver dressings are increasingly available and used in wound management. They are extensively marketed, with all major wound product manufacturers providing them. At the July 2004 World Union of Wound Healing Societies meeting in Paris, lavishly produced seminars heavily promoted silver products – one even had silver-coated acrobats performing a choreographed acrobatic routine.

These products are expensive and, to date, this cost is often born directly by the patient, who may pay in excess of $A200 a week just for the silver product. Do these products justify this usage and cost? This article will examine the rationale behind silver dressings, evidence for their effectiveness, and offer some suggestions on the place of silver dressings, based on the evidence we have.

History of silver in wound care

Precious metals have, throughout the ages, attracted interest regarding their health-giving properties [1]. Silver coins were used in the Middle Ages to purify water, an early recognition of the antimicrobial effects of silver. Numerous wound salves used metallic components, including silver. Silver nitrate was recognised as an antiseptic in the 19th century and is used to the present day.

The first appearance of silver sulphadiazine cream (SSDC) was in 1968 [2] when it revolutionised the management of burns by dramatically reducing *Pseudomonas aeruginosa* and other infections; this is an area where it is still extensively used today. Unfortunately, SSDC has several weaknesses, including a relatively short action, with the silver ions rapidly combining with tissue chloride, sulphydryl groups and other parts of proteins to produce insoluble and inactive silver compounds including silver sulphide. Thus, SSDC needs to be applied at least daily. It also produces an adherent eschar which needs to be removed for optimal wound management – often a difficult and painful process. SSDC can also macerate wounds.

Attempts to build on the benefits of silver, avoid the limitations of SSDC and utilise new moist wound management principles has led to the new generation of silver products. These products either provide a constant release of silver ions into the wound or absorb wound exudate and bacteria into the silver-containing dressing. The formulations of silver include inorganic silver compounds or a microcrystalline silver metal formed by nanotechnology (nanocrystalline) [3]. Worldwide, 10 separate silver products were available in mid 2004; the products currently available in Australia are shown in Table 1.

Microbial organisms and wound healing

The rationale for silver is largely based on the effects of microbes (bacteria and other microscopic organisms) on wound healing. Microbes are present in all chronic wounds

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Table 1. Silver products available in Australia (May 2005).

Product Name	Product type	Manufacturer	Silver formulation
Acticoat & Acticoat-7	Polyethylene mat	Smith& Nephew	Nanocrystalline
Acticoat Absorbent	Alginate	Smith& Nephew	Nanocrystalline
Atrauman Ag	Tulle	Hartmann	Metallic silver
Avance	Foam	Aaxis Pacific	Released silver ion remains in product
Aquacel Ag	Hydrofibre	ConvaTec	Slow-release ion
Contreet	Hydroactive	Coloplast	Metallic silver complex
Contreet-H	Hydrocolloid	Coloplast	Metallic silver complex
Polymem silver	Foam and additives	Ferris	Nanocrystalline
Actisorb 220*	Charcoal	Johnson& Johnson	Not released-bound to product

*Not available in Australia – included as an example of a product which does not deliver silver into the wound.

and can rapidly contaminate acute wounds open to the environment. It is useful to categorise the presence of microbes along a continuum – from contamination, through to critical colonisation, then infection.

Contamination may be helpful to wound healing, through promotion of beneficial inflammatory processes and an increase in blood flow [4]. Infection, however, is detrimental to wound healing. Bacteria, the most common microbes to cause wound infection, can produce endotoxins which result in elevation of cytokines such as interleukin-1 and tumor necrosis factor, which in turn adversely effect wound repair [5-7]. In particular, matrix metalloproteinases can increase in response to these cytokines, and growth factor production decreases [8, 9]. These changes impair wound healing. Local wound infection can extend to invasive infection which can directly damage surrounding healthy tissue, increasing wound size and further delaying healing. Bacterial infection is also associated with vessel occlusion which can cause wound hypoxia, further delaying healing [10].

An emerging concept is critical colonisation, a stage between contamination and infection which, unchecked, may progress to invasive wound infection. In this stage, the granulation tissue in the wound bed develops an unhealthy appearance but there is no invasion of tissue and the traditional clinical signs of infection, apart from delayed wound healing, are absent [11].

Bacteria on wound surfaces do not usually exist as free-living organisms but as complex communities called biofilms. These consist often of several types of microbes, embedded in a polysaccharide matrix excreted by the microbes. In many respects, a biofilm functions like a single organism – it has its own internal environment and forms channels which allow movement of nutrients and waste products [12]. A biofilm can even sense external environmental factors such as nutrient availability.

Bacteria within a biofilm alter their structure and may develop a slower metabolic rate and growth pattern. This slowing, along with the protective effect of the matrix, makes bacteria in biofilms up to 1,000 times more resistant to conventional antibiotics [13] and justifies other approaches to control such as topical enzymatic debridement agents and antiseptics. It is felt that biofilms are present in the majority of critically colonised wounds and harbour the bacteria that progress to cause infection. Similar processes are well recognised in the biofilms that invariably coat chronic in-dwelling catheters.

The importance of controlling microbes in wounds has been recognised in the recent emphasis on wound bed preparation to promote wound healing [11, 14, 15]. The European Wound Management Association has produced a practical document on wound bed preparation based on the acronym TIME (Tissue, Infection/Inflammation, Moisture imbalance and the Edge of the wound), clearly emphasising the importance of microbial load being controlled [16].

Whilst bacteria receive most attention in the context of infections and delayed wound healing, other organisms may also be detrimental. Fungi have been recognised as pathogenic to burns [17, 18]. A recent Australian study showed fungi may also contaminate leg ulcers [19], so an approach which is

effective across a range of microbial types may be more likely to promote wound healing.

The effects of silver on microbial organisms

Our understanding of the detrimental effects of bacteria and other microbes on wound healing is unfortunately not matched by an equally extensive range of effective approaches to control microbes. When wide clinical use of penicillin was beginning in the 1940s, it was felt that the age of infection was soon to be left behind, but now terms such as the 'post antibiotic era' are being used. The crux of this problem is antibiotic resistance – microbes have proven very resourceful in developing resistance to our ever-increasing antibiotic arsenal. The often inappropriate use of antibiotics has contributed to the problem – two thirds of world-wide antibiotic use in humans is without a prescription and there is extensive antibiotic use in animals.

The renewed emphasis on basic principles such as hand-washing is an important way to reduce infections [20], but it will never eradicate wound contamination and colonisation. Topical antibiotics can be used, but may also lead to resistance and can sensitise the skin. We need effective non-antibiotic local approaches to control critical colonisation in wounds.

Topical antiseptics can be rapidly effective against a range of organisms that contaminate and may infect wounds, and are less likely to be associated with resistance as they are short-acting. They may also more effectively penetrate biofilms through their topical application. Examples of topical antiseptics include silver, chlorhexidine, ethanol and iodine.

Unfortunately, there is a paucity of high quality randomised controlled clinical trials demonstrating the effects of topical antiseptics on wound healing, despite this seeming to be an important and not overly challenging area to investigate. The scant published evidence mainly studies cadexomer iodine, but lacks large, randomised trials [14, 21]. Nevertheless, topical antiseptics are an attractive alternative to antibiotics for critically colonised wounds. For clearly infected wounds, antibiotics and debridement are required – topical antiseptics alone should not be relied upon.

Silver is attracted to the proteoglycans in microbial cell walls. Mammalian cells lack this, so are generally not affected by silver – this is important, as any wound management product should spare new epithelium and other cellular components of healing. Silver has been shown to denature microbial proteins, impairing their ability to ingest and process food substances, reducing their metabolism and growth [22]. Silver has also been shown to affect microbial DNA [22]. It is thus a logical choice as a topical antiseptic. Importantly, very little resistance has been detected to date, although isolated cases have been reported [23, 24]. Encouragingly, cross resistance to antibiotics and silver is extremely rare.

To be effective, silver must be delivered to tissue in ionic form, and in sufficient concentration. Alternatively, microbes absorbed into the dressing must encounter silver in a sufficient concentration. Low silver concentrations in the wound are rapidly mopped up by tissue fluid and proteins. The needed concentrations require either application of large amounts of silver frequently, such as with silver nitrate and SSDC, or the use of a formulation that releases sufficient silver over prolonged periods of time.

The new silver wound products have been developed to provide this prolonged release. The wound environment is complex and, generally, the silver concentrations required to inhibit microbial growth will be higher than concentrations that are effective in a simple environment. Much has been published on the ideal wound fluid concentration of silver for greatest antimicrobial efficacy, with levels of between 20µg/mL and 60µg/mL quoted [25, 26]. The available silver products vary in silver concentrations and formulations as well as the

degree of silver release, but only good quality evidence will establish the relative merits of these different products.

The new silver products also avoid some of the problems associated with SSDC, including maceration and the formation of a pseudo-eschar. These products are also generally much easier to apply and require less frequent application than SSDC.

Properties of silver

Properties that should enhance the effectiveness of a silver wound management product are:

- Ionic silver is released or contained within the absorbent dressing.
- Silver release is controlled and prolonged.
- Optimal antimicrobial silver concentration is achieved.
- The carrier product provides an optimal wound healing environment.
- The product is not over used.

Silver may have more than an antiseptic effect in wounds. Its use is also associated with reduced inflammation and modulation of matrix metalloproteinases, although this has not been demonstrated in the absence of microbial contamination [27]. These effects may justify a trial of a silver product in a non-healing wound even in the absence of critical colonisation.

Evidence for the effectiveness of silver in wound management products

What is ideal evidence?

The theoretical basis for any benefits of the new silver products outlined above must be matched by high-quality evidence to justify the use of these expensive therapies. The research should demonstrate that these products are indeed antiseptic, and that they have beneficial effects on wound healing in trials, first in animal models then in human wounds.

The 'gold standard' evidence would be a large, randomised trial comparing a silver product to a standard therapy and showing improved wound healing, as measured by a range of outcomes including complete healing, percentage healing and rate of healing. Ideally, the rater wound be blinded to dressing type – it is more difficult to blind the patient or clinician, although at least one trial, described below, has achieved this. Such randomised trials should be performed across the range of wound types that the product was to be marketed for. If it was proposed to confine the product to wounds that had failed a reasonable trial of standard therapies, patients should only be included after such a trial. Trials should be of sufficient duration, as determined by the wound type – at least 12 weeks for chronic ulcers. The results for one product would not automatically be generalisable to other products and thus should be repeated with each product in each target wound type.

In vitro evidence

Preclinical, *in vitro* evidence does exist for silver products. However, caution must be exerted in interpreting *in vitro* results not followed with clinical evidence, as test conditions created in the laboratory significantly differ from the human wound environment [3].

In an elegant series of experiments, Bowler and colleagues partly simulated wound fluid by utilising foetal calf serum then inoculating the fluid with a range of organisms along with a single piece of a silver-containing hydrofibre dressing or a silver-free control [28]. The fluid was reinoculated at Days 4 and 9 to measure the sustainability of any silver effect, and to mimic repeated wound colonisation. The fluid was repeatedly cultured for persistent organisms. The results showed efficacy of this silver product against these organisms for up to 14 days. The organisms included *P. aeruginosa, Serratia marcescens,* Methicillin-resistant *Staphylococcus aureus* (MRSA), vancomycin-resistant *Enterococcus*, anaerobes such as *Bacteriodes fragilis* and yeast/fungi such as *Candida krusei* and *Aspergillus niger.* For most, the inoculum decreased to 0.01% of the original concentration, as compared to a steady concentration in the control fluid.

In an earlier trial, Wright and others compared the activity of SSDC, silver nitrate, nanocrystalline silver and a control against a range of antibiotic-resistant organisms [29]. The organisms were inoculated onto a dressing impregnated with the silver preparation or control, incubated for 30 minutes then washed with a recovery solution which was cultured to determine organism survival. In each case, the nanocrystalline silver dramatically controlled the organism. SSDC was partly effective against only some organisms, but was more effective than silver nitrate. For instance, there were less than two viable *P. aeruginosa* organisms after exposure to the nanocrystalline silver, as compared to eight after exposure to control, SSDC or silver nitrate (p values not given). The relative rate of killing of MRSA after exposure to the three silver forms was much greater for the nanocrystalline silver, although p values were not provided.

Four silver-containing dressings were compared in another *in vitro* experiment. This showed that antimicrobial activity was more rapid with the product containing nanocrystalline

silver, that it was as broad but slower with a silver-containing foam, and that it was less likely to occur in the wound itself with the product which absorbs microbes but does not release silver into the wound. There was little convincing evidence for antimicrobial activity with the fourth product, another silver-containing foam [30].

The same authors, later in the same year, published a larger trial of 10 silver products [31]. Again, products varied in their antimicrobial properties, with some showing little or no effect. Jones and colleagues showed one silver dressing was effective against both aerobic and anaerobic bacteria using a design where the dressing was applied to an inoculated plate and a zone of inhibition of bacterial growth was measured [32]. The control dressing showed no such inhibition.

Studies in animals

In a porcine contaminated wound model, a nanocrystalline silver dressing was shown to promote wound healing, reduce levels of matix metalloproteinases and promote favourable cell apoptosis (rather than pro-inflammatory cell necrosis) [27]. Full-thickness wounds were created on the backs of pigs, contaminated with three different microbes (*P. aeruginosa*, *Fusobacterium* sp. and coagulase-negative *Staphylococci*) then dressed with control or nanocrystalline silver-coated dressings. Healing was assessed either visually or by the ability of the wound to be successfully grafted, as a measure of the quality of the wound base.

By Day 7, all six grafts over the nanocrystalline silver-treated wounds had taken, but all grafts failed on the control wounds. The silver-treated wounds also demonstrated enhanced development of granulation tissue. Wound fluid and biopsies were used for the other assays including examining for microbial colonies. These showed reduced metalloproteinase levels in the silver-treated wounds, as compared with the placebo-treated, and reduced histological evidence of inflammation. Apoptosis was increased. Bacteria were generally seen in the control wounds but rarely seen in the silver-treated wounds.

It may be concluded from these experiments that, in this model, nanocrystalline silver promoted healing by reducing microbial burden and consequent effects on healing, and also improved healing by reducing inflammation and favourably affecting the proteolytic environment. These cellular effects may not be dependent on the presence of microbial organisms, as discussed above, but this trial did not assess this. Whilst pig and human skin have many similarities, they are not identical; indeed, no animal skin is identical – not even primate skin. Thus, these results may not be the same in humans.

Studies in humans

There have, to date, been no large, gold standard randomised controlled trials of silver products in humans. There have, however, been large numbers of individual case reports and case series, small comparator trials and one large non-randomised naturalistic trial. This latter trial, called CONTOP, plans to study 1,000 patients treated either with a silver foam dressing or by standard care. It was initially planned that a block-randomisation design would be used, but conference reports now indicate a naturalistic design has been used.

The results for the first 352 patients were presented in Paris in July 2004. Venous leg ulcers were present in 43-48%, mixed venous/arterial in 20-24%, pressure ulcers in 10% and diabetic foot ulcers in 5-9%. The primary dressing type consisted of a foam or alginate in 45%, hydrocolloid or film in 15%, gauze in 4%, antimicrobial in 30% (silver foam in 48% of these) and a range of other dressings in the remaining 6%. There was a 50% reduction in wound size by Week 4 in those treated with the silver foam, compared to a 30% reduction in the (combined) standard-care groups, with $p=0.002$ for the difference. Dressing type was changed significantly more frequently in the standard care group ($p=0.0001$ for this difference). There was also significantly less odour and pain in the silver group. This study must be interpreted with an awareness of the lack of randomisation or rater blinding and that it has not yet been peer-reviewed.

A small uncontrolled industry-funded case series of 25 patients treated with a silver-containing foam for chronic exudative venous ulcers showed a mean 56% reduction in ulcer area over 4 weeks [33]. In this study, ulcers were not selected for critical colonisation, somewhat supporting the potential role of silver-impregnated dressings in wounds without clear microbial burden. Two other studies funded by the same manufacturer and using a silver hydrocolloid in chronic venous ulcers demonstrated healing, but have not been published. One of these studies was prospective and used a double-blind comparative design, with the control being the same hydrocolloid without silver. The study is referred to in an industry-funded article which states that there was a mean 86% healing in the silver-treated group over 8 weeks, but does not give the healing results in the control group [34]. The article does indicate that the silver-treated group had less wound odour, improved wound granulation and less exudate than the control group.

Soriano and colleagues, in a randomised non-blinded trial, showed that, in chronic wounds with no clinical signs of infection, an activated charcoal silver dressing reduced bacterial

levels [35]. Some 85.1% of the 67 wounds in the silver-treated group showed reduced bacterial levels over 15 days, compared with 62.1% of wounds in the control group of 58 wounds. In this short study, healing times were not reported. It is thus possible that beneficial effects of silver do rely on microbial load reduction, even in the absence of features of critical colonisation or infection. This is important as clinical detection of wound colonisation or infection is not particularly sensitive or specific [36]. Consensus criteria for signs of wound infection have been developed (presented at the Paris 2004 World Union of Wound Healing Societies meeting) but require validation.

In an open-labelled non-comparative study with a SSDC-containing lipidocolloid (Tulle), not yet available in Australia, colonisation with *S. aureus* occurred in only one of 41 burns unit patients, and there were no secondary wound infections [37]. This supports a potential role for silver dressings in preventing infections. Wound infections have been recognised as a cause of poor outcomes in burns patients [38]; indeed, this was the original rationale for developing SSDC for burns. Another non-comparative trial in 24 burns patients showed satisfactory results with a silver hydrofibre dressing, with 17 patients healing within an average of 14 days [39]. Only one patient required skin grafting; pain was well controlled. Again, this study did not select for infection and the silver may have provided benefits from preventing infection or through other effects.

Whilst release of silver into the wound surface may be antimicrobial, organisms embedded deeper in the wound should ideally also be controlled. Sibbald and colleagues evaluated a nanocrystalline silver dressing and did show a reduction in wound surface bacteria but no reduction in deeper tissue [40]. However, this surface effect may be sufficient to tip the balance, and the efficacy of the product should be judged by its effect on wound healing, not solely on its effects on microbial levels.

In a non-randomised trial in 27 patients with diabetic foot ulcers, a silver-containing foam was used for 4 weeks [41]. Six ulcers in these patients were not treated with a silver dressing and served as a comparator group. Four treated patients healed completely and the average healing with the silver dressed ulcers was 56% of initial area. Two of the treated ulcers became infected, compared with all six of the comparator ulcers. Another small study showed the benefits of a different silver-containing foam in two patients with critically colonised leg ulcers [42].

In summary, the current evidence for silver products is well short of gold standard. If silver were a new medication, it would not, on the current evidence, be added to the registered drug list in most countries. Indeed, one could argue that it is a pharmaceutical, as topically-applied medications such as steroids and anti-inflammatory agents are. Currently, however, the evidence required for a dressing to be listed is less than that for a drug to be registered. It nevertheless seems remiss of the companies to not conduct high quality trials with silver products. Randomised blinded controlled trials have been recently successfully conducted in Australia with a range of potential new wound healing products, including direct and indirect growth factors and a protease inhibitor.

Role of silver products in wound healing

Faced with a slowly healing or critically colonised wound, it is unlikely that clinicians will avoid using silver products whilst awaiting higher quality evidence to guide them. So what role do these new products have based on our current knowledge?

The strongest evidence is for the use of these products in critically colonised wounds. Routine use on wounds without excessive microbial burden has some support from the research described, but is difficult to justify with such expensive products. Indiscriminate use may lead to the spread of the resistance that has already been recorded, although spread of resistance to an antiseptic is less likely than spread of antibiotic resistance. Silver should not be relied on to control infected wounds – this generally requires antibiotics and/or debridement. There may be a role for silver products in infected wounds along with these standard approaches, but this use has even less supportive evidence.

Silver products may also have a role in wounds that are slow or non-healing without evidence of critical colonisation or infection. Such wounds may have a high microbial burden that is not clinically apparent, and silver may also alter the inflammatory and other factors that are delaying healing. There may also be a role for silver products with specific wounds such as pyoederma gangrenosum, as was presented at the Paris meeting last year. Again, further evidence is required before routinely recommending these uses.

If the microbial burden is not controlled, or the silver product fails to improve wound quality and promote healing, an alternative silver product could be considered – some of the evidence presented above suggests that the various products may differ in their effects on microbes. Silver products should, however, not routinely be continued through to complete wound healing. Once the microbial burden is controlled, or the wound looks healthy, cheaper products should be considered. The silver product should only be reintroduced if the wound deteriorates with the cheaper product.

The choice of an initial silver product will be partly determined by patient characteristics, product availability and the product type, for example a more absorbent dressing for more exudative wounds. Where there are similar available silver products, there is only limited human evidence to guide the clinician in choosing. Head-to-head studies are not common with health products, and frequently suffer from methodological weaknesses such as non-equivalent dosages, too short a timeframe, too small sample sizes and inappropriate endpoints. Whilst some of the preclinical studies have compared products, it is unlikely that high quality clinical comparative trials will be conducted. Comparisons across separate trials are not a valid way of comparing products. This is therefore an area where individual practitioner preferences and marketing are likely to remain strongly influential.

Silver products should never replace basic wound management principles. The patient and wound should be fully assessed, appropriate investigations performed and treatment planned based on this knowledge. Thus, venous ulcers will require compression, which may be combined with the silver product but not replaced by it. Also, there are many factors apart from microbial burden that may explain why a wound is slow to heal – these should be assessed before a silver product is utilised to control colonisation. For instance, silver may not be an appropriate choice when a poor arterial supply is the major concern, or where the ulcer is due to malignancy.

The cost-effectiveness of silver products will always be controversial whilst they remain so expensive. Cost-effectiveness considers many factors, not just the cost of the product and the health practitioner's time. The companies providing these products will produce cost efficacy data which is invariably favourable to their product, and may indeed be very accurate, but this should be assessed against individual circumstances. A patient may prefer to have more frequent dressings with a cheaper product, even though this may incur higher nursing costs. An average 2 weeks longer to heal may be acceptable to the patient if she saves $60 a week on dressing costs. Currently, some patients can access subsidised products – for example, through the Repatriation Schedule of Pharmaceutical Benefits – but society is still ultimately bearing the cost of the product. More widely available and subsidised wound management products is a goal of the Australian Wound Management Association, but any progress here should favour products with the best supportive evidence.

Conclusions

Silver wound management products are here to stay. They are theoretically advantageous in wounds with a high microbial burden, in an era of increasing antibiotic resistance. Silver may also be effective even when there is no obvious microbial burden. However, clinical trial evidence of efficacy still lags behind the uptake of these products and should be a higher priority. Until then, clinicians should largely confine these products to wounds where there is evidence of critical colonisation and well-assessed chronic wounds that have not responded to cheaper dressings.

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