

Nanocrystalline silver dressings in wound management: a review

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Abstract: This paper describes the properties of nanocrystalline silver products (Acticoat™) and their applications and examines available evidence supporting their use in wound management. Acticoat utilizes nanotechnology to release nanocrystalline silver crystals. Acticoat releases 30 times less silver cations than silversulfadiazine cream or 0.5% silver nitrate solution but more of the silver released (by Acticoat). Silver-impregnated slow-release dressings release minute concentrations of silver which are quickly bound up by the chloride in the wound exudate. While extrapolations from in vitro and animal studies are cautious, evidence from these studies suggests Acticoat is: effective against most common strains of wound pathogens; can be used as a protective covering over skin grafts; has a broader antibiotic spectrum activity; and is toxic to keratinocytes and fibroblasts. Animal studies suggest a role for nanocrystalline silver in altering wound inflammatory events and facilitation of the early phase of wound healing. Quality human clinical trials into nanocrystalline silver are few. However, evidence suggests using Acticoat in wound management is cost effective, reduces wound infection, decreases the frequency of dressing changes and pain levels, decreases matrix metalloproteinase activity, wound exudate and bioburden levels, and promotes wound healing in chronic wounds. Although there is no in vivo evidence to suggest nanocrystalline silver is toxic to human keratinocytes and fibroblasts, there is in vitro evidence to suggest so; thus these dressings should be used cautiously over epithelializing and proliferating wounds. Future clinical research, preferably randomized controlled trials into nanocrystalline silver technology, may provide clinicians a better understanding of its applications in wound management.

Keywords: nanocrystalline, silver, burns, chronic, wounds, dressings

Introduction

Silver has been used as an antimicrobial since the 1800s. But since the discovery of systemic antibiotics in the early 20th century, the use of silver has declined. In the last two decades interest in silver for wound treatment resurged. The purpose of this paper is two-fold: to describe the properties of recently introduced nanocrystalline silver products and their applications in wound care; and to examine available evidence to support the use of nanocrystalline in wound care.

History of silver

Since ancient times silver was used for disinfecting stored water and liquids. The ancient Greeks and early Americans used silver coins for this purpose (Fong 2005). Historical review reveals silver being used to treat maladies. Prior to the 1800s, silver was used for treating epilepsy, venereal infections, acne, and leg ulcers. Silver foil applied to surgical wounds were known to improve wound healing and reduce post operative infections, and silver pencils were used to remove warts and to debride ulcers (Demling and DeSanti 2001; Dunn and Edwards-Jones 2004; Fong 2005).

In the late 19th century, 1% silver nitrate solution was instilled into conjunctiva sacs to reduce post-partum eye infections. In the late 1960s Moyer and Monafu introduced silver

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nitrate 0.5% solution for burn wound treatment (Demling and DeSanti 2001; Dunn and Edwards-Jones 2004; Fong 2005). However, silver nitrate dressings are labour intensive as they needed to be applied several times a day or re-moistened 2 hourly. The potency of silver as an antimicrobial was found to be related to the amount and rate of free silver released onto the woundbed (Lansdown 2002). In the late 1960s, Fox introduced silversulfadiazine cream for burn wound management. This dramatically revolutionized the management of burn wounds by reducing the incidence of burn wound infections. Silversulfadiazine cream has a relatively short action, its penetration of the burn eschar is poor and it forms a pseudo-eschar. Both silver nitrate dressings and silversulfadiazine cream require a high frequency of dressing changes.

Action of silver

Silver has antiseptic, antimicrobial, anti-inflammatory properties and is a broad spectrum antibiotic (Hoffman 1984; Klasen 2000; Demling and DeSanti 2001; Lansdown 2002; Dunn and Edwards-Jones 2004; Orvington 2004; Fong 2005). Silver is biologically active when it is in soluble form ie, as Ag^+ or Ag^0 clusters. Ag^+ is the ionic form present in silver nitrate, silversulfadiazine, or other ionic silver compounds. Ag^0 is the uncharged form of metallic silver present in nanocrystalline silver (Dunn 2004). Free silver cations have a potent antimicrobial effect which destroys micro-organisms immediately by blocking the cellular respiration and disrupting the function of bacterial cell membranes. This occurs when silver cations bind to tissue proteins, causing structural changes in the bacterial cell membranes which in turn cause cell death. Silver cations also bind and denature the bacterial DNA and RNA, thus inhibiting cell replication (Tredget et al 1998; Wright and Lam 1998; Yin et al 1999; Demling and DeSanti 2001; Lansdown 2002; Thomas 2003a, b; Dunn and Edwards-Jones 2004).

Properties and action of nanocrystalline silver

There are three types of nanocrystalline wound products: Acticoat™, Acticoat 7, and Acticoat Absorbent™. Acticoat (Acticoat™ and Acticoat 7) are three or five layered dressing constructs of a silver mesh containing silver nanocrystals applied to either side of a rayon/polyester core. Nanocrystalline silver utilizes nanotechnology to release clusters of extremely small and highly reactive silver particles (Smith and Nephew 2003). The smaller the particles of silver, the greater the wound

surface area that will be in contact with silver, thus increasing bioactivity and silver solubility. Acticoat is made by a process called physical vapour deposition. Argon gas is introduced into a vacuum chamber acting as an anode. When an electric current is passed into the chamber, the argon ions knock out the silver atoms travelling towards the substrate to be coated, depositing and developing nanocrystals each measuring 15 nanometres across and are between 30 and 50 atoms. These changes to the lattice structure of the crystal result in a high energy, meta-stable form of elemental silver (Dunn 2004).

Acticoat when moistened with sterile water and placed on the wound releases clusters of highly reactive silver cations up to 100 parts per million, causing electron transport, inactivation of bacterial cell DNA, cell membrane damage and binding of insoluble complexes in micro-organisms (Deitch et al 1987; Orvington 2001; Hegggers et al 2002; Lansdown 2002; Dunn 2004). Acticoat releases 30 times less silver cations than other forms of silver such as 0.5% silver nitrate or silversulfadiazine. However, more of the silver released is effective and release is sustained (Dunn 2004). If re-moistened, Acticoat produces a controlled release of clusters of silver cations onto the wound, for up to 3 days (if using Acticoat™) or 7 days (if using Acticoat 7). Research has demonstrated that sustained-release silver products have a bactericidal action providing effective management of odor and exudate, thus reducing the risk for colonization and preventing infection (Deitch et al 1987; Orvington 2001; Hegggers et al 2002; Lansdown 2002; Smith and Nephew 2003).

Moistening Acticoat has a two-fold benefit: it unleashes the antimicrobial power of nanocrystalline silver and assists in maintaining a moist environment to promote wound healing (Smith and Nephew 2003).

Acticoat Absorbent™ is an alginate dressing impregnated with nanocrystalline silver crystals. It has an absorbent property when in contact with wound exudate and forms a gel and releases nanocrystalline silver cations onto the wound bed. Its antibacterial action is similar to that of Acticoat™ (Smith and Nephew 2004).

Wound environment

Controlling micro-organisms within a wound environment promotes wound healing. Micro-organisms, ie, bacteria or fungi are found in chronic wounds and if present in an acute wound can rapidly contaminate and infect, seriously impeding wound healing. High levels of bacteria, multi-resistant organisms, and bacterial biofilms can impact on the wound-

healing process especially in chronic wounds (Templeton 2005). Bacteria delay wound healing by competing with host cells for nutrients and oxygen, their waste products are also toxic to host cells. Bacterial wound infection causes raised blood cytokines, raised matrix metalloproteinase, and decreased growth factors which can have adverse effects on wound healing. Local wound infection causes tissue death, increase in wound size, wound hypoxia, and vessels occlusion which all further delay the wound healing process (Woodward 2005).

Biofilms are complex communities of bacteria found on wound surfaces. They are embedded in a polysaccharide matrix and a biofilm functions as one organism in its own environment (Templeton 2005; Woodward 2005). A bacterial biofilm can have up to 1000 times more resistance to conventional antibiotics. Biofilms are prevalent in critically colonized wounds which can progress to wound infection (Templeton 2005; Woodward 2005).

A wound bioburden is when bacterial cells produce and secrete a variety of enzymes and toxins onto the wound. A bacterial population size of 10^5 colony forming units (cfu)/g or cm^2 indicates an infected wound and 10^4 cfu/g or cm^2 in complex wounds (White 2002). This bacterial load can be reduced by the removal of non-viable tissue with debridement or by using an antimicrobial dressing such as a sustained released silver dressing. In recent years, sustained released silver dressings has increasingly been used to treat both chronic and acute wounds in an effort to provide a more conducive wound healing environment by decreasing the wound bioburden level (Wright et al 2003).

Chronic wounds

Wounds that are slow or interrupted in their progress through the stages of wound healing are referred as chronic wounds (Wright et al 2002; Templeton 2005). They differ from acute wounds which heal in a timely and orderly sequential manner. Signs of chronic wounds are: presence of necrotic or non-viable tissue, lack of healthy granulations, recurrent wound breakdown, increasing wound size, and a stasis in wound improvement. The chronic wound environment has molecular and biochemical imbalance. There are elevated levels of matrix metalloproteinase and inflammatory cytokines, decreased levels of metalloproteinase tissue inhibitors, and growth factors in the chronic wound environment (Templeton 2005; Wright et al 2003). One of the major factors to delayed wound healing is prolonged inflammatory response within the wound environment which results in tissue destruction. A high

level of wound bioburden will also prolong inflammatory processes within the wound. Poorly controlled diabetes, avascularity, rheumatoid conditions, heart failure, smoking, poor nutrition, or continued pressure on the wound are some host factors which may impact on and delay wound healing causing an acute wound to become a chronic wound (Wright et al 2002; Templeton 2005).

Burn wounds and sepsis

Burn wounds are highly susceptible to infection due to the impairment of skin integrity and reduction in cell mediated immunity (Ayton 1985; Miller 1998; Tredget et al 1998; Heggers et al 2002; Fong 2005; Fong et al 2005). Once skin integrity is breached, wound colonization and bacterial invasion occur. Infection or sepsis is present in a burn wound when deposition and multiplication of bacteria in the tissue is associated with host reaction or invasion of nearby tissue and a bacterial count of 10^5 cfu/g of tissue (Ayton 1985; Heggers et al 1998; White 2002; Fong 2005; Fong et al 2005). Burn injury results in tissue destruction and the presence of avascular burn eschar provides an environment for infection that can progress to septicemia (Kumar et al 1999; Demling and DeSanti 2001). Infection is exacerbated by immunosuppression often associated with the burn injury (Cook 1998; Fong 2005). The rate of infection depends on the extent of the burn injury, general wound care and various host factors such as nutritional status, age, immune status, and co-morbidity conditions. The emergence of methicillin resistant *Staphylococcus aureus* (MRSA) and mMulti-resistant *Pseudomonas aeruginosa* concerns clinicians, as the control of burn wound sepsis is vital to the survival of the patient (Cook 1998; Kumar et al 1999; Yin et al 1999; Heggers et al 2002; Fong 2005). Burn wound infection remains as the main cause of morbidity and mortality for patients with burn injuries.

Evidence to support best practices in wound management

Research should be available to direct clinicians towards best practice. The efficacy, cost benefits and justification for using new technology such as nanocrystalline silver products should be thoroughly evaluated and tested prior to changes in practice. Randomized controlled trials are the highest level of evidence and their findings should be used to influence the decision making process in the selection of appropriate wound products and to support any changes in practice. The body of research falls into three categories: pre-clinical or

in vitro studies, animal studies, and human clinical trials (Woodward 2005).

In vitro evidence into nanocrystalline silver

In vitro studies are often the first steps to validate the efficacy of a wound product. Extrapolation of in vitro findings to the human environment must be cautious as laboratory test conditions are significantly different from the human wound environment (Woodward 2005).

Wright et al in 1998 compared 3 types of topical silver applications: silver nitrate solution, silver sulfadiazine cream, and Acticoat™ against a control dressing to determine their bactericidal efficacies against 11 clinical isolates of antibiotic resistant organisms. The organisms were inoculated onto each of the dressing, incubated for 30 minutes then washed with a recovery solution which then was cultured for organism survival rate. All the trial dressings demonstrated an ability to reduce the number of viable bacteria. The nanocrystalline dressing was the most efficacious and silver nitrate solution the least efficacious. The researchers concluded silver was efficacious for killing the antibiotic resistant bacteria strains that were tested. Acticoat™ was found to be particularly rapid at killing the tested bacteria and effective against a broader range of bacteria than the other trial dressings (Wright et al 1998).

Yin et al in 1999 compared the antibacterial activity of Acticoat™ with silver nitrate solution, silver sulfadiazine cream, and mafenide acetate against 5 clinically relevant bacteria. Acticoat™ was found to be more rapid in the delivery of silver cations and achieved a faster reduction of bacteria than the other experimental dressings. The mechanism of killing is similar in all forms of silver products but Acticoat™ killed faster as the bacteria take up silver faster in Acticoat™ samples (Yin et al 1999). Wright et al in 1999 examined the in vitro fungicidal efficacy of a variety of topical agents. Fungal isolates were inoculated onto mafenide acetate, silver nitrate, silversulfadiazine cream and Acticoat™ dressings, then incubated, and the fungi survival rate was evaluated. All the antimicrobial dressings were found to be effective against fungi. The nanocrystalline dressing provided the fastest kill rate and the broadest spectrum activity against fungi (Wright et al 1999).

Thomas et al in 2003 compared 4 silver containing dressings: Acticoat™, Actisorb™, Silver220™, Avance™, and Contreet-H™ in another in vitro experiment. They showed that antimicrobial activity was more rapid with nanocrystalline silver against Gram positive and Gram

negative bacteria and a yeast. The silver foam (Contreet-H™) product was shown not to release silver ions but will absorb the microbes (Thomas 2003a).

Another experiment was conducted by the same researchers in the same year using a larger variety of silver products. Again they demonstrated that silver products varied in their antimicrobial activity – some had little or no effect on the microbes tested. Acticoat 7 killed 99.9% methicillin resistant *Staphylococcus aureus* at all the intervals the samples were read (Thomas 2003b).

Wright et al in the same year questioned if antimicrobial efficacy alone is sufficient to justify their use. Acticoat™ was compared with a gauze dressing impregnated with hexamethylene biguanide against clinical inoculates of bacteria. Both dressings were demonstrated to have potent in vitro antibacterial effect. Acticoat activity diffused into the surrounding environment, whereas the activity of the gauze dressing with hexamethylene biguanide was confined within its borders (Wright et al 2003).

Holder et al in 2003 tested Acticoat™ and N Terface™ with filter paper as control dressing in 3 in vitro assays. Acticoat™ served as an impenetrable barrier for all organisms tested. They concluded that Acticoat™ was suitable for protection against environmental organisms for use with skin grafts on excised burns (Holder et al 2003). Fraser in 2003 conducted an in vitro study to test the efficacy of silversulfadiazine cream and Acticoat™ against 8 common burn wound pathogens. They demonstrated that silversulfadiazine cream was more efficacious against killing all tested organisms than Acticoat™ (Fraser 2003).

The same researcher conducted another in vitro study in the following year to determine the cytotoxicity of silversulfadiazine cream and Acticoat™ applied to the centres of culture plates seeded with keratinocytes, then incubated for 7 hours and the culture medium plates were read for keratinocyte survival rates. Silversulfadiazine cream was found to be more cytotoxic to keratinocytes than Acticoat™ (Fraser 2004). Poon et al in 2004 examined the effects of silver on keratinocytes and fibroblasts in another in vitro study. Silver nitrate solution and Acticoat™ were the two experimental dressings. They demonstrated that silver was toxic to skin cells, fibroblasts and keratinocytes as well as to bacteria. They cautioned the use of silver products where rapidly proliferating keratinocytes are exposed such as in donor sites, superficial partial thickness wounds and undifferentiated cultured keratinocyte applications (Poon and Burd 2004).

In summary, the literature indicates there is in vitro evidence to support the efficacy of using nanocrystalline silver for wound management. Nanocrystalline silver as an antimicrobial is effective against most common strains of bacteria, including multi-resistant strains and fungi spores. In vitro evidence indicates that nanocrystalline silver achieved the best killing rates for numerous micro-organisms, can be used as a protective covering over skin grafts, has a broader antibiotic spectrum activity, and is toxic to keratinocytes and fibroblasts.

Evidence from animal studies into nanocrystalline silver

Wright et al in 2002 examined early healing events and the efficacy of nanocrystalline silver on the levels of matrix metalloproteinase, cell apoptosis and healing in a porcine model of contaminated wounds. Full thickness wounds were created on the backs of pigs, contaminated with experimental inoculum of *Pseudomonas*, *Fusobacterium species*, and coagulative negative strains of *Staphylococci*, and covered with dressing products with or without nanocrystalline silver. They found the nanocrystalline silver product promoted rapid wound healing in the first few days post injury and the proteolytic environment of wounds treated with nanocrystalline silver was changed by the reduction of levels of matrix metalloproteinase. In chronic ulcers, matrix metalloproteinase levels have been shown to be pro-inflammatory and at abnormally high levels compared with acute wounds. This may contribute to the non-healing nature of these wounds. Cellular apoptosis occurred at a higher rate in non-nanocrystalline silver-treated wounds. This suggested nanocrystalline silver has a role in altering the inflammatory events in wounds and facilitate the early phase of wound healing (Wright et al 2002).

The same authors in 2003 questioned the antimicrobial efficacy of new silver dressings in reducing the bacterial bioburden in acute and chronic wounds. They compared nanocrystalline silver and a gauze dressing impregnated with polyhexamethylene biguanide in an animal model of wound healing. They found the wound dressed with nanocrystalline silver product progressed to full granulation faster and had lower bacterial bioburden levels than the wound dressed with non-nanocrystalline silver product. The authors concluded that being an antimicrobial is not sufficient, the dressing needed to promote wound healing. The gauze dressing with polyhexamethylene biguanide prolonged inflammatory response and had a negative effect on wound healing (Wright et al 2003).

The therapeutic efficacy of 3 silver dressings in an infected animal model were examined by Hegggers et al in 2005. Acticoat™, Silverlon™, Silvasorb™, and a control dressing were applied to 4 groups of rats. The rats received contact burns and were surgically infected with *Pseudomonas aeruginosa* and *Staphylococcus aureus* on day 3 post burns. The dressings were evaluated and quantitatively assessed in 10 days. Acticoat™ and Silvasorb™ treated wounds had significantly lower bacterial counts than the Silverlon™ treated wounds. They demonstrated that weekly dressing changes were feasible when treating wounds with Acticoat™ or Silvasorb™ (Hegggers et al 2005).

Ulkur et al in 2004 compared Acticoat™, chlorhexidine acetate, and silversulfadiazine cream as topical antibacterial in pseudomonas contaminated full thickness burn wounds in rats. All the experimental dressings were effective; however they concluded that Acticoat™ may be the dressing of choice due to the limited frequency of dressing changes (Ulkur et al 2005a).

The same authors in the following year compared Acticoat™, chlorhexidine acetate 0.5%, and fusidic acid 2% for topical antibacterial effect in methicillin resistant *Staphylococci*-contaminated full thickness rat burn wounds. Thirty-two male Wistar rats received full thickness dorsal scald burns to 15% of their body surface area, resuscitated and then infected with the experimental micro-organism, methicillin resistant *Staphylococcus aureus*, and placed in separate cages to recover. After 24 hours they were randomly assigned to topical applications of the experimental dressings and one group with no dressings applied to act as control. All animals were killed on day 7 and measurements of weight obtained. Cultures were obtained from punch biopsies of the eschars and tested for the test microbe. They found that fusidic acid was the most effective agent in treating methicillin resistant *Staphylococcus aureus*-contaminated burn wounds, but Acticoat™ was the preferred treatment due to its ability to limit the frequency of dressing changes (Ulkur et al 2005b).

Supp et al in 2005 evaluated the cytotoxicity and antimicrobial activity of Acticoat™ for management of microbial contamination in cultured skin substitutes grafted to athymic mice. The cytotoxicity of Acticoat™ was assessed after 1, 2, 3, and 4 weeks of grafting with cultured skin substitutes. They found contaminated wounds treated with Acticoat™ healed similarly to control treatments. These results suggested that Acticoat™ could be used as a protective dressing to reduce environmental contamination of cultured skin substitutes to control organisms present in the wound (Supp et al 2005).

In summary, there is a lack of animal studies on nanocrystalline silver, but the available literature reviewed suggested that nanocrystalline silver has a role in altering the inflammatory events in wounds and also facilitate the early phase of wound healing. There is evidence to suggest that Acticoat™ is an effective antimicrobial and is the dressing of choice in several cases as it limits the frequency of dressing changes. Acticoat™ may be suitable as a protection for contamination on cultured skin substitutes used for wound closure. Animals and humans differ in structure and function. Therefore extrapolations of findings from animal models to the human environment must be done with caution.

Evidence from human studies into nanocrystalline silver

There is a lack of high quality designed research such as randomized control trials in human studies into nanocrystalline silver dressings. However a search of the literature revealed many human comparative studies, case series, and individual reports of the applications of nanocrystalline silver in wound management.

In an earlier study in 1998 Tredget conducted a matched paired randomized study to evaluate the efficacy and safety of Acticoat™ for burn wound treatment. Thirty patients with symmetrical burns were randomly assigned to be dressed with Acticoat™ or silver nitrate solution dressings. They found that the Acticoat™-treated patients had less pain levels initially but the pain levels were comparable with that of the silver nitrate group of patients after 2 hours. They also found that the frequency of dressing changes and incidence of wound sepsis were less in the Acticoat™-treated group (Tredget et al 1998).

Voight presented case presentations of 6 patients with venous ulcers treated with Acticoat™. They reported wound healing in these patients, one patient with a 5 month old ulcer was healed with Acticoat™ in 194 days and another with a 5-week-old ulcer which healed in 27 days. In another case series, Voight demonstrated the effects of Acticoat™ on 4 patients with decubitus ulcers, one with a 24-month-old ulcer healed in 27 days and another 2-week-old ulcer healed in 14 days with Acticoat™. They demonstrated a reduction in exudate fluid volumes in all cases treated with Acticoat™. The same authors conducted a multi-centered (41 centers) survey for the use of Acticoat™ dressing. They reported that 61% of the centres surveyed used Acticoat™ and up to 52% of these used Acticoat™ as a cover for Integra, a dermal regeneration template for full thickness burns reconstruction. They also

reported that 4.8% of those surveyed used Acticoat™ as their principal dressing. They concluded that Acticoat™ is cost effective, improved wound healing and able to be applied to all types of wounds (Voight and Paul 2001).

Innes in 2001 investigated the use of Acticoat™ and Allevyn foam on donor sites in a prospective controlled matched pair study on 15 patients with bilateral donor sites. They found that donors treated with Allevyn foam were more than 90% re-epithelialised at a mean 9.1 days, whereas the Acticoat™-treated donor sites were more than 90% re-epithelialised at 14.5 days. They concluded Allevyn was significantly better than Acticoat™ for treating donor sites and the Acticoat™-treated donor sites had worse scars at 2 weeks than Allevyn-treated donors but showed no difference at 3 months (Innes et al 2001).

The role of silver in wound healing was examined in a single center, open-label, unblinded pilot study of 11 extended-care facility outpatients or residents with chronic wounds of mixed etiology by Kirshner et al in 2002. All wounds had a history of at least 3 months and had no decrease in wound size in the 3 weeks preceding the study. The patients were all treated with Acticoat™ and had their dressings changed daily in the first week and on alternate days thereafter. All used dressings were reserved for analyses and fluid collection. Eight patients completed the study, the authors found a decrease in matrix metalloproteinase activity in the first 2 days of treatment. This suggested that once matrix metalloproteinase activity is altered it can remain so with the continued use of the nanocrystalline silver dressing (Kirshner 2002).

Demling and DeSanti in 2002 examined the effects of Acticoat™ and Xeroform™ as dressings over meshed skin grafts. Twenty patients, each having 2 areas of meshed skin grafts were treated with Acticoat™ in one and Xeroform™ with 0.01% neomycin and polymyxin on the other wound. Wounds were evaluated every 3 days and wound swabs obtained. They found that Acticoat™ greatly increased the rate of wound closure than the standard Xeroform™ dressings (Demling and DeSanti 2002).

Dunn in 2004 presented reports from the 2003 European Burns Association meeting of success with the use of Acticoat™ on burn patients by several clinicians across Europe. Acticoat™ dressings were applied to children with partial to full thickness burns. Besides the antimicrobial effects Acticoat™-treated wounds generally improved and healed naturally or in conjunction with surgical interventions. There were reports of improved pain levels, reduction in the

frequency of dressing changes, wound exudate and number of surgical procedures (Dunn 2004).

Lansdown in 2005 conducted a sequential microbiology examination of wound swabs from 7 patients with chronic wounds and sampling wound exudates and wound scale. They compared Acticoat 7, Actisorb Silver, Contreet-H™, Aquacel^{Ag}, and Flamazine™. They found in all cases the bacterial bioburden to be reduced but not completely eliminated (Lansdown et al 2005).

In a randomized control study Varas et al in 2005 examined 14 burn patients pain levels after dressing changes. Patients had 2 areas of burns and were randomly assigned to Acticoat™ or silversulfadiazine cream dressings. Patients were used as their own control. They found that Acticoat™-treated wounds were less painful than the silversulfadiazine cream treated wounds (Varas et al 2005).

Fong et al in 2005 conducted 2 comparative patient care audits and a historically controlled matched paired comparison to examine the use of Acticoat™ in decreasing the incidence of early burn wound infection and its cost effectiveness. Patient care audits demonstrated that the Acticoat™ treated group (treatment group) had a significantly lower infection rate (5.2%) than the silversulfadiazine cream treated group (control group) with 55% infection rate. They demonstrated cost savings for the matched paired sample (4 pairs of patients) comparison of the two treatments, the Acticoat™ treated sample saved AU\$7612 per patient. They also reported lower pain levels in the Acticoat™ patients and subjective observations made by staff who looked after both the Acticoat™ and silversulfadiazine cream groups of patients suggested that the Acticoat™ group of patients had higher levels of feelings of wellbeing due to lower pain levels and less frequent dressing changes (Fong et al 2005). Sibbald in 2005 in an open pilot study of prolonged release nanocrystalline silver dressing (Acticoat 7): reduction of bacterial burden treatment in the treatment of chronic venous leg ulcers reported a case series of 15 patients. Patients were treated with Acticoat 7 under a four layer of Profore compression bandages for a 12-week period or until healed. Results demonstrated an ionized silver dressing with prolonged release of nanocrystalline silver (Acticoat 7) can decrease bacterial burden and accelerate wound healing in venous ulcers not healing at the expected rate (Sibbald et al 2005a).

The same authors reported in the same study the anti-inflammatory activity of prolonged released nanocrystalline silver (Acticoat 7) in the treatment of chronic venous leg ulcers, nanocrystalline silver dressing has an antibacterial and

permissive but selective anti-inflammatory action in reducing the size of venous ulcers (Sibbald et al 2005b).

Rustogi et al in 2005 evaluated the safety and efficacy of Acticoat™ use in primary burn injuries and other skin injuries in premature neonates. An audit of eight premature neonates who sustained burn injuries and other cutaneous injuries from various agents were treated with Acticoat™. The percentage of skin loss was from 1 to 30%. The wounds were assessed for infection and blood cultures were taken to exclude sepsis.

Four neonates went on to heal within 28 days, the other four neonates died, secondary to problems from extreme prematurity. They reported no wound infections or positive blood cultures in the trial period and concluded that Acticoat™ is suitable for use as a dressing for neonates (Rustogi et al 2005).

In summary, the literature review of nanocrystalline silver used on humans for wound management suggested nanocrystalline silver is: cost effective, reduces burn wound incidence, decreases pain levels during dressing changes, decreases the frequency of dressing changes, decreases the matrix metalloproteinase activity, reduces the wound exudate and bioburden levels, and promotes wound healing in chronic wounds. There is no in vivo evidence to suggest that nanocrystalline silver is toxic to skin cells such as keratinocytes and fibroblasts.

Conclusion

Research indicates nanocrystalline silver dressing is an effective antimicrobial for treating wounds especially burns and chronic wounds. Acticoat™ reduces the inflammatory processes and promotes wound healing and is less toxic than other forms of silver dressings due to the prolonged release of silver onto the wound. There has been no in vivo reports of toxicity of nanocrystalline silver on keratinocytes or fibroblasts, but there is in vitro evidence to suggest so. Thus, clinicians should be cautious in the use of nanocrystalline dressings over epithelializing and proliferating wounds. Evidence from clinical trials, various case presentations, and reports suggests that the use of Acticoat™ is cost effective, reduces pain levels, and has a longer wear time, thus limiting the frequency of dressing changes. There has been no reports of resistance to Acticoat dressings; however, clinicians should use Acticoat dressings judiciously, applying the dressings to the appropriate wounds and ceasing their use appropriately to prevent the development of bacterial resistance. Clinicians are increasing in their use of nanocrystalline silver dressings

for wound management either for their antimicrobial or anti-inflammatory properties. More quality clinical research should be conducted in order to direct clinicians in their decision making process in choice of dressings and to provide more evidence for best practices in wound management.

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