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Do silver-based wound dressings reduce pain? A prospective study and review of the literature

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ABSTRACT

Silver-containing dressings are a mainstay in the management of burn injury and acute and chronic wounds. In addition to antimicrobial activity, there is anecdotal evidence that silver dressings may modulate or reduce wound pain. Pain is subjective and difficult to quantify, and most studies of silver-containing dressings evaluate pain as a secondary rather than a primary outcome. Nevertheless, a dressing with a proven ability to reduce pain independent of systemic analgesics would have great utility.

In this study, we compared patient-reported pain levels in patients previously randomized to receiving silver-nylon dressings vs. conventional gauze dressings in a study of surgical site infection. Compared to gauze dressings, patients in the silver dressing group reported less pain between postoperative days 0 and 9 ($p < 0.02$). Post hoc analysis of analgesic use did not reach statistical significance between the groups. The study was completed with a literature review of the effect of silver on pain.

Silver-based dressings may reduce wound pain by providing an occlusive barrier or by other as-yet undefined mechanisms. The role of silver in pain relief, however, cannot be definitively stated until well-designed prospective randomized studies evaluating pain as a primary endpoint are carried out.

1. Introduction

Intact skin performs a number of homeostatic functions, including regulation of heat and water loss, and also provides a barrier against microbial invasion. An ideal temporary wound dressing replicates the essential functions of intact skin, while providing a protective environment to allow normal wound healing to proceed.

In the design or development of new wound dressings, desirable characteristics include robust antimicrobial activity, improved (or faster) wound healing, and pain relief. A dressing that is efficacious but painful to apply will have little clinical utility. Of these desirable characteristics, only antimicrobial activity is easily quantifiable. Wound healing is multifactorial and may take months to occur, and pain, in particular, is difficult to characterize, document or measure.

The medicinal properties of silver have been known for centuries. Silver ion (Ag^+) has broad antimicrobial activity against bacteria, fungi, and viruses. Since Fox revitalized interest in the use of silver in the form of silver sulfadiazine (SSD) in 1968 [1], many studies have demonstrated the efficacy of silver for burn care or wound infection management [2–18].

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Additionally, minimal development of resistance to silver has been reported, giving it an advantage over other antimicrobial agents [17]. Silver-impregnated dressings have been shown to reduce iatrogenic infection rates and improve wound healing in a number of clinical circumstances [4,9,12,13,15,17,19–23], and the use of silver dressings in the treatment of various wounds including ulcers, burns, and surgical sites is commonplace.

Recent evidence suggests that silver may also reduce wound-associated pain [9,19,22,24–29] although the exact mechanism or mechanisms responsible for this observation are unknown. The pain-relieving effects of silver dressings, while anecdotal, appears to occur over a wide spectrum of clinical situations, including dental pain, skin graft donor sites, thermal burns, and anal fistulae [4,9,19,24–31].

We recently completed a randomized controlled trial evaluating the efficacy of a silver-nylon dressing in reducing surgical site infection (SSI) in patients undergoing elective colorectal surgery with an abdominal incision of at least 3 cm [21]. This study demonstrated a significant reduction in SSI in the silver-nylon dressing group compared to the patients receiving standard gauze dressings (13% vs. 33%, $p = 0.011$). As a secondary outcome of the study, postoperative pain, as self-reported by the patients, was also lower in the silver-nylon dressing group. This prompted our interest in a literature review of the analgesic effects of silver, as well as a re-examination of the patient data to see if any objective measure of pain could be found to complement the subjective finding of pain reduction as reported each postoperative day by the enrolled patients.

2. Materials and methods

The prospective clinical study of SSI reduction was performed at a university-based tertiary referral center under a protocol approved by the University of South Florida Institutional Review Board. The study also collected daily prospective data asking patients to describe their level of postoperative pain. Detailed description of the study population of the SSI study is given in print [21]. To summarize, the study consisted of 110 patients undergoing elective colorectal surgery between July 2009 and April 2010, with a skin incision at least 3 cm in length. Exclusion criteria were: incisions less than 3 cm in length, a known allergy to silver metal, indicators of an abdominal wall infection, the presence of an abdominal mesh that was not planned to be removed at the time of operation, conditions that prevent closure of the primary wound, pregnancy, lactating women, and antibiotics one week prior to surgery. Patients were randomly assigned to receive either silver-nylon or sterile gauze dressings upon closure of the primary wound. All the patients were asked to rate their pain twice daily (every 12 h), using an analog scale of zero (no pain) to 10 (worst pain imaginable). These numbers were recorded by the nurses in the patients' medical charts. Upon completion of the original study, a post hoc review of patient data was undertaken to determine the amount and class (narcotic vs. non-narcotic) of analgesics administered to each patient on a daily basis. All values were obtained from the patients' electronic medical records, and converted into morphine equivalents using parenteral and PO (per os) equianalgesic conversion [32]. It was thought that documentation of analgesic use would provide an objective, but indirect measure of level of patient pain.

The literature search utilized multiple databases including PubMed, EbscoHost, and ScienceDirect. The search terms included "silver", "pain," "wound management," "wound infection," and "patient satisfaction." The search was then further narrowed to articles that included the study and discussion of silver and its effect on pain.

3. Results

3.1. *Clinical study: patient self-reported pain*

120 patients were originally enrolled in the study. 110 patients were included in the final randomization. Fig. 1 (CONSORT diagram) describes the patient population [21]. Detailed description of the results of the SSI study is given in the publication by Krieger et al. [21]. Patient demographics are summarized in Table 1, taken directly from script [21]. In the group of patients receiving the silver-nylon dressing, there was a statistically significant decrease in the self-reported pain scores from postoperative days zero to nine (Fig. 2). All p values, calculated on half-day intervals using the Mann–Whitney U Test, were found to be <0.02. This reduction in pain was independent of SSI status (p values > 0.21). Although the pain scores in the silver-nylon group continue to show a trend of decreased pain beyond postoperative day nine, statistical significance is lost.

3.2. *Clinical study: correlation with analgesic use*

Although our post hoc analysis revealed a significant decrease in pain scores in the silver group between days zero and nine, this did not successfully correlate with analgesic use. Looking at the in-hospital analgesic history of all 110 patients, the silver group was found to have a total average morphine equivalent of 3069.8 (median = 112.7; range = 0–163,005), while the control group averaged 4428.9 (median = 133.3; range = 3.3–205,114.8) over the entire study period. However, this difference was not statistically significant ($p = 0.78$). Excluding patients who had re-operations and/or received involuntary or basal opioid doses, the total average morphine equivalent in the silver group vs. the control group was found to be, respectively, 166.3 (median = 112.7; range = 0–1149) vs. 215.9 (median = 130.8, range = 3.3–11,442.5). This again, however, did not reach statistical significance ($p = 0.21$).

3.3. *Literature review*

Silver-based dressings, including silver nitrate and silver sulfadiazine (SSD), have been a mainstay of burn wound care for nearly 50 years. Several burn studies have reported decreased pain with the use of silver-based dressings [4,9,27,30,31]. Mabrouk et al. [4] demonstrated that the use of a silver-containing hydrofiber dressing is associated with less pain and discomfort compared to a moist open dressing in patients with partial-thickness facial burns. The mean time

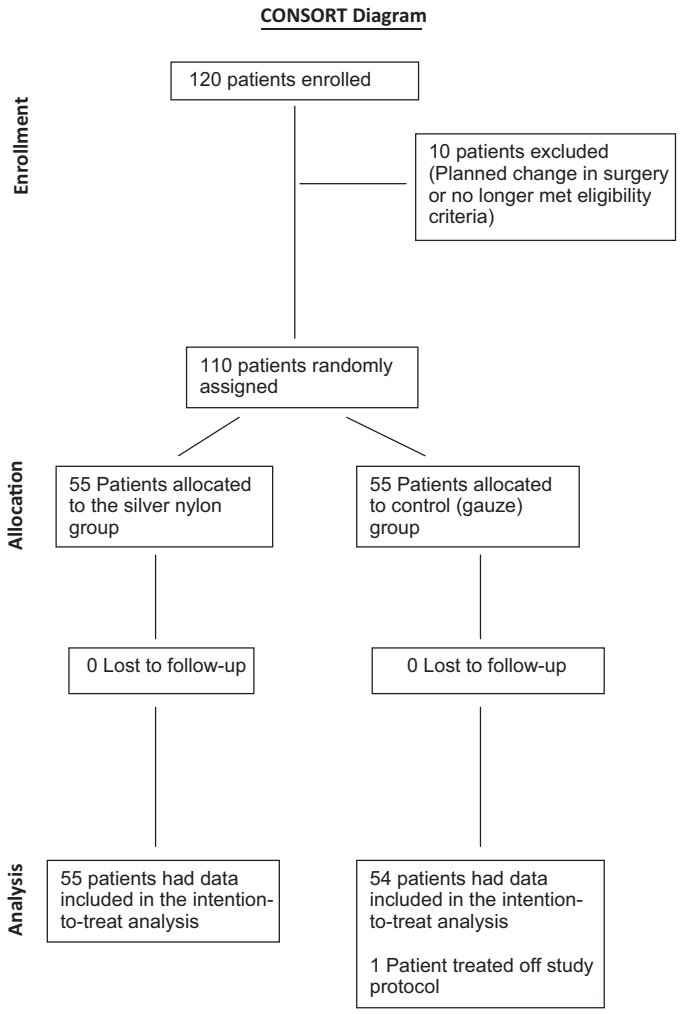

Fig. 1 – Enrollment, randomization, and follow-up of patients (21).

for re-epithelialization in the silver group was 10.5 days vs. 12.4 in the control group ($p < 0.05$), with a lower frequency of dressing changes, less patient discomfort, and a lower perception of pain. Five patients in the silver group described increased pain vs. 10 in the control group. It was also noted that, unlike in the control group, no patients in the silver group required analgesics or anesthesia. Blome-Eberwein and colleagues [9] discussed that a silver-containing hydrofiber dressing, whether adherent or gelled, reduced pain levels in the management of split-thickness donor sites. In a focused review of the pharmacological treatment options for burns, slow release silver dressings were supported as the preferred antimicrobial for burn wound management [27]. In addition to decreasing infection rates, these dressings were found to require fewer changes and reduce discomfort.

Shirani and associates [30] evaluated a silver-nylon dressing, with or without application of a direct current, in the healing of skin graft donor sites. A total of 57 patients were evaluated. Donor sites are a popular wound-healing model, as harvest of split-thickness skin results in a reproducible partial-thickness injury at the donor site. For patients with large burns, matched donor sites on thighs can be harvested, allowing a patient to act as his or her own control. Compared to the standard of care at the time (fine mesh gauze), silver-nylon treated donor sites healed faster (9.3 vs. 12.4 days, $p < 0.05$). Silver-nylon sites were 'pain-free' while fine mesh gauze sites were 'painful until completely healed' [30]. A shortcoming of this study is that silver-nylon sites were kept moist, while fine mesh gauze sites were purposefully dried.

Albrecht et al. [31] repeated the Shirani donor site study 14 years later in 18 burn patients, using a commercially available silver-nylon dressing (Silverlon®) vs. a newer standard of care (Xeroform™ gauze). The average time to wound healing was quicker with silver-nylon dressings (10.2 vs. 11.4 days, $p < 0.05$). Patient-reported pain on postoperative days 1, 2, and 3 was significantly decreased by the use of the silver-nylon dressing ($p < 0.05$).

The effect of silver on pain has also been studied in areas other than burns [19,24–26,28,29]. A silver-containing hydrofiber dressing was found to yield significantly lower pain scores in patients who require surgery for anal fistulas [29]. Wound pain was assessed during the first dressing change following surgery. Of the 29 patients in the silver group, none reported intolerable pain. In contrast, 17 of the 28 patients in

Table 1 – Study group demographics [21].

	Silver nylon ($n = 55$)	Control ($n = 54$)	p
Pateint age, y			**0.049**[a]
Median	62	58	
Sex, n (%)			0.773[b]
Male	28 (51)	26 (48)	
Female	27 (49)	28 (52)	
BMI	27.5	27.3	0.868
Tobacco, n (%)	8 (15)	14 (26)	0.139[b]
Immunosupression, n (%)	4 (7)	6 (11)	0.527[c]
Diabetes, n (%)	5 (9)	4 (7)	1.00[c]
pRBC transfusion, n (%)	7 (13)	0	**0.013**[c]
Type of operation, n (%)			0.778[b]
Laparoscopic-assisted	30 (55)	28 (52)	
Open	25 (45)	26 (48)	
Operation, n (%)			
Small-bowel resection	1 (2)	1 (2)	
Ileocecectomy	2 (4)	3 (6)	
Right colectomy	9 (16)	9 (17)	
Left colectomy	3 (5)	0	
Sigmoid resection	9 (16)	11 (20)	
Hartmann procedure	1 (2)	0	
Subtotal colectomy	3 (5)	7 (13)	
Proctocolectomy	3 (5)	3 (6)	
Proctectomy	1 (2)	3 (6)	
LAR	15 (27)	9 (17)	
APR	2 (4)	5 (9)	
Enterostomy creation	3 (5)	1 (2)	
Enterostomy reversal	2 (4)	2 (4)	
Colovesicle fistula repair	1 (2)	0	
Surgical indication, n (%)			0.353[b]
Neoplastic	36 (65)	34 (63)	
IBD	5 (9)	10 (19)	
Other	14 (25)	11 (19)	
Hospitalization, days			0.210[d]
Median	6	6.5	
Range	3–21	2–17	

pRBC, packed red blood cells; LAR, low anterior resection; APR, abdominoperineal resection.
[a] Student test.
[b] χ^2 test.
[c] Fisher exact probability test.
[d] Mann-Whitney U test.

the gauze control group reported intolerable or higher pain at the first dressing change [29]. In a recent study, 92 randomly assigned emergency department patients requiring incision and drainage of cutaneous abscesses were selected to receive either a silver-containing hydrofiber dressing or iodoform dressing. Average patient pain scores were reported lower at first follow-up visit in the silver group [19]. A study performed in 2011 reported a significant decrease in postoperative pain following circumcision when using a silver-containing dressing [25]. Another study looked at the combination of ibuprofen and silver in a foam dressing for leg ulcers, and found it to effectively reduce pain and promote healing [28]. However, it is not clear as to whether this reduction in pain is entirely attributable to the presence of silver.

Dentistry also utilizes silver-containing products to reduce both tooth hypersensitivity and pain [24,26]. Silver diamine fluoride is used for the prevention of dental caries, and it has also been shown to decrease tooth sensitivity when compared to sterile water [26]. This action of silver on dental sensitivity is re-enforced by a recent study of 126 patients, showing that silver diamine fluoride reduces pain significantly more than oxalic acid in response to a cold stimulus [24].

While several studies show that silver reduces pain, some publications were found to report contradicting evidence. At least one study demonstrated increased rather than decreased pain with the use of silver in wound management [12], and several others suggested that other options were more effective at reducing pain [2,5,8,10,33,34].

A retrospective study in 2008 showed that the use of silver-nylon dressings in patients with painful chronic ulcers decreased pain in only 8.8% of cases, while 35.3% reported an increase in pain and 55.9% reported no change [12]. An ionic hydrogel has been compared to a SSD cream for the treatment of burns, showing it to improve pain scores significantly more than SSD [8]. SSD has also been compared to an aloe vera cream in patients with superficial or partial-thickness burns, revealing faster healing and lower pain scores in the aloe vera group [2]. To put this in perspective, it should be mentioned that the burn topicals developed in the 1960s (silver nitrate, mafenide acetate and SSD) were originally designed to control

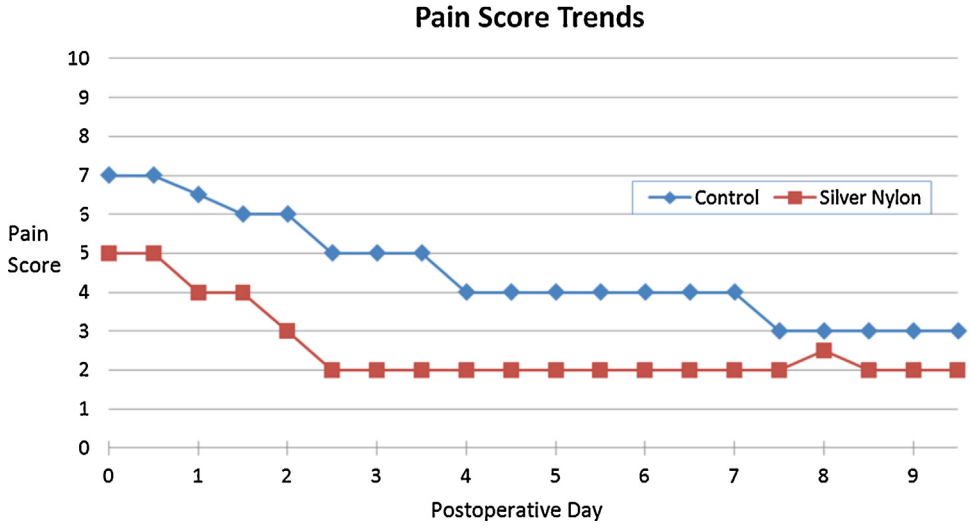

Fig. 2 – Pain score trends: mean daily self-reported pain scores in silver-nylon group vs. control group.

Table 2 – Summary of literature search. Year of publication (reference).

Silver: decreases pain	Silver: increases pain	Silver: other products better
2013 (19). Cutaneous incision & drainage. Hydrofiber SD > iodoform dressing.	2008 (12). Chronic ulcers. SND: ~78% no change in pain, 18% more pain, 4% less pain.	2013 (33). Skin graft donor sites. Transforming methacrylate dressing > carboxymethylcellulose SD.
2013 (29). Anal fistula surgery. Hydrofiber SD > standard gauze dressing.		2013 (2). Second degree burns. Aloe vera > SSD.
2012 (24). Tooth hypersensitivity. Diamine silver fluoride/potassium iodide > oxalic acid.		2012 (34). Infected wounds. Polyhexanide-containing biocellulose dressing > SD.
2012 (4). Partial-thickness facial burns. Aquacel SD > Mebo.		2011 (5). Second degree burns in children. Human amnion > SSD.
2011 (26). Tooth hypersensitivity. Diamine silver fluoride > sterile water.		2010 (8). Minor burns. Procutase > SSD.
2011 (25). Circumcision. Nanometer SD > Vaseline dressing.		2009 (10). Second degree burns. Lyophilized porcine skin > SSD.
2010 (9). Skin graft donor sites. Silver hydrofiber dressing, whether adherent or gelled, decreases pain.		
2008 (27). Review, burn treatment. Silver reduces burn pain/discomfort.		
2008 (28). Infected leg ulcers. Silver/Ibuprofen dressing.		
2007 (31). Skin graft donor sites. SND > occlusive petrolatum dressing.		
1993 (30). Skin graft donor sites. Silver nylon dressing > fine mesh gauze.		

SD: silver dressing; >: is better than; SND: silver nylon dressing; SSD: silver sulfadiazine.

burn wound sepsis in patients with large burns, and were not intended for use on small superficial injuries. In a prospective trial of 78 burn patients randomized to receive either a SSD or lyophilized porcine dermis treatment for their wounds, it was reported that the porcine dermis group required significantly fewer doses of analgesics than the SSD group (oral analgesic mean = 11.5 vs. 4.5, $p = 0.0005$; intravenous analgesic mean = 4.08 vs. 0.92, $p = 0.02$) [10].

A prospective study comparing the use of silver-impregnated carboxymethylcellulose dressings to transforming methacrylate (TMD) dressings in skin graft donors showed that the silver dressing provided faster healing; however, pain was reduced and comfort increased in the TMD group [33]. Silver was also found to be inferior to sterilized human amniotic membrane for pain management in the treatment of pediatric burn patients [5]. In critically colonized or infected wounds, polyhexanide-containing biocellulose dressings were found to produce better pain control (before dressing changes) compared to silver dressings [34].

The results of our literature search are summarized in Table 2.

4. Discussion

Pain is a complex phenomenon, easy to describe but difficult to quantify. There are few, if any, accurate or ethical animal models of pain. In clinical practice, there is no direct objective measure of pain, and administration of analgesics is based on patient self-description of pain, often on an analog scale of 0–10. In burn practice, there are at least three aspects of pain which must be managed: background, procedural, and breakthrough pain. Anxiety, sleep deprivation, and inadequate sedation are factors that also impact pain management.

Both pain and its management with opioids are associated with deleterious effects. Pain produces physiological stress and adrenaline release and can delay the healing process [15,35]. Opioids have several adverse effects, including respiratory depression, mental status changes, delay in return of bowel function, longer hospital length-of-stay, and the risk of dependence. A dressing that could control wound pain at the source, eliminating or lessening the need for systemic analgesics, is highly desirable.

Wound-related pain has been described as having two etiologies. Somatic pain occurs when neurons detect an endogenous change in the temperature, vibration, and swelling or pressure. This pain is described as dull, intense, and ongoing in nature. Event-related pain results from an external source, a direct result of clinical intervention, such as an incision or dressing change [36]. This pain tends to be acute and sharp. Microorganisms involved in wound infections stimulate an inflammatory response, causing the release of inflammatory mediators [37]. Peripheral pain receptors are also directly stimulated by the resultant tissue damage, swelling, and pain mediators, which also increase the

sensitivity of pain receptors, causing an increase in pain perception.

The mechanism by which silver dressings may control pain is unknown. The two most plausible explanations are the provision of a moist and protective air-free wound environment, and the ability to leave dressings in place for extended periods of time. Compared to the twice-daily dressing changes required when burn creams are used, the ability to leave one silver-based dressing in place for up to seven days unquestionably causes less procedural pain. These two mechanisms are the only ones currently accepted by the United States Food and Drug Administration (FDA) when a silver-based dressing claims pain relief. Argentum Medical, LLC, maker of the silver-nylon dressing evaluated in our prospective SSI study, as well as other manufacturers of silver-based dressings, make no claim for any other possible mechanism of action for the reduction of pain.

Other theories have been proposed as to the mechanism by which the silver reduces pain. One theory is that silver reduces inflammation, which consequently decreases pain perception [15,38]. Nadworny and colleagues [39] demonstrated that the use of nanocrystalline silver significantly reduces the inflammatory process of induced dermatitis in pigs. The silver treatment was found to reduce erythema and edema, decrease proinflammatory cytokines and matrix metalloproteinases, and increase apoptosis of dermal inflammatory cells [39].

Bacterial contamination and associated endotoxin concentrations may also prevent wound healing [40]. Kawaguchi et al. [41] demonstrated that the endotoxin-induced production of tumor necrosis factor-alpha (TNF-alpha) inhibits growth factors, resulting in decreased collagen production and impaired wound healing. Another study on rats showed endotoxin to inhibit the early development of tensile strength in wounds [42]. It is possible that the antimicrobial properties of silver may reduce nociception by the reduction of the bioburden in chronically infected wounds and sequestration of bacterial endotoxins [15]. A charcoal dressing containing silver was found to have bactericidal effects on *Pseudomonas aeruginosa* without any consequent endotoxin release, as well as high in vitro endotoxin-binding capacity [40]. This reduction in endotoxin levels promotes re-epithelialization and faster healing [43,44]. It has also been shown that by reducing the levels of matrix metalloproteinases, nanocrystalline silver attenuates the proteolytic environment of the wound, thus promoting more rapid wound healing [45]. While much effort has been made to elucidate the exact mechanisms by which silver reduces pain, these may be multimodal, and further studies are necessary.

Most of the current literature investigating the effect of silver on pain is limited by study design. Trials looking at the efficacy of silver on pain must consider and control for the physical characteristics of the dressing and other confounding factors. For example, providing an occlusive barrier, by itself, has pain-relieving effects. Ideally, the presence of silver would be the only variable in such a trial. Studies have been performed that investigate the effects these physical characteristics have, and their contributions to pain.

Dressings have inherent characteristics that may influence their effect on pain regardless of the active ingredients. A dressing's absorbent properties, for example, may reduce patient discomfort by removing excess fluid from the wound environment [19]. Some wounds benefit from a moist environment, and dressings that provide this moisture may improve pain in such cases [15]. Although there are limited studies that investigate the relationship between these various factors, some have been established which appear to increase pain. The presence of adhesive in a product is one such factor due to the mechanical action of the adhesive on tissue during dressing changes [15]. The phenomenon behind this has been termed 'cyclic acute wound trauma' by Krasner [46], during which removal of the dressing causes trauma to the wound bed and peri-wound epithelium. The World Union of Wound Healing Societies' Principles of best practice [47] and European Wound Management Association's Position document [48] have reported ways to avoid this cyclic trauma. By reducing the occurrence of adhesion to skin, dried-out dressings, and the use of adhesives in designing the dressing, and by decreasing the incidence of maceration, dressing-associated pain can be minimized [15,47,48]. Cutting and Harding [36] asked panel members to subjectively rate dressings according to potential to cause pain at dressing change. Where one represents no potential and nine represents high potential to cause pain, foams were rated lowest and adhesives were rated highest (mean pain potential = 4.2 vs. 8.4, respectively). Overall, silver dressings were rated an average of 4.8, placing them on the lower end of the scale.

Other physical factors which may influence pain include the specific material used in the dressing, and the frequency of dressing change [15]. The effect of difference in material is made evident by Hoekstra and associates [49], comparing a hydrofiber dressing to tulle dressings on partial-thickness rat wounds. The hydrofiber was found to capture granulocytes, thus reducing the number of inflammatory cells within the wound, while repair macrophages remained in the wound bed. In addition, unlike the hydrofiber dressing, the tulle dressing was noticed to embed into the superficial epidermis and cause a disturbed pattern of epithelial outgrowth.

Finally, it is evident that the procedural pain related to dressing change can be minimized by limiting the frequency of changes. Some commercially available silver dressings can be left in place for up to seven days, providing a significant pain advantage over daily dressing changes.

To conclude, the antimicrobial properties of silver are well demonstrated. Anecdotal evidence and clinical experience strongly suggest that silver-based dressings also reduce pain. Unfortunately, studies that support this assertion are limited by small size, poor design, non-control of potential confounding factors, and the examination of pain as a secondary rather than the primary outcome. More rigorous prospective randomized controlled trials looking at pain as the primary endpoint are needed to better evaluate the various silver products available, and their effects on different types of wounds. Further study is also needed to elaborate on the exact mechanisms involved in the reduction of pain before this useful property of silver can be fully appreciated and utilized. The possibility that silver may help in alleviating pain is of great interest, and confirmation of this observation will make silver even more valuable in the treatment of wounds.

Conflict of interest statement

Elia Charbel Abboud: Cura Surgical research funding, 2013.

Jaime E Sanchez: Cura Surgical research funding to the University of South Florida, 2011 (PMID: 21730792).

Jorge E Marcet: Cura Surgical research funding to the University of South Florida, 2011 (PMID: 21730792). Cura Surgical stock ownership, 2012.

Dave Barillo: A paid consultant to Argentum Medical, LLC and serves as co-principal investigator of a research study run by Argentum and funded by the Biomedical Advanced Research Development Agency.

All the other authors have no potential conflict of interest.

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