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SYMPOSIUM

Novel Use of Insulin in Continuous-Instillation Negative Pressure Wound Therapy as "Wound Chemotherapy"

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Abstract

Negative pressure wound therapy (NPWT) is frequently employed in the treatment of complex wounds. A variety of wound chemotherapeutic agents such as insulin, which acts as a growth factor, may prove helpful in treatment as well. We present a case report in which insulin was used as a chemotherapeutic agent in continuous-instillation NPWT. To our knowledge, this is the first report in the literature describing this method of delivery.

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Introduction

Negative Pressure Wound Therapy (NPWT) became popular for use in wound healing over a decade ago.[1,2] Theoretically, NPWT assists in development of granulation tissue, leads to wound contracture and neo-epithelization, removes interstitial fluid and infectious materials when applied to wound edges, and provides a closed, moist wound-healing environment.[3] Negative pressure wound therapy assists in preparing wounds to heal by secondary intention or to be closed through simple reconstructive means but can also provide an ideal dressing to help increase the chances of skin graft incorporation.[3] It has been indicated for use in diabetic foot wounds, pressure ulcers, chronic wounds, acute or traumatic wounds, dehisced surgical wounds, partial-thickness burns, and flaps or grafts.

Positive effects of NPWT on wound healing have been demonstrated in both the laboratory[2,4] and in a multicenter randomized controlled study of NPWT use after partial diabetic amputations.[5] These data suggest that NPWT may yield a higher proportion of healed wounds, a faster time to wound closure, and a more rapid and robust granulation tissue response.[5,6]

Negative Pressure and Fluid Instillation Therapy

Modifications to traditional NPWT devices now allow the use of fluid instillation therapy in combination with NPWT. Instillation therapy was designed to reduce the bioburden within the wound and promote healing and has been shown in select cases to help in pain control.[7–9]

There are currently two instillation-based NPWT devices—Wound V.A.C.® Instill System (Kinetic Concepts, Inc., San Antonio, TX) and Svedman's Sved™ Wound Treatment

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Abbreviations: (IGF) insulin-like growth factor, (NPWT) negative pressure wound therapy, (STSG) split-thickness skin graft

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Systems (Innovative Therapies, Inc., Hunt Valley, MD)—offering fluid instillation therapy applications. Wound V.A.C. Instill System offers intermittent periods of instillation (instillation of fluids for 20 s, hold for 5 min, and repeat every 3 h) along with continuous or intermittent suction. This weighs 14.5 lbs and has a battery life of only 4 h. Svedman's Sved Wound Treatment Systems offers continuous streaming of instillation fluids, weighs only 1.9 lbs, and has a battery life of 12 h.

The solutions currently being used for instillation NPWT are currently limited to normal saline. Solutions such as insulin, phenytoin (Dilantin), sodium hypochlorite (Dakin's solution), and polyhexanide (Prontosan, Braun Medical) have been proposed as potentially useful agents. We prefer the use of what we call "real-time streaming" therapies rather than the instillation therapies that involve hold periods. It has been our experience that the latter do not address problems like periwound maceration as well as real-time streaming. For this reason, we have either modified the standard V.A.C. device to input a second instillation port or we have used the currently available Sved device.[10]

Historical Development of Insulin in Wound Healing

Insulin has long been recognized as an important contributor to wound healing,[11] and many studies have demonstrated the positive effects of insulin on wound healing.[11–18] Insulin-like growth factor (IGF), which has a high sequence similarity to the hormone insulin, has been shown through *in vivo* studies to stimulate the proliferation, migration, and extracellular matrix excretion by keratinocytes, endothelial cells, and fibroblasts, and even promote the reformation of granulation tissue.[18–20] Topical formulations of insulin was utilized in the 20th century in an attempt to control local hyperglycemia of peripheral tissue. However, later investigations have focused on topical insulin applications as it relates to insulin growth factors.

Belfield *et al.*[21] tested the application of a cream compound with 10 U of zinc protamine insulin and 1 g of base (Ulcerin) on chronic and debilitating wounds (such as pressure sores, ulcers, and fistulae) in canine and feline subjects. The results from their study demonstrated a normalization of cell permeability, increased vascularization, enhanced phagocytosis (autodebridement), and stimulated proliferation. Additional benefits included reduced exudation, arrested bacteria, decreased tissue hypoxia, reduced edema, increased wound contraction, reduced inflammation, and greatly reduced healing time. Pierre and associates,[14] in their study of systemic administration of insulin in nondiabetic burn patients, found that chronic administration of high doses of insulin with glucose significantly decreased donor-site healing time by two to three days and improved structural wound matrix formation and protein kinetics.

Lopez and Mena[22] reported on the use of local insulin irrigation (30–60 IU of isophane insulin daily) in two cases of diabetic infectious gangrene that were resistant to all other current therapies and found that the treatment accelerated wound healing with no notable systemic side effects.

Greenway et al.[17] published results from a randomized double-blind placebo-controlled trial that tested the relative roles of insulin (lletin-II) and zinc in the acceleration of wound healing of the forearm in diabetic and non-diabetic human subjects. The investigators concluded that topical application of insulin accelerated wound healing in both diabetic and nondiabetic human wounds.

Zhang and colleagues[23] reported on the use of an insulin–zinc suspension delivery by local injection into skin donor sites. These investigators concluded that local injection of a small dose, 0.2 U, of long-acting insulin–zinc suspension stimulated wound DNA synthesis without any major systemic side effects and thereby provided a safe and effective approach to accelerate wound healing.

Journal of Surgical Research published a study on the use of local insulin–zinc injection into skin donor site wounds in rabbits. In this study, Zhang and associates[24] found that injections of an extended insulin–zinc suspension (Humulin, Eli Lilly and Co., Indianapolis, IN), which was added to an albumin–saline solution (75 mg albumin per ml of 0.9% sodium chloride) at a final concentration of 0.25 or 1.0 U/ml, to four sites of the wound periphery and a fifth at the wound center accelerated skin wound healing, reduced mean healing time by 25%, and did not increase plasma insulin concentration. Histological analysis of wound tissues in this study suggested that the accelerated healing was likely due to the insulin-induced stimulation of epidermal growth factor and keratinocyte proliferation, which was consistent with previous reports.[25]

Wilson *et al.*[26] reported a case of topical irrigation with 20 ml normal saline and 2 U of human soluble insulin (Actrapid) being used in a chronic nonhealing wound

following laparotomy of an 80-year-old woman after conventional dressing attempts and a three-week NPWT course all failed. The investigators reported that, after seven days of normal saline and insulin irrigation, there was visible improvement in wound healing without any systemic side effects such as hypoglycemia.

Rezvani and colleagues,[27] in a double-blind randomized placebo-controlled trial, evaluated the effects of topical insulin on wound healing and concluded that the healing rates of the insulin treatment group was higher than in the control group, regardless of initial wound size and did not cause any major systemic side effects.

Case Presentation

A 71-year-old male patient with a past medical history of hypertension, diabetes mellitus, and peripheral vascular disease received an emergency amputation at the midfoot level. Following this urgent procedure, the wound was treated with traditional NPWT and subsequently with a split-thickness skin graft (STSG) application to the dorsal lateral aspect of his right foot. After the STSG failed, several weeks of subsequent traditional NPWT was initiated, but also proved unsuccessful. The patient was referred to our clinic with a four-month history of ulceration (**Figure 1**) at the site of the STSG to his right foot. After intraoperative debridement and reapplication of traditional NPWT, the wound continued to show peri-wound maceration and clinically apparent colonization. We discontinued traditional NPWT, favoring a device along with insulin infusion (Sved; **Figure 2**) using the dosing defined by Wilson and associates.[26] We ran the infusion drip into the NPWT foam at 40 ml/h for 48 h.

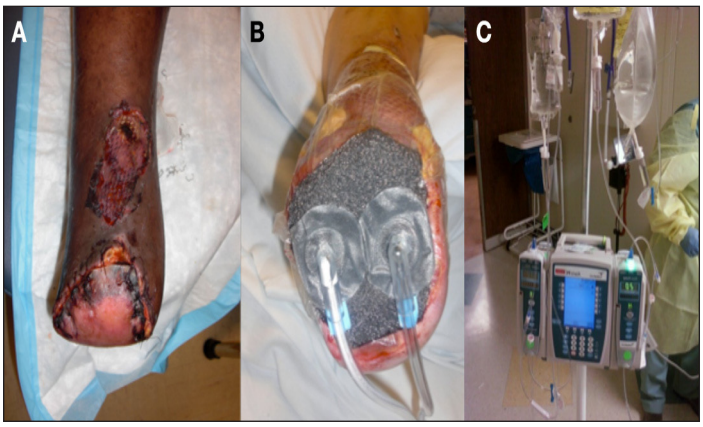

Figure 1. (A) Full-thickness skin flap/graft done after the emergency midfoot amputation. **(B)** Continuous streaming of insulin infusion through NPWT device (Sved). **(C)** Insulin infusion drip into the NPWT foam at 40 ml/h for 48 h.

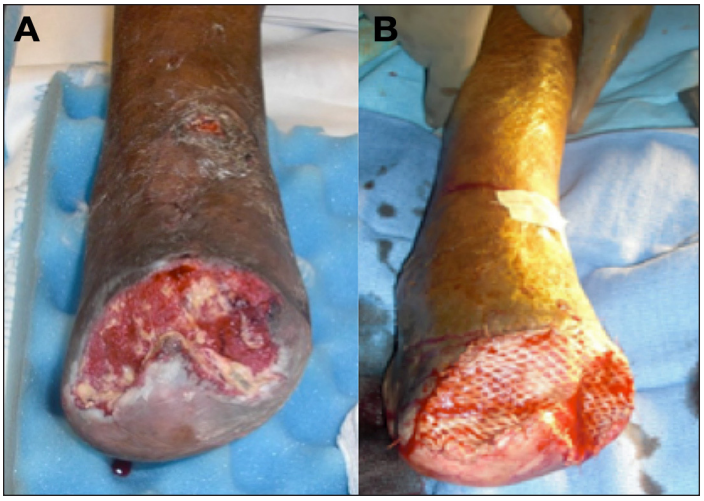

Figure 2. (A) After insulin infusion drip into the NPWT foam at 40 ml/h for 48 h, the wound base is 90% granular with only mild maceration noted at distal wound periphery, and donor site is nearly healed. **(B)** After a granular wound bed was achieved, the full-thickness skin graft was applied.

Discussion

The epidemiology and morbidity of diabetic foot wounds is, in many ways, not dissimilar to cancer.[28] This comparison has, over the years, made us rethink how we treat patients—in terms of counseling, a team approach to care, as well as with technology. Additionally, we believe that "infusion" of various modalities over a wound using a proven method of matrix stimulation (such as NPWT) might be a promising way forward. We have called this "wound chemotherapy."[10] We have been very active in modifying many of the techniques first described by Wim Fleischmann and others to both provide active matrix management (NPWT) with other chemotherapeutic tools to manipulate the wound environment (e.g., antimicrobials/antiseptics and analgesics).

The authors' unit frequently employs 0.025% Dakin solution run at approximately 30 cc/h (six or so drips/min using standard intravenous tubing inserted separately into a V.A.C. device at 125 mm Hg or an ITI SVED unit as part of its standard kit. We have described this technique previously.[10] However, we believe that many other modalities might prove helpful at different times during the healing process if delivered appropriately. In addition to insulin, which we describe here, and the aforementioned dilute Dakin, other possibilities might include the following:

1. Doxycycline: Its antimicrobial coupled with anti-matrix metalloproteinase and anti-tumor necrosis factor may prove useful.

2. Dilute Betadine: In addition to being antimicrobial, iodine may stimulate inflammation. This may be helpful in some "stalled" circumstances.[29]

3. Lactoferrin: It offers antimicrobial, antibiofilm, and immunomodulatory qualities.[30–33]

4. Phenytoin: It stimulates fibroblast proliferation.[34,35]

5. Biguanide antiseptics: It is antimicrobial and offers wound optimization.[36]

In conclusion, NPWT involving continuous streaming (in this case, with insulin) may provide a promising method to promote a healthy wound environment. Preliminary reports seem to suggest that insulin can be applied topically with minimal systemic side effects and successfully achieve a decrease in time to wound healing. Further studies on a larger scale should be done in the future to confirm or refute these results.

References:

1. Argenta LC, Morykwas MJ. Vacuum-assisted closure: a new method for wound control and treatment: clinical experience. Ann Plast Surg. 1997;38(6):563–76.
2. Morykwas MJ, Argenta LC, Shelton-Brown EI, McGuirt W. Vacuum-assisted closure: a new method for wound control and treatment: animal studies and basic foundation. Ann Plast Surg. 1997;38(6):553–62.
3. Andros G, Armstrong DG, Attinger CE, Boulton AJ, Frykberg RG, Joseph WS, Lavery LA, Morbach S, Niezgoda JA, Toursarkissian B, Tucson Expert Consensus Conference. Consensus statement on negative pressure wound therapy (V.A.C. Therapy) for the management of diabetic foot wounds. Ostomy Wound Manage. 2006;Suppl:1–32.
4. Morykwas MJ, Faler BJ, Pearce DJ, Argenta LC. Effects of varying levels of subatmospheric pressure on the rate of granulation tissue formation in experimental wounds in swine. Ann Plast Surg. 2001;47(5):547–51.
5. Armstrong DG, Lavery LA, Diabetic Foot Study Consortium. Negative pressure wound therapy after partial diabetic foot amputation: a multicentre, randomised controlled trial. Lancet. 2005;366(9498):1704–10.
6. Blume PA, Walters J, Payne W, Ayala J, Lantis J. Comparison of negative pressure wound therapy using vacuum-assisted closure with advanced moist wound therapy in the treatment of diabetic foot ulcers: a multicenter randomized controlled trial. Diabetes Care. 2008;31(4):631–6.
7. Wolvos T. Wound instillation--the next step in negative pressure wound therapy. Lessons learned from initial experiences. Ostomy Wound Manage. 2004;50(11):56–66.
8. Baxter CR. Immunologic reactions in chronic wounds. Am J Surg. 1994;167(1A):12S–4S.
9. Falanga V. Growth factors and chronic wounds: the need to understand the microenvironment. J Dermatol. 1992;19(11):667–72.
10. Giovinco NA, Bui TD, Fisher T, Mills JL, Armstrong DG. Wound chemotherapy by the use of negative pressure wound therapy and infusion. Eplasty. 2010;10:e9.
11. Grewal RS, Gupta SC, Singhal GM, Gupta SN. Wound healing in relation to insulin. Int Surg. 1972;57(3):229–32.
12. Rosenthal SP. Acceleration of primary wound healing by insulin. Arch Surg. 1968;96(1):53–5.
13. Rosenthal SP, Enquist IF. The effect of insulin on granulating wounds in normal animals. Surgery. 1968;64(6):1096–8.
14. Pierre EJ, Barrow RE, Hawkins HK, Nguyen TT, Sakurai Y, Desai M, Wolfe RR, Herndon DN. Effects of insulin on wound healing. J Trauma. 1998;44(2):342–5.
15. Edmonds T. Evaluation of the effects of topical insulin on wound-healing in the distal limb of the horse. Vet Med Small Anim Clin. 1976;71(4):451–7.
16. Hanam SR, Singleton CE, Rudek W. The effect of topical insulin on infected cutaneous ulcerations in diabetic and nondiabetic mice. J Foot Surg. 1983;22(4):298–301.
17. Greenway SE, Filler LE, Greenway FL. Topical insulin in wound healing: a randomised, double-blind, placebo-controlled trial. J Wound Care. 1999;8(10):526–8.
18. Sureshbabu A, Okajima H, Yamanaka D, Shastri S, Tonner E, Rae C, Szymanowska M, Shand JH, Takahashi S, Beattie J, Allan GJ, Flint DJ. IGFBP-5 induces epithelial and fibroblast responses consistent with the fibrotic response. Biochem Soc Trans. 2009;37(Pt 4):882–5.
19. Yao F, Visovatti S, Johnson CS, Chen M, Slama J, Wenger A, Eriksson E. Age and growth factors in porcine full-thickness wound healing. Wound Repair Regen. 2001;9(5):371–7.
20. Wang JM, Hayashi T, Zhang WR, Li F, Iwai M, Abe K. Reduction of ischemic damage by application of insulin-like growth factor-1 in rat brain after transient ischemia. Acta Med Okayama. 2001;55(1):25–30.
21. Belfield WO, Golinsky S, Compton MD. The use of insulin in open-wound healing. Vet Med Small Anim Clin. 1970;65(5):455–60.
22. Lopez JE, Mena B. Local insulin for diabetic gangrene. Lancet. 1968;1(7553):1199.
23. Zhang XJ, Chinkes DL, Sadagopa Ramanujam VM, Wolfe RR. Local injection of insulin-zinc stimulates DNA synthesis in skin donor site wound. Wound Repair Regen. 2007;15(2):258–65.
24. Zhang XJ, Wu X, Wolf SE, Hawkins HK, Chinkes DL, Wolfe RR. Local insulin-zinc injection accelerates skin donor site wound healing. J Surg Res. 2007;142(1):90–6.
25. O'Keefe EJ, Chiu ML. Stimulation of thymidine incorporation in keratinocytes by insulin, epidermal growth factor, and placental extract: comparison with cell number to assess growth. J Invest Dermatol. 1988;90(1):2–7.
26. Wilson JM, Baines R, Babu ED, Kelley CJ. A role for topical insulin in the management problematic surgical wounds. Ann R Coll Surg Engl. 2008;90(2):160.
27. Rezvani O, Shabbak E, Aslani A, Bidar R, Jafari M, Safarnezhad S. A randomized, double-blind, placebo-controlled trial to determine the effects of topical insulin on wound healing. Ostomy Wound Manage. 2009;55(8):22–8.

28. Armstrong DG, Wrobel J, Robbins JM. Guest editorial: are diabetes-related wounds and amputations worse than cancer? Int Wound J. 2007;4(4):286–7.

29. Durani P, Leaper D. Povidone-iodine: use in hand disinfection, skin preparation and antiseptic irrigation. Int Wound J. 2008;5(3):376–87.

30. Lyons TE, Miller MS, Serena T, Sheehan P, Lavery L, Kirsner RS, Armstrong DG, Reese A, Yankee EW, Veves A. Talactoferrin alfa, a recombinant human lactoferrin promotes healing of diabetic neuropathic ulcers: a phase 1/2 clinical study. Am J Surg. 2007;193(1):49–54.

31. Wolcott RD, Rhoads DD, Dowd SE. Biofilms and chronic wound inflammation. J Wound Care. 2008;17(8):333–41.

32. Wolcott RD, Rhoads DD. A study of biofilm-based wound management in subjects with critical limb ischaemia. J Wound Care. 2008;17(4):145–8.

33. Rhoads DD, Wolcott RD, Percival SL. Biofilms in wounds: management strategies. J Wound Care. 2008;17(11):502–8.

34. El-Nahas M, Gawish H, Tarshoby M, State O. The impact of topical phenytoin on recalcitrant neuropathic diabetic foot ulceration. J Wound Care. 2009;18(1):33–7.

35. Qunaibi EA, Disi AM, Taha MO. Phenytoin enhances collagenization in excision wounds and tensile strength in incision wounds. Pharmazie. 2009;64(9):584–6.

36. Hirsch T, Koerber A, Jacobsen F, Dissemond J, Steinau HU, Gatermann S, Al-Benna S, Kesting M, Seipp HM, Steinstraesser L. Evaluation of toxic side effects of clinically used skin antiseptics in vitro. J Surg Res. 2009. [Epub ahead of print.]