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REVIEW

A review of the applications of the hydrofiber dressing with silver (Aquacel Ag®) in wound care

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Abstract: Aquacel Ag® (ConvaTec, Princeton, NJ, USA) is a new hydrofiber wound dressing consisting of soft non-woven sodium carboxymethylcellulose fibers integrated with ionic silver. It is a moisture-retention dressing, which forms a gel on contact with wound fluid and has antimicrobial properties of ionic silver. We present a current literature review on Aquacel Ag®, of both in vitro and in vivo efficacy and clinical applications. In vitro and in vivo studies have demonstrated the wide antimicrobial properties of Aquacel Ag®, and additionally demonstrated the cytotoxicity of ionic silver to keratinocytes and fibroblasts that cause delay in wound re-epithelialization. Clinical studies confirmed that Aquacel Ag® is an effective and safe dressing for a variety of wound types, both acute and chronic. Incorporation of ionic silver into the hydrofibers does not cause undue alteration in the performance properties of the base dressing, which continues to provide favorable wound moisture and exudate management. The addition of ionic silver reduces local pain and dressing changes, and provides significant broad-spectrum antimicrobial properties, with no delay in wound healing.

Keywords: Aquacel Ag®, silver, wound dressing, hydrofiber, carboxymethylcellulose

Introduction

The ideal dressing needs to ensure that the wound remains moist with exudates but not macerated; free of infection, excessive slough, toxic chemicals, particles, and fibers; at the optimum temperature and pH for healing; and undisturbed by the need for frequent changes.

Aquacel® Hydrofiber dressing (ConvaTec, Princeton, NJ, USA) is a moisture-retention dressing that consists of soft non-woven sodium carboxymethylcellulose fibers which forms a gel on contact with wound fluid. The gel promotes a moist wound-healing environment yet retains wound exudates by vertical absorption. Fibrin collects between the dressing and wound surface and acts as an adhesive, fixing the dressing in place and providing adherence of the dressing to the wound without ingrowth of tissue into the dressing. This was found to be beneficial for both caregivers and patients in terms of ease of application and removal, and reduction in pain at dressing change. Aquacel has been applied to many types of wound care with favorable results and cost-effectiveness.[1–7]

Silver has been used widely for many years in wound care to help manage local infection. Historically, silver has been presented as metallic (silver foil), solution (eg, silver nitrate), or cream (eg, silver sulfadiazine). Ionic silver (Ag^+), which is the oxidized active state of silver, has received renewed interest and research for use as a prophylactic antimicrobial agent in wound dressings due to its broad

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spectrum antibacterial range, including aerobic, anaerobic, Gram-negative and Gram-positive bacteria, as well as yeast and fungi. The antimicrobial effect of silver can be explained by various mechanisms: silver interferes with the respiratory chain in the cytochromes of microbacteria; additionally, silver ions also interfere with components of the microbial electron transport system, bind DNA, and inhibit DNA replication. Little current evidence of emerging microbial resistance to silver has been reported.[8–12]

Dressings, as opposed to cream formulations, are designed to have a more controlled and prolonged release of silver during wear-time. Aquacel Ag® dressing combines 1.2% silver to Aquacel Hydrofiber, which is distributed throughout the dressing material. The concept of Aquacel Ag® is to retain the hydrofiber's physical properties with the additional benefits of silver, which is slowly released into the wound for up to 2 weeks, creating a moist antimicrobial environment. The dressing entraps microorganisms within its fibers. Controlled release of silver ions reduces the bioburden within the dressing, minimizing the risk of infection.

Aquacel Ag® is intended for the management of a wide range of acute and chronic wounds, based on the clinical experience with Aquacel hydrofiber dressing. Various silver-impregnated wound dressings are available for the management of critically colonized and locally infected wounds. These dressings differ in structure and physical properties, the form and amount of silver contained in the dressing, and the mechanism by which silver is delivered.

This article provides a review of current data regarding the use of Aquacel Ag® in wound care.

In vitro efficacy

The significant antimicrobial effect of silver raised concerns regarding its cytotoxic effect on host cell viability and proliferation in wound tissue. The in vitro cytotoxic safety and antimicrobial efficacy of Aquacel Ag® were studied and compared to other commercially available silver-containing dressings.

Paddle-Ledinek and colleagues[13] studied the effect of different wound dressings on cell viability and proliferation. Keratinocyte cultures were exposed for 40 hours to extracts of wound dressings. Silver-containing dressings (carboxymethylcellulose, nanocrystalline, polyurethane foam, and hydrocolloid/alginate) induced greater cytotoxicity and morphological disorder compared to dressings with no silver impregnated. Aquacel Ag® was found to contain approximately 20 μg/cm^2 of silver and induced the death of almost all exposed keratinocytes.[8,13] The authors' recommendation was to use silver-based dressings with caution in situations where rapidly proliferating cells may be harmed, as in donor sites, superficial burns, and cultured cell applications.

Further evidence of the in vitro cytotoxic effect of Aquacel Ag® was presented by Burd and colleagues,[8] who found Aquacel Ag® to be lethal to monolayer cultured keratinocytes and fibroblasts in a comparative study of the cytotoxicity of silver-based dressings. Furthermore, epidermal reepithelialization, examined in a pig mid-dermis explant culture model, was delayed in silver-based dressings compared to non-silver controls. Explants treated with Aquacel Ag® had a significantly smaller re-epithelialization area per hair follicle compared to non-silver control.[8]

Duc and colleagues[14] performed an in vitro cytotoxic analysis of a variety of antiseptic medications on skin substitutes and autograft. They found that Aquacel Ag® was not toxic to autograft or skin substitutes based on assessments of graft histology and metabolism, including RNA staining.[14] The antimicrobial spectrum of activity and efficacy of Aquacel Ag® was examined in vitro and compared to other silver-impregnated dressings in numerous studies.[15–21] Aquacel Ag® was shown to be microbicidal against a wide range of burn wound and chronic wound pathogens, including aerobic and anaerobic bacteria, antibiotic-resistant bacteria, yeast.[15–21] Antibiotic-resistant bacteria included methicillin-resistant *Staphylococcus aureus* (MRSA), vancomycin-resistant enterococci (VRE), Pseudomonas aeruginosa (PA), and *Serratia marcescens* (SM). The microbicidal effect was sustained over a period of 14 days.[15]

Antibacterial, physical, and chemical comparisons of the various silver-containing dressings demonstrated wide variance in their antipathogenic capability.[16–18,20,21] Parsons and colleagues[20] plotted silver content and silver release at 3 and 48 hours against antibacterial activity at 7 days of culture for each silver-containing dressing. They found that antimicrobial activity is not directly correlated with increasing silver release. Aquacel Ag® demonstrated superior antibacterial activity, compared to other silver-containing dressings, particularly nanocrystalline silver-containing dressing.[18,20,21] Its fluid handling properties, moisture retention, and conformability were also superior.

Other studies showed superior antibacterial activity of nanocrystalline dressings compared to Aquacel Ag®,[16,17] although Castellano and colleagues[16] demonstrated that both Aquacel Ag® and nanocrystalline dressings have inferior antibacterial properties compared to commonly used topical antimicrobial agents, including silver sulfadiazine, mafenide acetate, and silver calcium alginate.

Gaisford and colleagues[22] reported an in vitro method for the quantitative determination of the antimicrobial efficacy of silver-containing dressings. By using isothermal calorimetric measurements, the authors estimated the silver load and bioavailability in the wound environment. Results showed that not all of the silver in Aquacel Ag® was bioavailable, reducing the potential for silver toxicity and extending the bactericidal effect over time.[22]

Other effects of silver containing dressings on wound healing were studied. Aquacel Ag® and other silver-containing dressings were found to sequester matrix wound metalloproteinases in vitro.[23] This finding may have a positive effect on wound healing in chronic recalcitrant wounds.

In vivo efficacy

Animal models have been used to study the performance and cytotoxicity of Aquacel Ag® and other silver-based dressings in vivo.[8,24,25] In a partial thickness exudating porcine model, two common silver-containing dressings were tested for exudate management, wound-site adherence, dressing integrity, retention of dressing debris within wounds, and wound tissue integrity.[24] Aquacel Ag® was found to be less effective in exudate management compared to hydrocolloid/alginate. On exposure to exudates, Aquacel Ag® formed a fluid gel with minimal mechanical integrity and low adherence to the wound bed. There was some level of trapped dressing debris with ensuing foreign body reaction.

In a full-thickness infected mouse wound model, Yates and colleagues showed that infected wounds treated with Aquacel Ag® had lower wound bacteria loads, superior wound tensile strength, and accelerated epithelialization compared to untreated infected wounds.[25] Histological analysis correlated with macroscopic findings, demonstrating accelerated proliferation, remodeling, and maturation of the wound in the Aquacel Ag® treated group. Aquacel Ag® showed significant wound bacterial reduction compared to Aquacel treated- and untreated wounds.[25]

The cytotoxic effect of Aquacel Ag® was studied on an excisional mouse wound model.[8] Silver-based dressings showed delayed or inhibited wound re-epithelialization compared to non-silver control dressing. The authors commented that previous studies demonstrating enhanced wound healing with silver was performed on acute incisional wounds where keratinocyte proliferation is not a major feature.[8,26]

Dressing requirements in a chronic wound healing situation are different when control of the wound bioburden is more important.[9,10] Aquacel Ag® showed decreased inhibition of wound epithelialization compared to nanocrystalline and hydrocolloid silver-based dressings.[8]

Clinical applications

Multiple clinical studies have been performed to assess Aquacel Ag®'s effectiveness for the treatment of a variety of acute and chronic wounds, managed in acute and chronic settings, as summarized in Table 1.[27–39]

Aquacel Ag® has been evaluated for use in adult and pediatric patients with partial-thickness burns.[27,28,32,33,35–37] Caruso and colleagues performed a phase II non-comparative trial using Aquacel Ag® in partial thickness burns and found a good wound re-epithelialization rate, with reduced wound pain, good conformability, and ease of use.[28] Some side-effects were noted, including burning on initial application and minor difficulties with joint movement due to dressing hardening over the joint. All side-effects were classified as minor and did not cause any functional deficits.[28] Caruso et al continued their research with a stratified, randomized prospective, though unblinded study, comparing Aquacel Ag® and silver sulfadiazine (SSD) in the management of partial thickness burns.[27] Aquacel Ag® was associated with significantly less pain and anxiety during dressing changes, significantly fewer procedural and opiate medications, significantly less burning and stinging during wear, a significantly better achievement of normal scar height by the end of study treatment, significantly fewer dressing changes, less nursing time, and greater cost-effectiveness than SSD. SSD was associated with significantly greater flexibility and greater ease of movement than the Aquacel Ag® dressing. Both dressings had comparable overall burn wound healing and incidence of adverse events, including infection rates, as well as total dressing cost.[27]

Other clinical studies on partial thickness burns treatment showed good wound healing, reduced pain, fewer dressing changes, and better cost-effectiveness Aquacel Ag® compared to standard treatment.[32,33,35–37] In patients with acute split-thickness skin graft donor sites and acute traumatic wounds,[31,34] Aquacel Ag® showed superior re-epithelialization rates and ease of use, and was associated with less pain on dressing removal, in comparison with standard treatment.

Aquacel Ag® was also evaluated for the treatment of chronic wounds,[29,30,38,39] which have an increased bacterial burden that can impair healing, albeit without all the clinical signs of infection. Silver can provide a mechanism for controlling the wound bacterial burden. Two open-label

Table 1 Comparison between clinical studies done on Aquacel Ag®

Authors and references	Study type	Number patients	Clinical background	Aquacel Ag® versus	Endpoint/outcome	Results
Caruso[28]	Prospective Phase II	22	Partial thickness burns	Non-comparative	Clinical performance	Positive re-epithelialization rate, ease of use, comfort, flexibility, conformability
Lohana[33]	Prospective Phase II	22	Pediatric partial thickness burns	Non-comparative	Clinical performance	Good wound healing, reduced pain, ease of use, comfortable
Coutts[29]	Case series	30	Chronic wounds	Non-comparative	Wound healing	Decreased size, exudate, and maceration, increased granulation tissue
Vanscheidt[39]	Prospective	15	Chronic leg ulcer	Non-comparative	Clinical performance	Reduction in pain, wound slough, and size, improved wound healing
Paddock[36]	Retrospective	38	Pediatric partial thickness burns	Silver sulfadiazine	Cost-effectiveness	Reduced hospital costs, greater cost-effectiveness
Saba[37]	Retrospective	10	Pediatric partial thickness burns	Xeroform gauze with bacitracin zinc	Clinical performance	Reduced in-hospital stay and pain, shorter re-epithelialization
Caruso[27]	Prospective, Randomized	42	Partial thickness burns	Silver sulfadiazine	Cost-effectiveness	Less pain and burning, fewer dressing changes, greater cost-effectiveness
Lohsiriwat[34]	Prospective, Randomized	11	Split-thickness skin graft donor sites	Paraffin gauze	Clinical performance	Reduced pain and faster re-epithelialization
Jurczak[31]	Prospective, Randomized	35	Acute surgical and traumatic wounds	Povidone-iodine gauze	Clinical performance	Better pain management, comfort, exudate handling, and ease of use
Jude[30]	Prospective, Randomized	67	Diabetic foot ulcers	Calcium alginate	Wound healing	More reduction in ulcer depth and better infection control

noncomparative case studies evaluated Aquacel Ag® in the management of chronic wounds of different etiologies, including clinically infected wounds.[29,39] Most patients treated with Aquacel Ag® had a decrease in wound size, improved maceration, and decreased slough.[29] There were no serious adverse events. One patient reported temporary burning and stinging on initial application, and one on malposition of the dressing.[29,39] In an economic analysis of one month treatment of chronic venous leg ulcers with various silver dressings, Aquacel Ag® was less cost effective than silver-releasing foam dressings.[38]

Jude and colleagues[30] performed a prospective randomized controlled study on Aquacel Ag® versus calcium alginate dressings in managing nonischemic foot ulcers in patients with diabetes. Aquacel Ag® was found to be safe, with minor dressing-related adverse effects encountered in the study. Both dressings showed similar wound-healing capabilities, but the group treated with Aquacel Ag® had significantly greater depth reduction and overall wound bed improvement. This was emphasized in a subset of patients that were treated with systemic antibiotics during the study period, suggesting a potential synergy between topical silver dressings and systemic antibiotics.[30]

Discussion

The search for the ideal dressing is ongoing, with many new advanced dressings on the market aspiring to achieve this status. No currently available dressing suits all patients or all wounds, at all stages of the healing process. The aim of new dressings is to improve the quality of care and clinical outcomes coupled with a significant reduction in the cost of providing such care.

The development of wound infection is an ongoing problem for many patients. It is well documented that if a wound becomes infected, normal healing is disrupted as the inflammatory phase becomes chronic, suppressing the regenerative phase.[9–12] Infected wounds may cause great distress in terms of associated morbidity and mortality, increased length of hospital admission, delayed wound healing, and increased discomfort; they also increase health care costs significantly.[9–12]

Aquacel Ag® was developed with the goal of combining the benefits of Aquacel carboxymethylcellulose hydrofiber in wound healing, with the addition of silver as a proven antimicrobial.[25] Resurgence in the use of silver-based antiseptics may be linked to their broad-spectrum activity and far lower propensity to induce bacterial resistance than antibiotics, in parallel with recent availability of new, advanced dressings impregnated with this antiseptic agent.[9–12] The addition of silver to advanced dressings with proven healing benefits has advantages in both acute and chronic wounds. In acute wounds, especially partial thickness burn wounds, the antibacterial substance is intended to prevent infection, while in chronic wounds the goal is to reduce bacterial load.

The integration of silver into these dressings has been shown to provide a wide range of antibacterial activity in vitro, including demonstrated toxicity against highly resistant bacteria.[15,17–21] The antimicrobial efficacy of silver-containing dressings may vary, depending on the mechanism of silver's bioavailability. In Aquacel Ag®, silver is displaced from the carboxymethylcellulose carrier as it is hydrated; thereby achieving a gradual, sustained release, and thus sustained antimicrobial capability.[15,17–21] Perhaps bacteria are also sequestered by the carboxymethylcellulose.

In addition to its wide range of antimicrobial activity, silver may have other beneficial effects on the wound bed. Reduction of matrix metalloproteinases, inhibition of proinflammatory cytokines, and a higher frequency of apoptosis alter inflammatory processes in the wound.[23]

The use of silver raised concerns regarding wound cytotoxicity. Indeed, the cytotoxicity of Aquacel Ag® was found to be multifactorial, relating to silver content and affinity for moisture, as well as silver composition – the chemical and physical form of the silver.[8] In vitro and in vivo studies have shown that silver has a cytotoxic effect against rapidly proliferating cells, including keratinocytes and fibroblasts, and thus may delay wound epithelialization.[8,13] However, clinical studies in patients with partial-thickness wounds (partial-thickness burns and skin graft donor-sites) demonstrated good wound re-epithelialization, with no delay in wound healing.[27,28,32–37] Moreover, an in-vivo infected wound model demonstrated similar wound healing properties between Aquacel and Aquacel Ag®, with significant lower bacterial loads in the Aquacel Ag® treated group.[25] This can be explained by the fact that the wound healing process has many phases and levels, and only clinical trials, as opposed to in vitro studies, can effectively assess the net effect of a dressing on the wound healing process. The presence of serum plasma alters the silver dissociation in interactions between wound tissue and silver.

In addition, there is a concern that pathogens may develop resistance to silver if it is widely used in medical devices. Resistance is thought to develop when bacteria are exposed to low levels of silver for extended periods of time. To date, no clinical study has reported bacterial resistance to silver during treatment with Aquacel Ag®.[27–39]

Another concern relating to the use of advanced silver-impregnated dressings is the cost of care. Silver-containing dressings are relatively expensive, although the higher cost is partially offset by; reduced use of secondary gauze, retention dressings, and improved wound healing together with the reduced costs of other care. Cost-effectiveness calculations comparing Aquacel Ag® to standard of care in patients with acute and chronic wounds showed favorable results using Aquacel Ag®.[27,32,33,36–38]

Aquacel Ag® was found to be a safe dressing, with only minor adverse effects reported in clinical trials.[27–39] Adverse effects included local burning and stinging on initial application, dressing hardening over joints, dressing slippage, and isolated cases of deep infection in initially infected wounds. Patients treated with Aquacel Ag® reported favorable outcome regarding ease of use, conformability, limited dressing changes, and reduced pain from dressing changes.[27–39]

The majority of clinical studies with Aquacel Ag® and other advanced silver-containing dressings have limitations, namely lack of treatment blinding, lack of stratification and randomization, lack of objective wound pain assessment, heterogeneous study populations, and the lack of objective wound healing assessment. Most studies provided low levels of evidence on clinical efficacy; there have been only a few prospective randomized controlled studies.[30,31,34] Furthermore, many studies on the efficacy of new silver products are sponsored by the manufacturers, who tend to promote the benefits of the product under investigation.

Conclusions

Aquacel Ag® was shown to be an effective and safe dressing for a variety of wound types, both acute and chronic. Incorporation of ionic silver into the hydrofibers did not cause undue alteration in the performance properties of the base dressing, which continues to provide favorable wound moisture and exudate management. The addition of ionic silver reduces local pain and dressing

changes, and provides significant broad-spectrum antimicrobial properties. Further prospective randomized controlled studies are needed to assess the appropriate indications for the use of Aquacel Ag®, and compare its performance with that of other advanced silver-containing wound dressings.

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Disclosures

The authors have no conflicts of interest to declare.

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