A Novel Topical Wound Therapy Delivery System

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Abstract: *Introduction.* Wound care dressings have evolved over time, from bandaging to the development of occlusive dressings to negative pressure wound therapy. A novel therapeutic delivery system dressing has been cleared by the United States Food and Drug Administration. This semi occlusive wound dressing has been developed to provide local, continuous delivery of aqueous topical agents, such as therapeutics (anesthetics, antiseptics, antibiotics, steroids, topical beta-blockers, immune modulatory agents, growth factors, and fibrinolytic agents, among others), at a rate of about ¾ mL per day, thus maintaining a hydrated environment and providing topical treatment. This type of system may be beneficial in situations where systemic therapies cannot be used, wounds are small and few, wounds may need frequent application of medication or moisture, or low and steady delivery of medications is needed. *Objective.* The authors assessed a delivery system dressing with different types of liquid medications for the management of hard-to-heal, chronic lower extremity wounds. *Materials and Methods.* Patients aged ≥ 18 and ≤ 90 years with stalled chronic wounds > 30 days' duration were selected for the use of a topical delivery system, which consists of a semi occlusive wound dressing and fluid delivery unit that can provide local application of small therapeutic quantities of medication directly to the wound. *Results.* Several successful cases with the use of this device are presented in which pain relief, enhancement of epithelial migration, inflammation reduction, bacterial control, and wound size reduction were achieved. *Conclusions.* This delivery system dressing is an effective and safe treatment option for wounds. Advantages include reduced potential of systemic side effects, flexibility in what can be delivered, constant rate of medication delivery, and convenience.

Key words: topical delivery system, wound dressing, negative pressure wound therapy, wound irrigation.

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Dressings for acute and chronic wounds have evolved over time. In fact, reference to wound care has been made throughout man's recorded history and has grown significantly. In the mid-1900s, covering wounds was considered objectionable because of fear of increased infection. However, work by Winter and Scales, Hinman and Maibach, and others[1,2] demonstrated improved healing when wounds were covered. An occlusive, and therefore

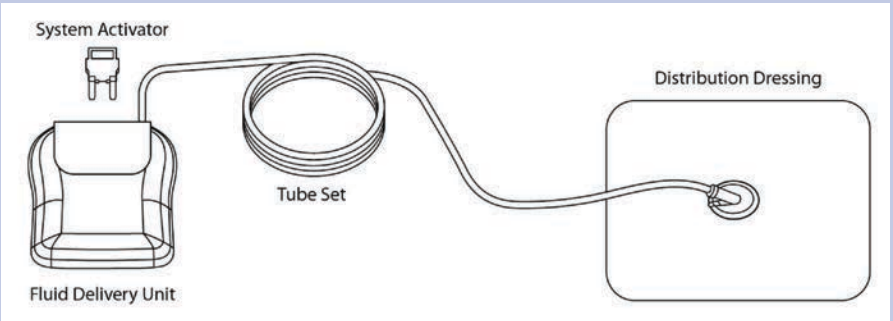

Figure 1. System set-up: activator, fluid delivery unit, tube set connection, and distribution dressing.

moist, environment (as opposed to a dry environment leading to a desiccated wound) facilitates healing through the retained presence of growth factors and matrix materials, improved keratinocyte migration, fibroblast growth, and maintenance of the electrical gradient within the wound bed and at the wound edge.[3]

Wounds managed in a moist environment heal faster with less pain, fewer infections, and less scarring.[4-6] This suggests that the natural formation of a dry scab on an exposed wound is an impediment for wound healing. Other studies[7,8] involving dry techniques showed a decrease in the speed of epidermal regeneration when the surface of the wound was dried.

A prevalent but unjustified concern with the use of occlusive dressings has been risk of infection and contamination. The search for an alternative to occlusive dressings that provides a moist healing environment in these situations led, in part, to treatment with topical irrigation, which not only provides a moist wound environment but also cleans contaminated wounds and removes debris, exudate, and bacteria.[9] Initially conceived for burns, the use of instillation and wound irrigation has now been incorporated into treatment for chronic wounds. Negative pressure wound therapy (NPWT) and negative pressure wound therapy with instillation (NPWTi) have been used in infected and noninfected surgical wounds, traumatic wounds, pressure ulcers, wounds with bone exposure, diabetic foot ulcers, and venous ulcers, among others.[10] In the most recent iteration, NPWTi uses a highly porous polyurethane foam, a semipermeable covering, connecting tubing, and a vacuum source.[11,12]

New therapies for moist wound healing with the use of devices to deliver antimicrobials, analgesics, and a variety of bioactive molecules (ie, growth factors and micrografts) are emerging.[13] The authors evaluated Acton Topical Delivery System (Aplion Medical, Salt Lake City, UT), a semi occlusive wound dressing that provides a steady delivery of multiple types of medications to a wound. In this case series, 4 patients with stalled lower extremity wounds were treated with different types of medication. Distinct from irrigation systems, this technology allows for the local application of small quantities of medication as opposed to larger volume irrigation of the wound. To the best of the authors' knowledge, this is the first published series to evaluate this dressing.

Materials and Methods

Novel delivery technology. Cleared by the United States Food and Drug Administration and recently marketed, this topical delivery system is a semi occlusive wound dressing and fluid delivery unit that can provide continuous delivery of fluid at a rate of approximately ¾ mL per day. The choice of fluid, such as a prescribed medication, solution, or topical agent to the wound, is at the discretion of the provider, and this technology allows for the local application of small therapeutic quantities of medication. The device is for a single use only and will provide a hydrated wound environment enhanced with specific liquid agents for an extended period of up to 7 days.

The device's primary dressing is in direct contact with the wound (Figure 1). It is a trilayer, comfortable dressing that is able to be trimmed to size and distribute fluid to the wound. It allows for the exchange of water vapor, and the nonstick contact layer avoids adherence to the wound, making removal easier and less traumatic. The outer layer protects the dressing and wound from contaminants and has an aperture in the center to allow fluid to pass from the tube set directly into a distribution layer. The tube set is designed to connect the dressing to the outlet port of the fluid delivery unit; it transports the fluid from the fluid delivery unit to the wound dressing.

The fluid delivery unit is small, lightweight, and consists of a flexible fluid bag contained in rigid housing along with a flexible pressure bag. The fluid path within the fluid delivery unit is sterile and operates when the system activator is inserted into the unit. The insertion of the activator initiates the mechanical process (expansion of the pressure bag which presses on the fluid bag), and this pressure

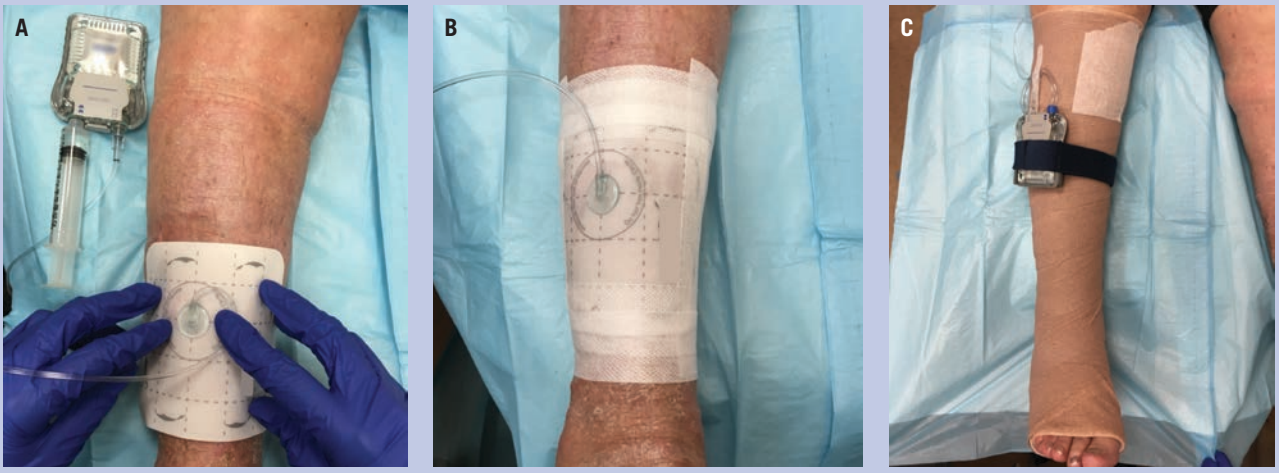

Figure 2. Application of the delivery system dressing: (A) dressing application; (B) dressing secured with provided bandage; and (C) placement of unit over the dressing.

displaces fluid from the fluid bag into the connected tube set and consequently into the wound dressing. Envisioned for acute and chronic wounds, including infected surgical wounds, traumatic wounds, diabetic foot ulcers, and venous ulcers, the delivery technology is not recommended in heavily exudating wounds and actively bleeding wounds. It should be removed while receiving hyperbaric chamber treatment or while undergoing a magnetic resonance imaging procedure. The system should not be used for ophthalmic application.

Application consists of (1) trimming the dressing, placing it over the wound with some overlap of the surrounding normal skin, and securing it with the provided tape; (2) connecting to the fluid delivery unit and filling it with the treatment solution or suspension with an additional fluid bolus to wet the dressing and provide the initial loading of medication; and (3) insertion of the activation chip into the fluid delivery component to begin therapeutic administration (Figure 2). The system is later removed and discarded after the desired fluid volume has been delivered or the desired treatment time has elapsed.

Patients. Patients aged ≥ 18 and ≤ 90 years, with stalled chronic wounds > 30 days' duration, able to bear adequate compression therapy (if applicable), and with satisfactory blood supply (considered by palpable pulse and ankle-brachial index > 0.65) were included. Written informed consent was obtained prior to inclusion in the study. Patients with evidence of wound infection were excluded.

At baseline, demographic information and medical history were collected for all patients. This information included sex, age, weight, known allergies, past medical history, medications, vital signs, pain level, wound location, duration, and size. Wound size was calculated by measuring the highest length and width with a standard paper ruler. Wounds with < 30% healing within the previous 4-week period were categorized as chronic and hard-to-heal and were enrolled in the study.

Patients were treated according to wound care recommendations, such as offloading therapy for diabetic foot ulcers and appropriate compression for venous leg ulcers. Necrotic tissue was removed with sharp debridement prior to the study. The delivery system dressing was applied weekly in contact with the wound and covered with adequate secondary dressing, ie, nonelastic/elastic bandages. Medications used in this series included anesthetics, adrenergic beta blockers, steroids, and antiseptics.

During treatment, weekly photographs of the wound; self-reported patient pain level using a 0-10 point scale, eg, Verbal Numerical Rating Scale (VNRS); and clinical signs were assessed and recorded. Change in wound size was determined by comparing wound size measurements at each week. Treatment was stopped if the patient decided not to participate in the study anymore or due to lack of treatment compliance.

Results

Case 1: anesthetic for pain. A 78-year-old man, with severe peripheral vascular disease with bilateral stent placement 5 years prior and a recent recanalization of his left superficial femoral artery, presented with 2 very painful left leg ulcers of 6 months' duration. His previous medical history included pulmonary embolism, chronic obstructive

pulmonary disease, and smoking (40 pack-year) prior to presentation. On physical examination, the left leg was erythematous and tender (5/10 via VNRS) with 2 superficial, granulating ulcers 2.2 cm x 1.9 cm and 1.9 cm x 2.1 cm in size. The patient agreed to try the delivery system dressing with a different solution for each wound: 2% lidocaine and NaCl 0.09%. After 1 week, there was a significant superior pain decrease in the ulcer treated with lidocaine (1/10 via VNRS) and a slight decrease of pain (4/10 via VNRS) with the use of saline.

Case 2: beta blockers for healing. An 89-year-old woman presented with a superficial ulcer on the anterior surface of the right lower leg. The patient stated that the ulcer began after she bumped her leg 7 months before. Since then, the ulcer had increased in size despite seeking dermatological medical attention. She had a history of lymphedema for which lymphatic massage and compression bandaging were applied with only mild improvement. Upon physical exam, a shallow ulcer of 4.1 cm x 3.4 cm was found on the right anterior lower leg. The delivery system dressing was used to deliver timolol 0.25% to the wound bed. After 2 weeks of this therapy and 2-layer compression, the wound showed epithelialization over almost its entirety with decreased wound size. The wound healed completely 1 week after the last treatment (ie, 4 weeks after presentation).

Case 3: steroids for inflammatory ulcers. A 62-year-old man presented with a nonhealing ulcer on his left anterior leg after bumping it at the gym 2 months prior. He had a previous medical history of diabetes mellitus, hypertension, and coronary artery disease with bypass. The physical examination showed small, coalescing, and punched-out ulcers covering an area of 4 cm x 5.1 cm associated with mild edema and pain (8/10 via VNRS); pulses were palpable. Clinical diagnosis of pyoderma gangrenosum was corroborated by histology and negative tissue cultures. The patient initially received intralesional triamcinolone and topical clobetasol in combination with full compression, with 10% reduction of wound size and pain in 4 weeks. The patient was then treated with the delivery system dressing for the delivery of triamcinolone 0.1% for 1 week. Ulcers further reduced in size (3.7 cm x 4.9 cm), and the patient reported a significant decrease in pain (3/10 via VNRS). Patient achieved full wound closure 4 months after presentation with systemic therapy.

Case 4: topical dilute betadine for bacterial control. A 67-year-old man presented with a posttraumatic, chronic, nonhealing ulcer on the medial aspect of his left lower extremity that had fluctuated in size over the past 9 years but never achieved complete closure. Base therapy consisted of multilayer compression wrap composed of Unna's boot (BSN medical, Charlotte, NC), Ace (3M, St Paul, MN), and Coban (3M), with adjuvant treatment of several cellular-tissue products over the years. The patient had a previous medical history of bilateral chronic venous hypertension, posttraumatic Charcot foot, chronic kidney disease, hepatitis C infection, chronic pain, and asthma. Physical exam showed an ulcer of 6 cm x 2.5 cm with a red granulating base, slight yellow slough, and a dry periwound area on the left medial malleolar region without excessive odor or drainage. Gram-positive cocci in pairs, chains, and clusters; Gram-negative bacilli, and *Enterococcus* spp were found on the wound bed culture.

The device was utilized to deliver dilute betadine at 0.35% to the wound bed for the purpose of bacterial control via a semiquantitative method along with a 3-layer wrap. Weekly culture swabs were obtained during office visits. After 2 weeks of therapy, a 50% reduction of bacterial burden was noticed on the wound bed, especially for Gram-positive cocci in pairs and chains and *Enterococcus* spp that were completely eliminated from the ulcer. By therapy week 4, the burden of Gram-negative bacilli and Gram-positive cocci in clusters was reduced in 75%. Along with the bacterial reduction, a reduction in size was noted, with wound measurements of 3.5 cm x 1 cm at the end of the 4-week trial period.

Discussion

Depending on the wound etiology and pathophysiology in question, situations in which the new delivery system dressing should be considered are: clinical conditions where systemic therapy is associated with deleterious side effects; wounds not exceeding 100 cm^2 in size; recurrent wounds; wounds that may benefit from an application of moisture; wounds that are dry to moderately exudative, in need of pain control, with dry, hardened bases; and wounds that could benefit from a small but continuous, steady dose of medication. Considering these needs and experiences with other topical forms of medication application, some drugs may be suitable for sustained delivery and may prove useful in the delivery system dressing, such as:

Anesthetics. Lidocaine, part of the amide group of anesthetics, is the most available and accessible representative drug of this class. The more commonly used presentation of anesthetics for cutaneous procedures is the injectable form, lidocaine hydrochloride, which is a sterile, nonpyrogenic, aqueous solution. The pH of the solution is approximately 6.5 (5.0–7.0) and can be used with or without epinephrine. The maximum dose of injected lidocaine without

epinephrine is 4 mg/kg. It has been asserted that topical bioavailability is very limited, under 3%.[14] Lidocaine is metabolized in the liver. It works by stabilizing the neuronal membrane by inhibiting the ionic fluxes for the initiation and conduction of impulses. Bupivacaine, another amide anesthetic solution, can be used as well. The proposal of a system that delivers the medication continuously at a steady, low rate seems to be an alternative to circumvent the short time of effect after only a 1-time application. There should always be a cautious application of this medication in patients with compromised liver function, as this can alter lidocaine kinetics.

Antiseptics. Multiple randomized controlled trials (RCTs) have used instillation of different antiseptics such as polyhexanide, povidone, and sodium hypochlorite solution.[15] Polyhexanide has been used for more than 60 years without evidence of resistance. On the surface of the bacterial cell, polyhexanide forms a molecular net that changes the osmotic pressure and increases permeability, resulting in the release of lipopolysaccharides (Gram-negative bacteria) and potassium ion efflux as well as eventual organism death. It has shown great activity against fungi, yeast, and Gram-negative and Gram-positive bacteria, including methicillin-resistant *Staphylococcus aureus* (MRSA), *Pseudomonas aeruginosa*, and vancomycin-resistant enterococci. Timmers et al[16] showed less recurrence of wound infection and shorter hospital stay than the control. While concentrated povidone-iodine is cytotoxic, low concentrations have broad-spectrum antimicrobial activity without inhibiting cell growth. Low concentrations are bactericidal against some resistant strains of bacteria such as MRSA via destabilization of the bacterial cell wall and disruption of the membrane that results in leakage of the intracellular components. Clinical studies have confirmed that sodium hypochlorite solution (Dakin's solution) is bactericidal to the organisms commonly found in open wounds such as *S aureus, P aeruginosa*, *Escherichia coli, Enterococcus* spp, and *Bacteroides fragilis*.[17-19] Therefore, delivery of topical antiseptics can be a treatment option for chronic wounds.

Antibiotics. Junker et al[20] demonstrated that topical delivery of high concentrations of gentamicin is highly effective in reducing bacterial levels in infected porcine full-thickness wounds. Decubitus ulcers may benefit from the use of topical metronidazole gel to reduce bacterial load on fungating malignant wounds or sites prone to anaerobic growth.[21] Also, topical vancomycin has been shown to be safe and effective in reducing surgical site infections after craniotomy and spine surgery.[22] Thus, prevention and control of infection seem to be feasible through topical medication delivery. Several antibiotics have been used with NPWTi such as vancomycin, gentamycin, tobramycin, polymyxin B, bacitracin, and neomycin; their use is off label in the United States and consensus is still an issue.[19] Further studies are needed on this new mode of delivery to build consensus on its use.

Steroids. Depending on changes in the basic structure of the glucocorticosteroid molecule, topical agents will have different solubility, lipophilic properties, degrees of percutaneous absorption, and glucocorticoid receptor-binding activities. The glucocorticosteroid enters the cells and binds to its receptors in the cytoplasm. They are then translocated to the nucleus of the cell to bind to genes at promoter regions, which will affect transcription, production of messenger ribonucleic acid, and protein synthesis. Some of the transcription that is affected relates to inflammatory responses. The main cytokines and proinflammatory molecules inhibited are leukotrienes; prostaglandins; tumor necrosis factor alpha; granulocyte-macrophage colony-stimulating factor (GM-CSF); interleukin (IL)-1, IL-2, IL-6, and IL-8; and intercellular adhesion molecule 1. These anti-inflammatory effects are achieved by topical, intralesional, intramuscular, and oral therapies, among others. For the delivery system dressing, the corticosteroids used for intralesional therapy (triamcinolone acetonide) and ophthalmic therapy are good choices given that they are in aqueous solutions. As a reminder, despite the fact that the delivery system dressing can use solutions that are intended for other purposes, clinical judgment should be used in selecting the appropriate medication.

Topical beta-blockers. Beta-2 adrenergic antagonists are thought to promote wound healing through stimulation of keratinocyte migration as demonstrated by some studies.[23,24] A representative drug readily available through prescription is timolol, a topical beta-2 adrenergic receptor antagonist originally indicated for treatment of glaucoma. It has shown to promote the healing of chronic, recalcitrant wounds in several studies, such as in venous leg ulcers and diabetic foot ulcers.[23,25-27] In these studies, the concentration of timolol maleate ophthalmic solution used was 0.5% and the dose averaged about 1 drop per cm^2. Application varied from daily to weekly depending on the type of wound care the patient was receiving. This represents another potential agent for a sustained delivery system this product

Immune modulatory agents. Cyclosporine has been used in the treatment of various inflammatory diseases in dermatology and studied in pyoderma gangrenosum.[28] Cyclosporine inhibits cellular and humoral immune responses by modifying inflammatory responses. It prevents pathological

apoptosis of secretory epithelium induced by the occlusion of nonspecific pores in the mitochondrial membrane. Cyclosporine decreases expression of IL-2, among other cytokines, and inhibits helper T-cell activation. Recently, more research has focused on its topical use on the skin. Kumar et al[29] demonstrated safety and success with the use of liposomal formulations in limited chronic plaque psoriasis. In ophthalmology, it has been used topically in an extensive manner.[29] One of the drawbacks of cyclosporine therapy in the eye is that the 0.05% ophthalmic emulsion has rapid elimination and does not reach certain areas of the eye, making the treatment duration crucial to reach a therapeutic effect. A novel vehicle with cationic properties has been launched and is available in some European countries to overcome the latter difficulty with the emulsion.[30] Again, this represents a niche where the continuous delivery of medication could be a solution.

Growth factors. Granulocyte-macrophage colony-stimulating factor is another potential medication that has proven its efficacy and safety profile for topical use. It is a cytokine shown to have important biological effects on in vivo wound healing. It promotes myofibroblast differentiation and wound contracture, local recruitment of inflammatory cells and Langerhans cells, and epidermal proliferation; GM-CSF also stimulates the immune system as it aids in the differentiation of hematopoietic progenitor cells.[31] Although GM-CSF has shown efficacy in wound healing through local application, it has not done so by systemic administration.[31] In the works by Zhang et al,[32] Liu et al,[33] and Wang et al,[34] there was evidence of accelerated wound healing in patients with second-degree burns with topical application of GM-CSF hydrogel. For many clinical trials on growth factors, the method of delivery has been a question; this novel delivery system dressing may have applications more widely in this area.

Fibrinolytic agents. Stanozolol is a synthetic steroid derived from dihydrotestosterone. It has anabolic properties and high oral bioavailability. In addition, it has been used in several endocrine conditions, on hereditary angioedema, and as an anabolic to improve muscle growth. This medication has been shown to stimulate collagen synthesis[35] and to increase plasminogen activator activity, reduce plasma fibrinogen, and increase protein C and antithrombin III, resulting in fibrinolysis.[36,37] Most studies were performed on patients taking the medication orally. Nevertheless, this medication is also available in aqueous suspension for intramuscular injections.

Anti-inflammatory agents. Ketorolac is a nonsteroidal, anti-inflammatory drug used as an analgesic for moderate to severe pain. This class of medication works by nonselectively blocking the cyclooxygenase pathway, inhibiting prostaglandins synthesis. Besides oral administration, there is also an intramuscular administration and an ophthalmic solution. A study on the effects of anti-inflammatory agents on surgical wounds found subcutaneous instillation of ketorolac with bupivacaine was significantly more associated with decreased surgical pain after caesarian delivery compared with hydromorphone with bupivacaine.[38] Also, Carvalho et al[38] were able to demonstrate significant reduction of IL-10 on the wound exudate of patients receiving ketorolac with bupivacaine. Another RCT[39] found topical anti-inflammatory propylbetaine-polihexanide solution superior to normal saline for reducing inflammatory signs and accelerating the healing of vascular leg ulcers and pressure ulcers.

Sodium thiosulfate (STS). Administration of STS in patients affected by calciphylaxis has shown some favorable results amidst no treatment options.[40] Calciphylaxis, or calcific uremic arteriolopathy, is a rare disorder that leads to calcification of cutaneous vessels, causing severe painful ulcerations. It is most commonly seen in patients with end-stage renal disease. The physiopathology is unknown and may be related to the unique abnormalities in mineral metabolism and vascular calcification in these patients.[41] Mortality is high, and sepsis is the leading cause of death. Recent case reports[42,43] demonstrated benefits of the use of intralesional STS for patients with calciphylaxis. The proposed mechanism of action is through chelation and increased calcium solubility in the blood, transforming calcium into calcium thiosulfate salts, which are more soluble than other salts. It also may increase the production of hydrogen sulfide, which has vasodilatory, antioxidant, and anti-inflammatory properties and may inhibit vascular calcifications. A report of 4 cases of calcinosis cutis with the use of topical sodium meta-bisulfite (SM), which yields the same metabolite that STS does (sodium sulfate), showed favorable response with the use of SM topically.[44] The mechanism of action proposed is inhibition of calcium oxalate agglomeration. It is plausible to infer that the delivery system dressing would be an excellent option for patients afflicted with painful calciphylaxis ulcers once a soluble vehicle could be developed to deliver SM to the wounds.

In addition, in an initial poster presentation[45] on 15 patients who received 57 applications primarily of gentamicin in different types of wounds, there was antidotal evidence of improved wound healing. The work consisted primarily of a 0.3% gentamicin solution, or sterile water, or normal saline in the dressing system for up to 5 days. Analysis of

device functionality and ability to apply and remove the device as well as evaluation of interference with activities with daily leaving (ADL) with a questionnaire was performed. Ninety-one percent of patients had no limitations of ADL. The majority of the wounds had improved healing rates compared with prior treatments.[46] In addition, the device was used in another 44 applications and found to reduce pain and bioburden in yet unpublished work by the same authors.

Conclusions

Based on results with the system herein, the authors could assert that the delivery system dressing is appealing for various reasons: (1) the topical delivery of medication avoids the systemic effect of drug therapy; (2) medications are delivered on a steady rate, overcoming the issues of time to absorption and inconsistent therapy application; (3) it has shown to significantly help a patient with pain related to the wound; and (4) the system does not depend on the patient or on a skilled wound care nurse for frequent dressing changes for medication application. Limitations that can play a role in the outcomes relate to the type of solution used, the pH, temperature, and osmolality of the medications vehicles. These factors affect absorption and availability of the active components. Contact dermatitis to the dressing adhesive or maceration may occur. Taking into account all of these observations, the authors believe the delivery system dressing is a promising form of therapy that will bring convenience and ease of use that would otherwise not be applied to patients at an optimal rate.

References

1. Winter GD, Scales ST. Effect of air drying and dressings on the surface of a wound. *Nature*. 1963;5(197):91–92.
2. Hinman CD, Maibach H. Effect of air exposure and occlusion on experimental human skin wounds. *Nature*. 1963;200:377–378.
3. Eaglstein WH. Moist wound healing with occlusive dressings: a clinical focus. *Dermatol Surg*. 2001;27(2):175–181.
4. Doughty DB, McNichol LL; Wound, Ostomy and Continence Nurses Society. *Wound, Ostomy and Continence Nurses Society Core Curriculum: Wound Management*. Philadelphia, PA: Wolters Kluwer; 2016:112–114.
5. Ousey K, Cutting KF, Rogers AA, Rippon MG. The importance of hydration in wound healing: reinvigorating the clinical perspective. *J Wound Care*. 2016;25(3):122,124–130.
6. Beam JW. Management of superficial to partial-thickness wounds. *J Athl Train*. 2007;42(3):422–424.
7. Winter GD, Scales JT. Effect of air drying and dressings on the surface of a wound. *Nature*. 1963;197:91–92.
8. Joseph J, Townsend FJ. The contribution of migratory epithelium and the relation of wound enlargement to healing. *J Anat*. 1961;95(Pt 3):403–410.
9. Kim PJ, Attinger CE, Steinberg JS, et al. Negative-pressure wound therapy with instillation: international consensus guidelines. *Plast Reconstr Surg*. 2013;132(6):1569–1579.
10. Venturi ML, Attinger CE, Mesbahi AN, Hess CL, Graw KS. Mechanisms and clinical applications of the vacuum-assisted closure (VAC) device: a review. *Am J Clin Dermatol*. 2005;6(3):185–194.
11. Fleischmann W, Strecker W, Bombelli M, Kinzl L. Vacuum sealing as treatment of soft tissue damage in open fractures. [Article in German.] *Unfallchirurg*. 1993;96(9):488–492.
12. Fleischmann W, Lang E, Kinzl L. Vacuum assisted wound closure after dermatofasciotomy of the lower extremity. [Article in German.] *Unfallchirurg*. 1996;99(4):283–287.
13. Junker JP, Kamel RA, Caterson EJ, Eriksson E. Clinical impact upon wound healing and inflammation in moist, wet, and dry environments. *Adv Wound Care* (New Rochelle). 2013;2(7):348–356.
14. Paudel KS, Milewski M, Swadley CL, Brogden NK, Ghosh P, Stinchcomb AL. Challenges and opportunities in dermal/transdermal delivery. *Ther Deliv*. 2010;1(1):109–131.
15. Wilkins RG, Unverdorben M. Wound cleaning and wound healing: a concise review. *Adv Skin Wound Care.* 2013;26(4):160–163.
16. Timmers MS, Graafland N, Bernards AT, Nelissen RG, van Dissel JT, Jukema GN. Negative pressure wound treatment with polyvinyl alcohol foam and polyhexanide antiseptic solution instillation in posttraumatic osteomyelitis. *Wound Repair Regen*. 2009;17(2):278–286.
17. Lineaweaver W, Howard R, Soucy D, et al. Topical antimicrobial toxicity. *Arch Surg*. 1985;120(3):267–270.
18. McKenna PJ, Lehr GS, Leist P, Welling RE. Antiseptic effectiveness with fibroblast preservation. *Ann Plast Surg*. 1991;27(3):265–268.
19. Kim PJ, Attinger CE, Olawoye O, et al. Negative pressure wound therapy with instillation: review of evidence and recommendations. *Wounds*. 2015;27(12):S2–S19.
20. Junker JP, Lee CC, Samaan S, et al. Topical delivery of ultrahigh concentrations of gentamicin is highly effective in reducing bacterial levels in infected porcine full-thickness wounds. *Plast Reconstr Surg*. 2015;135(1):151–159.
21. Witkowski JA, Parish LC. Topical metronidazole gel. The bacteriology of decubitus ulcers. *Int J Dermatol*. 1991;30(9):660–661.
22. Abdullah KG, Attiah MA, Olsen AS, Richardson A, Lucas TH. Reducing surgical site infections following craniotomy: examination of the use of topical vancomycin [published online ahead of print June 19, 2015]. *J Neurosurg*.

2015;123(6):1600–1604.
23. Braun LR, Lamel SA, Richmond NA, Kirsner RS. Topical timolol for recalcitrant wounds. *JAMA Dermatol*. 2013;149(12):1400–1402.
24. Arbabi S, Ahrns KS, Wahl WL, et al. Beta-blocker use is associated with improved outcomes in adult burn patients. *J Trauma*. 2004;56(2):265–269.
25. Sivamani RK, Shi B, Griffiths E, et al. Acute wounding alters the beta2-adrenergic signaling and catecholamine synthetic pathways in keratinocytes [published online ahead of print March 10, 2014]. *J Invest Dermatol*. 2014;134(8):2258–2266.
26. Tang JC, Dosal J, Kirsner RS. Topical timolol for a refractory wound [published online ahead of print October 31, 2011]. *Dermatol Surg*. 2012;38(1):135–138.
27. Lev-Tov H, Dahle S, Moss J, Isseroff RR. Successful treatment of a chronic venous leg ulcer using a topical beta-blocker. *J Am Acad Dermatol*. 2013;69(4):e204–e205.
28. Alavi A, French LE, Davis MD, Brassard A, Kirsner RS. Pyoderma gangrenosum: an update on pathophysiology, diagnosis and treatment. *Am J Clin Dermatol*. 2017;18(3):355–372.
29. Kumar R, Dogra S, Amarji B, et al. Efficacy of novel topical liposomal formulation of cyclosporine in mild to moderate stable plaque psoriasis: a randomized clinical trial. *JAMA Dermatol*. 2016;152(7):807–815.
30. Ambroziak AM, Szaflik J, Szaflik JP, Ambroziak M, Witkiewicz J, Skopinski P. Immunomodulation on the ocular surface: a review [published online ahead of print July 15, 2016]. *Cent Eur J Immunol*. 2016;41(2):195–208.
31. Barrientos S, Brem H, Stojadinovic O, Tomic-Canic M. Clinical application of growth factors and cytokines in wound healing. *Wound Repair Regen*. 2014;22(5):569–578.
32. Zhang L, Chen J, Han C. A multicenter clinical trial of recombinant human GM-CSF hydrogel for the treatment of deep second-degree burns. *Wound Repair Regen*. 2009;17(5):685–689.
33. Liu L, Fang Y, Yao M, Yu W, Li X. Effect of recombinant human granulocyte-macrophage colony-stimulating factor on wound debridement and healing of deep II thickness burn. [Article in Chinese.] *Zhongguo Xiu Fu Chong Jian Wai Ke Za Zhi*. 2011;25(9):1059–1062.
34. Wang ZY, Zhang Q, Liao ZJ, et al. Effect of recombinant human granulocyte-macrophage colony stimulating factor on wound healing in patients with deep partial thickness burn. [Article in Chinese.] *Zhongguo Xiu Fu Chong Jian Wai Ke Za Zhi*. 2008;24(2):107–110.
35. Wright JK, Smith AJ, Cawston TE, Hazleman BL. The effect of the anabolic steroid, stanozolol, on the production of procollagenase by human synovial and skin fibroblasts in vitro. *Agents Actions*. 1989;28(3–4):279–282.
36. Kluft C, Preston FE, Malia RG, et al. Stanozolol-induced changes in fibrinolysis and coagulation in healthy adults. *Thromb Haemost*. 1984;51(2):157–164.
37. Small M, Kluft C, MacCuish AC, Lowe GD. Tissue plasminogen activator inhibition in diabetes mellitus. *Diabetes Care*. 1989;12(9):655–658.
38. Carvalho B, Lemmens HJ, Ting V, Angst MS. Postoperative subcutaneous instillation of low-dose ketorolac but not hydromorphone reduces wound exudate concentrations of interleukin-6 and interleukin-10 and improves analgesia following cesarean delivery [published online ahead of print December 4, 2012]. *J Pain*. 2013;14(1):48–56.
39. Bellingeri A, Falciani F, Traspedini P, et al. Effect of a wound cleansing solution on wound bed preparation and inflammation in chronic wounds: a single-blind RCT. *J Wound Care*. 2016;25(3):160, 162–166, 168.
40. Generali JA, Cada DJ. Sodium thiosulfate: calciphylaxis [published online ahead of print November 24, 2015]. *Hosp Pharm*. 2015;50(11):975–977.
41. McCarthy JT, El-Azhary RA, Patzelt MT, et al. Survival, risk factors, and effect of treatment in 101 patients with calciphylaxis. *Mayo Clin Proc*. 2016;91(10):1384–1394.
42. Ossorio-García L, Jiménez-Gallo D, Arjona-Aguilera C, Linares-Barrios M. Intralesional sodium thiosulfate to treat calciphylaxis [published online ahead of print December 28, 2015]. [Article in English, Spanish.] *Actas Dermosifiliogr*. 2016;107(4):359–362.
43. Strazzula L, Nigwekar SU, Steele D, et al. Intralesional sodium thiosulfate for the treatment of calciphylaxis. *JAMA Dermatol*. 2013;149(8):946–949.
44. Del Barrio-Diaz P, Moll-Manzur C, Alvarez-Veliz S, Vera-Kellet C. Topical sodium metabisulfite for the treatment of calcinosis cutis: a promising new therapy [published online ahead of print April 17, 2016]. *Br J Dermatol*. 2016;175(3):608–611.
45. Robins M GA. Evaluation of an innovative new device for wound healing. Poster presented at: WOCN Society & CAET Joint Conference; June 4–8, 2016; Montreal, Quebec, Canada.
46. Gwilliam A. Kick-start stalled wounds: case series evaluating an innovative fluid delivery system for wound healing. Poster presented at: WOCN Society & CAET Joint Conference; June 4–8, 2016; Montreal, Quebec, Canada.