An Effective Method of Treating Long-Enduring Wounds and Ulcers by Topical Applications of Solutions of Nutrients

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A safe and effective method of improving repair and controlling infection of wounds is presented. It consists of debridement daily and application topically of a balanced solution of salts, amino acids, a high-molecular-weight, D-glucose polysaccharide, and ascorbic acid. Wounds of several causes were treated, namely, second- and third-degree thermal burns, decubitus, varicose, and stasis ulcers, and diabetic lesions. Local infection was controlled early and the majority of the cases responded with quick formation of highly vascular, smooth, infection-free granulation tissue and centripetal epithelial growth. Small- and medium-sized lesions healed spontaneously in 4 to 8 weeks. Larger lesions were readily managed with autografts of skin as soon as satisfactory beds were obtained.

INTRODUCTION

The healing of wounds continues to be a challenging problem in spite of great advances in surgical technique, immunology, and parenteral and enteral nutrition and the development of new systemic and topical antibiotics and bactericidal agents.[1-6]

It is well established that healing of wounds is inhibited by ischemia,[7,8] necrotic tissue, and poor perfusion of systemic nutrients.[9] Wounds suffer from low pO_2, high pCO_2, and increased concentrations of lactic acid and other non-beneficial metabolites.[10,11]

In most cases, necrotic tissue becomes an excellent culture medium for microorganisms, and local infection that is frequently unresponsive to systemic antibiotics ensues. Topical treatment with topical antiseptics is not always effective, and often retards wound healing.[2,12]

Since wounds tend to be ischemic lesions, it is understandable why nutrients from the bloodstream may not reach where they are most needed for the repair process. Earlier studies[13] have indicated that local hyperalimentation of wounds is beneficial. In this paper we report the results of a study of a new, safe, and effective method of treating various types of acute and chronic cutaneous wounds by topical application of several nutrients.

MATERIALS AND METHOD

Since 1970, 58 patients,* ranging in age from 6 days to 95 years, who had large open wounds of traumatic origin, decubitus ulcers because they were paraplegics, quadraplegics, and hemiplegics, ulcers due to venous stasis and diabetes, or second- and third-degree burns have been treated by the staff of the Human Tissues Reconstruction Laboratory at Saint Mary of Nazareth Hospital Center and Bethany Methodist Hospital in Chicago, Illinois, with the topical applications of nutrients. Most of the patients were hospitalized at the time

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* All clinical research was conducted in accordance with the principles for human experimentation as defined in the Declaration of Helsinki.

of initiation of treatment; the rest were ambulatory and were treated as out-patients.

All patients were first subjected to a standardized work-up of a comprehensive medical history, a complete physical examination, and laboratory studies inclusive of X-ray examination of the chest, complete blood count, urinalysis, S.M.A. 12, blood electrolytes, microbial cultures of their lesions, and determination of sensitivities to antibiotics of the microorganisms found.

Whenever possible, initial and serial photographs of the lesions were taken until healing had been achieved, tracings of the lesions on sterile transparent films were drawn to record changes in sizes of the wounds, and initial and serial biopsies were performed.

Most of the patients had been treated previously by conventional methods for several months to several years without improvement. As controls, we first observed progress under previous methods of treatment for a period of one week. When it was well established that no improvement was occurring, topical treatment with our mélanges of nutrients was instituted. When possible, in patients with multiple lesions, treatment of one lesion by a conventional method was continued longer as a control while others were treated by the nutritional method. Subsequently, the control lesion, showing no progress, was also treated by our method.

Our topical materials were as follows:

1. A sterile, nonpyrogenic, phosphate-buffered, balanced solution of salts with a pH of 6.5.

2. A sterile, nonpyrogenic, aqueous solution of essential amino acids, namely, L-isoleucine (720 mg), L-leucine (940 mg), L-lysine (720 mg), L-methionine (400 mg), L-phenylalanine (440 mg), L-threonine (520 mg), L-tryptophan (160 mg), and L-valine (800 mg), and the following nonessential amino acids, namely, L-tyrosine (44 mg), L-alanine (1280 mg), L-arginine (980 mg), glycine (1280 mg), L-proline (860 mg), L-histidine (300 mg), and L-serine (420 mg). The solution of amino acids was made to consist of 10% weight/volume.

3. A sterile D-glucose polysaccharide powder obtained by controlled enzymatic and acid hydrolysis of plant starches with molecular weights up to 100,000. The powder was tightly packaged in polyethylene bags and sterilized by gamma radiation with reagent-grade powder of ascorbic acid added.

All lesions were debrided surgically in the operating room or at bedside initially and whenever it seemed necessary during the course of the treatment. Control lesions were treated by irrigations with the solution of balanced salts and soaks of Betadine® daily. Treatment of all other lesions was done daily in the following sequential steps: First, the wound was irrigated with the solution of balanced salts by means of a 50-cc syringe and 16-gauge needle or a pulsating jet (Water-Pik®), then irrigated with the solution of amino acids, and finally covered with the sterile D-glucose polysaccharide powder, which contained varying percentages of ascorbic acid. Dressings were made with a nonadherent, sterile material, sterile sheeting, and rolled gauze.

RESULTS

Our results are best recounted by several representative case reports.

Case 1. A 73-year-old white man with uncontrolled diabetes mellitus and in keto-acidosis had severe and extensive cellulitis of the right foot. In spite of intensive treatment with systemic antibiotics and conservative local care, the fifth toe and the area around the fifth metatarsal became gangrenous. An extensive transmetatarsal amputation was carried out under general anesthesia and included extensive debridement of the dorsal and plantar aspects of the foot that exposed joints, bones, and plantar tendons (Figs. 1A and 1B). On the ninth postoperative day advancing cellulitis and the poor general condition of the patient made it appear that an above-the-knee amputation would be necessary. Bacteriological studies had revealed the following microorganisms in the wound: beta-hemolytic streptococcus (Group B), nonhemolytic streptococcus, *Staphylococcus epidermidis* (coagulase negative), *Peptostreptococcus anaerobius*, enterococci, *Streptococcus morbillorum*, *Staphylococcus aureus* (coagulase positive), *Fusobacterium nucleatum*, *Candida albicans*, *Enterobacter cloacae*, and *Enterobacter aerogenes*.

Called into consultation, we ascertained that the pulse of the dorsalis pedis artery was good and advised a trial of our method of management. That advice was taken and daily topical applications of our nutrient materials after debridements were begun in the manner outlined under Methods. As early as the fourth day, the massive and extensive infection began to subside and highly vascularized, rapidly growing granulation tissue became appreciable. From that time on, infection continued to subside and healthy granulation tissue continued to grow and cover the exposed tendons, the metatarsophalangeal joints, and the bones (Fig. 1C). Throughout the progress the patient did not complain of pain and his general condition began to improve as soon as the local infection came under control and granulation tissue began to fill the open wound. By the 77th day, the condition appeared as is seen in Figure 1D. In order to expedite restoration of the patient, an autograft was applied to the remainder of the wound. It took well. Two years later the healed foot appeared as in Figure 1E and the patient was able to function satisfactorily.

FIGURE 1A. *Dorsolateral appearance of the wound resulting from amputation of a gangrenous small toe and debridement of adjacent tissue.* FIGURE 1B. *Plantar appearance of the wound.* FIGURE 1C. *Dorsolateral appearance of the wound 20 days after initiation of topical treatment.* FIGURE 1D. *Plantar appearance of the wound 45 days after initiation of topical treatment.* FIGURE 1E. *Appearance of the healed wound after good take of a graft 77 days after initiation of treatment.*

Case 2. A 38-year-old white man became paraplegic five years before when, working as a tree-surgeon, he came into contact with live electric wires and was thrown from a tree. He now suffered from deep decubitus ulcers over both hips and over the sacrum. Autografts and rotated flaps failed to hold up; the ulcers recurred.

When the patient came under our care, he had two large, deep decubitus ulcers over the trochanters, a large ulceration over the sacrum, and another on a heel. Cultures of his ulcers revealed *Pseudomonas aeruginosa, Staphylococcus epidermidis, Proteus mirabilis, Klebsiella pneumoniae, Staphylococcus aureus,* and enterococci. Treatment by our method was initiated on the very day of admission. Purulent exudate and foul smell disappeared on the second day. Highly vascularized granulation tissue began to proliferate and fill the ulcers (Fig. 2A). Epithelization began as promptly. In this case the powder of D-glucose polysaccharide and the patient's serum formed a crust, which when detached caused bleeding and under which clean, infection-free granulation tissue was apparent. By the end of eight weeks, the ulcers were largely closed, except for that on the sacrum, which took another two months to heal firmly (Fig. 2B).

Case 3. A 76-year-old white man became paraplegic at the age of 20 following a car accident in which he suffered a fracture of the spinal column at the level of the second dorsal vertebra. For the past 10 years he has been suffering from decubitus ulcers over the trochanters on both sides.

The patient was admitted to our facility because of severe bleeding from the ulcer on the right side, which measured 10.0 × 6.0 cm and had a very deep crater at the bottom of which the denuded femur could be seen (Fig. 3A). The ulcer was grossly contaminated and culture of it revealed *Staphylococcus aureus,* enterococci, *Pseudomonas aeruginosa, Serratia narcescens,* and *Proteus mirabilis.* X-ray examination of the pelvis revealed a displaced transtrochanteric fracture of the right femur. Daily irrigations with our material were begun and within 48 hours the wound began to look cleaner. Highly vascular granulation tissue began to proliferate as quickly and came to cover the bottom of the deep crater completely by the seventh day. Start of epithelization became apparent after the fourth day. The crater continued to fill with granulation tissue and bridges of connective tissue and small blood vessels could be seen bridging the site of the femoral fracture (Fig. 3B). By the end of the third month, the ulcer was reduced to 0.7 cm in length, by 0.3 cm in breadth, and by 0.2 cm in depth (Fig. 3C). X-ray examination of the femur now showed the transtrochanteric fracture to be healing with abundant callus formation and in good alignment.

Case 4. A one-year-old female infant was admitted to our service for treatment of severe necrosis of tissue on the plantar and lateral aspects of her right foot, which had been caused by extravasation of fluid administered intravenously for treatment of an upper respiratory infection and by too hot, moist packs subsequently applied. There was an eschar as of a third-degree burn (Fig. 4A). Surgical debridement and grafting were advised, but the mother turned down operative procedures. Consequently, we resorted to our routine of daily irrigations and applications of our materials four days after an ointment containing collagenase had been used to enzymatically dissolve the hard eschar, which was also carefully debrided mechanically. Highly vascularized, confluent buds of granulation tissue began to develop so that shortly the wound appeared as in Figure 4B. Epithelization became appreciable as early as the seventh day after treatment, and by the 31st day the wound was completely healed. At 1½ years of age, when the child began to walk, she was able to do so without difficulty. The wound then appeared as in Figure 4C.

Case 5. A 64-year-old white woman with uncontrolled diabetes was admitted for treatment of extensive cellulitis of the right foot and necrosis of the great toe and adjacent plantar aspect over the first metatarsal bone of the right foot (Fig. 5A). The area was grossly contaminated and purulent exudate issued as soon as debridement of the plantar eschar was undertaken. Bacteriological studies revealed *Staphylococcus aureus* (coagulase positive), a nonhemolytic streptococcus, an alpha-hemolytic streptococcus, *Pseudomonas putida,* and species of peptococcus. Orthopedic and plastic surgeons called into consultation advised amputation of the foot. Instead, we decided to give the condition a trial of our method of treatment with daily irrigations of our solutions and applications of powder. Shortly, necrotic tissue began to be replaced by highly vascularized granulation tissue and infection subsided. By the end of the 45th day a good, clean, well-vascularized bed of granulation tissue had been attained and then a split-thickness autograft was successfully applied (Fig. 5B). Follow-up one year later showed the patient to be well and having no problems with her foot.

Case 6. A 67-year-old, extremely obese woman had ulcers of several years' duration on both legs. On the right leg there were two ulcers, one oval and measuring 11 × 6 cm and the other circular with a diameter of 7 cm (Fig. 6A). The ulcer on the left leg measured 6.0 × 6.0 cm. The ulcers on both legs were deep and covered by abundant, purulent, foul-smelling exudate. Initial bacteriological cultures showed the following microorganisms: *Staphylococcus aureus* (coagulase

FIGURE 2A. *Appearance of a decubitus ulcer over the trochanters of a paraplegic.*

FIGURE 2B. *The healed appearance of the wound pictured in Figure 2A after topical treatment.*

FIGURE 3A. *Appearance of a deep decubitus ulcer exposing bone that had a transtrochanteric fracture.* FIGURE 3B. *Appearance of the wound pictured in Figure 3A seven days after initiation of topical treatment.* FIGURE 3C. *Appearance of the wound pictured in Figure 3A five months after initiation of topical treatment.*

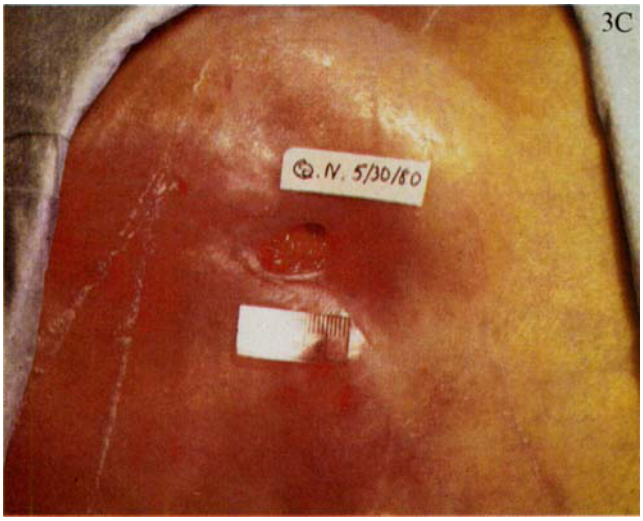

FIGURE 4A. *Appearance of a wound on a foot of an infant that resulted from extravasation of fluid being given intravenously and then aggravated by hot, wet dressings.* FIGURE 4B. *Appearance of the wound pictured in Figure 4A 12 days after initiation of topical treatment.* FIGURE 4C. *The healed appearance of the wound pictured in Figure 4A 30 days after initiation of topical treatment.*

FIGURE 5A. *Massive cellulitis and gangrene in a patient with uncontrolled diabetes.*

FIGURE 5B. *The healed appearance of the condition pictured in Figure 5A at 42 days after topical treatment and placement of a graft.*

FIGURE 6A. *Appearance of ulcers of two years' duration on a leg of an obese woman.*

FIGURE 6B. *Healed appearance of the ulcers pictured in Figure 6A 43 days after initiation of topical treatment.*

positive), enterococci, *Klebsiella pneumoniae*, *Pseudomonas aeruginosa*, and *Proteus mirabilis*. The treatment was started with soaks of a solution of dilute silver nitrate (0.01%) for 15 minutes, then irrigation with our solution of salts, and then application of the glucose powder. The soaks with the solution of silver nitrate were discontinued after the third day because they were too irritating and promoted more inflammatory exudate. With our materials alone, purulent, foul-smelling exudate began to decrease almost immediately. Highly vascularized, clean granulation tissue started to proliferate by the third day and the epithelium was seen to creep in at the margins of the wounds by the fifth day. By the 43rd day, all the ulcers were completely healed (Fig. 6B).

DISCUSSION

All patients tolerated our agents and methods well. There were no untoward local or systemic reactions to the application of any of the solutions or the powder. In only three cases there was no improvement, in two of them because the patients were in terminal condition and in one, an alcoholic, lack of compliance. Most of the patients related a cessation of pain following the applications; a few reported tolerable, transient stinging sensations from the powders that contained high percentages of ascorbic acid. Infection and purulence were quickly controlled. Necrotic tissue was sloughed or was easily removed; clean, smooth, vivid-red, highly vascularized, rapidly growing granulation tissue ensued. Epithelization proceeded parri passu. Small and medium-sized wounds, even those that had endured for 5 to 20 years, healed spontaneously and completely in two to eight weeks. Large lesions were brought to smaller sizes so that they could then be covered by grafts. In some of these latter cases, the decision to graft was made because of hospital costs and insurance-related problems.

In short, our experience has been that with our materials and methods we have been able to achieve healing of severe, long-enduring wounds and ulcers in reasonable times and with excellent structural and functional results. Its rationale rests on the reasonable assumption that certain nutrients are necessary to repair tissue and that in certain wounds and ulcers they are not available in proper quality or sufficient quantity from the circulation. Many previous studies[13–21] seem to confirm it. True or not, our materials and methods seem to work.

REFERENCES

1. Peacock, E. E., and Van Winkle, W. Repair of skin wounds. In: Wound Repair, Chap. 6, pp. 204–270. Philadelphia, Saunders, 1976.
2. Peacock, E. E., and Van Winkle, W. Skin grafting and treatment of burns. In: Wound Repair, Chap. 7, pp. 271–366. Philadelphia, Saunders, 1976.
3. Hunt, T. K. Disorders of repair and their management. In: Hunt, T. K., and Dunphy, J. E., eds., Fundamentals of Wound Management, Chap. 2, pp. 68–168. New York, Appleton-Century-Crofts, 1976.

4. Niinikoski, J. The effect of blood and oxygen supply on the biochemistry of repair. In: Hunt, T. K., ed., Wound Healing and Wound Infection, Chap. 5, pp. 56–70. New York, Appleton-Century-Crofts, 1980.
5. Haury, B., Rodeheaver, G., Vensko, J., et al. Debridement: An essential component of traumatic wound care. In: Hunt, T. K., ed., Wound Healing and Wound Infection, Chap. 18, pp. 229–241. New York, Appleton-Century-Crofts, 1980.
6. Burke, J. F. The physiology of wound infection. In: Hunt, T. K., ed., Wound Healing and Wound Infection, Chap. 19, pp. 242–253. New York, Appleton-Century-Crofts, 1980.
7. Order, S. E., and Moncrief, J. A. The Burn Wound. Springfield, Ill., Charles C Thomas, 1956.
8. Order, S. E., Mason, A. D., Walker, J. L., et al. Vascular destructive effects of thermal injury and their relationship to burn wound sepsis. J. Trauma 62:62, 1965.
9. Hunt, T. K., and Van Winkle, W. Normal repair. In: Hunt, T. K., and Dunphy, E., eds., Fundamentals of Wound Management, Chap. 1, pp. 53–63. New York, Appleton-Century-Crofts, 1976.
10. Silver, A. The physiology of wound healing. In: Hunt, T. K., ed., Wound Healing and Wound Infection, Chap. 2, pp. 11–28. New York, Appleton-Century-Crofts, 1980.
11. Hunt, T. K., Zederfeldt, B., and Dunphy, J. E. Respiratory gas tensions and pH in healing wounds. Am. J. Surg. 114:302, 1967.
12. Moncrief, J. A. Topical antibacterial treatment of the burn wound. In: Artz, C. P., Moncrief, J. A., and Pruitt, B. A., eds, Burns: A Team Approach, Chap. 17, pp. 250–269. Philadelphia, Saunders, 1979.
13. Viljanto, J., and Raekallio, J. Local hyperalimentation of open wounds. Br. J. Surg. 63:427, 1976.
14. Majno, G. The Healing Hand, p. 117. Cambridge, Mass. Harvard University Press, 1975.
15. Silvetti, A. N., Cotton, C., Byrne, R. J., et al. Preliminary experimental studies of bovine embryo skin grafts. Transplant. Bulletin 4:25, 1957.
16. Rogers, B. O., Converse, J. M., and Silvetti, A. N. Preliminary clinical studies on bovine embryo skin grafts. Transplant. Bulletin 4:24, 1957.
17. Rogers, B. O., Converse, J. M., and Silvetti, A. N. Étude clinique sur la peau d'embryons de bovine employée comme pansement biologique. Colloq. Int. Ctr. Natl. Recherche Sci. 78:167, 1957.
18. Rogers, B. O., and Converse, J. M. Bovine embryo skin zoografts as temporary biologic dressings for burns and other skin defects. Plast. Reconstr. Surg. 22:471, 1958.
19. Silvetti, A. N., Teresi, P., Luangkesorn, P., et al. Bovine embryonic skin allografts in treatment of skin ulcers and burns in man. Transplant. Proc. 11:1512, 1979.
20. Serri, F., Montagna, W., and Mescon, H. Studies of the skin of the fetus and the child. J. Invest. Dermatol. 39:199, 1962.
21. Hoopes, Y. E., and Im, J. C. Glycogen metabolism in epidermal wound healing. J. Surg. Oncol. 6(5):409, 1974.