

The Effect of Short-Contact Topical Tretinoin Therapy for Foot Ulcers in Patients With Diabetes

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Objective: To determine the efficacy and safety of short-contact administration of topical tretinoin on foot ulcers in patients with diabetes.

Design: Randomized, double-blind, placebo-controlled trial.

Setting: Outpatient clinic at a Veterans Affairs medical center.

Patients: Twenty-four volunteers with diabetic foot ulcers but without evidence of peripheral arterial disease or infection.

Interventions: Patients were randomized to 4 weeks of daily treatment with either topical 0.05% tretinoin solution (Retin-A) or placebo saline solution. Photographs and assessment of wound size and appearance were assessed every 2 weeks for a total of 16 weeks.

Main Outcome Measures: The proportion of ulcers that healed in each group and the degree of change in ulcer size.

Results: Twenty-two patients, with a total of 24 foot ulcers, completed the study. At the end of 16 weeks, 2 (18%) of 11 ulcers in the control group and 6 (46%) of 13 ulcers in the tretinoin treatment group healed completely. Topical tretinoin therapy significantly decreased ulcer area and depth compared with placebo treatment over the 16 weeks of the study ($P < .01$ for surface area; $P = .02$ for depth). Adverse effects mainly consisted of mild pain at the ulcer site.

Conclusions: Short-contact application of topical tretinoin improved the healing of foot ulcers in patients with diabetes. The tretinoin therapy was generally well tolerated, without serious local or systemic adverse effects.

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LOWER EXTREMITY ULCERS affect approximately 2% to 3% of the 16 million Americans with diabetes mellitus each year, with 15% of the patients with diabetes experiencing an ulcer at some time during their life.¹ These ulcers significantly impact the quality of life of the patient and often lead to adverse sequelae, including infection, osteomyelitis, gangrene, and amputation of the affected limb.² Agents able to stimulate wound healing in these patients have the potential to reduce the large amount of morbidity and mortality associated with lower extremity ulcers.

*See also pages 1368
and 1449*

Topical tretinoin (all-*trans*-retinoic acid) has been found to improve healing of partial- and full-thickness wounds when applied before wounding.³⁻⁵ The effects of tretinoin therapy on open wounds are still unclear. A recent report by Paquette et al⁶

found that short-contact daily application of topical tretinoin improved the healing of chronic leg ulcers in 5 patients who were taking immunosuppressive agents for systemic illnesses. Topical tretinoin therapy stimulated increased granulation tissue, new vascular tissue, and new collagen formation. We compared the effects of treatment with short-contact topical tretinoin and placebo in 24 patients with diabetic foot ulcers.

METHODS

This study was approved by the University of California, San Diego, Committee for Human Research and performed with written informed consent from all volunteers. Study design was a prospective, randomized, double-blind, placebo-controlled clinical trial in 24 human volunteers. The volunteers were patients of the Foot Clinic at the Veterans Affairs Medical Center, San Diego, who had a lower extremity ulcer and a diagnosis of diabetes mellitus. Patients who (1) were unable to give informed consent, (2) had a known bleeding disorder, (3) were pregnant

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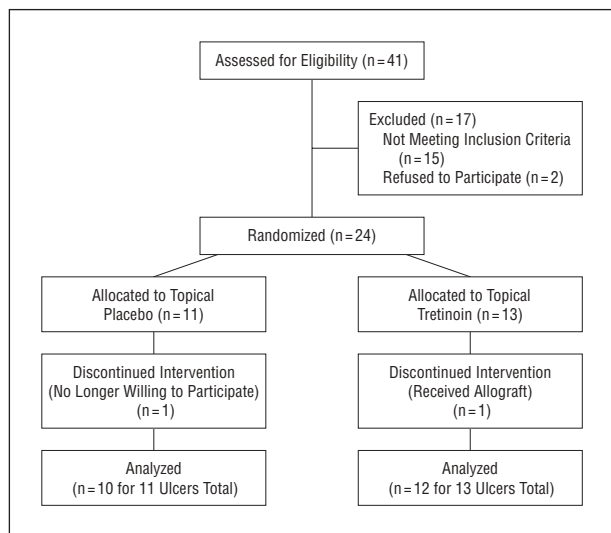


Figure 1. Patient disposition.

Table. Patient Characteristics*

Characteristic	Control Group†	Tretinoin Group‡
Age, y	61.2 ± 3.9	58.3 ± 1.5
Duration of ulcer, mo	11.9 ± 5.1	6.3 ± 2.0
Location of ulcer	Plantar surface, 9 ulcers	Plantar surface, 12 ulcers
	Lateral aspect of ankle, 2 ulcers	Dorsum of foot, 1 ulcer
Baseline ulcer surface area, cm ²	1.17 ± 0.69	0.87 ± 0.26
Baseline ulcer depth, cm	0.34 ± 0.07	0.24 ± 0.05
Duration of diabetes, y	12.5 ± 2.9	14.8 ± 2.3
Hemoglobin A _{1c} level	8.3 ± 0.5	7.7 ± 0.4

*Values other than location of ulcer are expressed as mean ± SE.

†Ten patients; 11 ulcers.

‡Twelve patients; 13 ulcers.

at the time of enrollment, (4) had infected ulcers or nearby tissues, or (5) had lower extremity ulcers due to large artery disease (by clinical examination and/or abnormal ankle-brachial index) were excluded from the study.

Forty-one patients with diabetic foot ulcers were evaluated between June and September 2002. Twelve patients did not qualify for the study because of clinical evidence of lower extremity peripheral arterial disease; 3 patients were excluded because of known or possibly infected ulcers; and 2 patients who did not meet any exclusion criteria were not willing to participate in the study. Twenty-four patients, all male, were enrolled in the study (Figure 1).

Patients were randomly divided into 2 groups: treatment with topical 0.05% tretinoin solution (Retin-A; Ortho Pharmaceutical Corp, Raritan, NJ) and treatment with normal saline solution that was colored the same as the topical tretinoin. Randomization was performed by an uninvolved third party who used a computer-generated random sequence to balance the numbers of the 2 treatment groups. Each newly enrolled patient was assigned a topical solution in ascending order. The study was double-blind in that all dispensed bottles of solutions were identical in appearance (identified by number only), and neither the investigators nor the patients were aware of the treatment group

to which patients were assigned until the study was completed. Cadexomer iodine gel (Iodosorb; Healthpoint Ltd, Fort Worth, Tex) was the topical agent used by the Foot Clinic for its diabetic patients as part of standard wound care; it was the only other topical treatment continued in all study patients.

Patients had photographs taken of their foot ulcer for evaluation of initial size and appearance. The photographs (Macro 3 SLR Camera; Polaroid Corp, Waltham, Mass) were taken with standardized lighting and positioning for each patient. The randomly assigned solution was applied directly to the wound bed and left in contact for 10 minutes every day; it was then rinsed off with normal saline. The 10-minute application time was chosen based on the case series of chronic wounds reported by Paquette et al.⁶ In their series, a short-contact 10-minute application of topical tretinoin improved healing, with mild local irritation; longer periods were too irritating to the surrounding area. After rinsing off the randomly assigned solution, the patients applied cadexomer iodine gel to the wound bed, which was left on until the next day. This procedure was carried out once a day for 4 weeks. Use of the assigned study solution was then discontinued, and treatment with cadexomer iodine gel alone was continued once a day. Photographs and measurements of ulcer size were taken every 2 weeks after the patients started the assigned treatment, for a maximum of 16 weeks after the initiation of the study or until complete healing of the ulcer occurred, whichever came first. Various wound parameters, including erythema, edema, purulence, and necrotic tissue, were assessed at each visit by the same investigator (W.L.T.). The patients continued to receive routine care for their ulcers, including wound off-loading with shoes modified to reduce pressure to the ulcer area, debridement of callus and dead tissue, and protection of the ulcerated area with appropriate dressings. Routine care was provided by the 3 podiatrists (D.H. and 2 uninvolved colleagues) in the Foot Clinic, based on the appearance of the ulcer and clinic protocol, without knowledge of the assigned treatment group. Ulcer surface area was measured with computerized planimetry (Sigma Scan Pro; SPSS Inc, Chicago, Ill), and ulcer depth was measured at the deepest part of the wound with a probe.

Patient demographics were compared with a *t* test (SigmaStat Version 2.03; SPSS Inc). The proportion of healed ulcers over time was assessed with Kaplan-Meier curves, which were compared using the log-rank test. Repeated-measures analysis of variance was used to test for significance of changes in ulcer surface area and depth between the 2 study groups (SAS System; SAS Institute, Cary, NC). All results are reported as mean ± SE; *P* ≤ .05 was taken as significant for all statistical analyses.

RESULTS

Twenty-two patients completed the 16-week study. Of these, 20 patients had a single foot ulcer. The other 2 patients, each of whom had 2 foot ulcers, were treated with the same randomly assigned solution. Two enrolled patients dropped out of the study before completing the initial 4-week treatment period. One patient did not continue because he received a skin allograft for his ulcer. The other patient chose to drop out of the study in the first week because he no longer wanted to change his previous treatment regimen.

A comparison of the 2 groups of patients (topical tretinoin and control) is shown in the Table. The 2 sets of patients were not significantly different in regard to age (*P* = .47), duration of diabetes (*P* = .82), or hemoglobin A_{1c} level (*P* = .39). Initial ulcer size (surface area [*P* = .66] and

depth [$P = .28$]) and duration of ulceration ($P = .29$) were not statistically different between the 2 groups. The location of the ulcers was also similar.

Five (45%) of 11 ulcers in the control group demonstrated 50% or greater reduction in size by the end of the study period, compared with 11 (85%) of 13 ulcers in the tretinoin group. Two ulcers (18%) in the control group healed completely, compared with 6 ulcers (46%) in the tretinoin group. The progress of healing in the 2 groups during the study is shown as Kaplan-Meier curves in **Figure 2**. Tretinoin therapy increased the proportion of ulcers that healed completely over the 16-week period ($P = .03$).

A comparison of the changes in surface area and ulcer depth are shown in **Figure 3** and **Figure 4**, respectively. Tretinoin therapy significantly decreased ulcer area and depth compared with placebo treatment over the 16-week study period ($P < .01$ for surface area; $P = .02$ for depth). At the end of the study period, the ulcer area had changed by $-54.7 \pm 28.8\%$ in the tretinoin-treated group ($P = .02$ vs at the start of the study) and by $+2.7 \pm 47.2\%$ in the placebo-treated group ($P = .18$). The ulcer depth was $-60.1 \pm 13.8\%$ in the tretinoin-treated group ($P = .004$ vs at the start of the study) and $-29.6 \pm 12.6\%$ in the placebo-treated group ($P = .04$).

Two patients who were treated with 0.05% tretinoin solution reported a very mild pain/burning sensation during the first few days of application; this reaction did not affect compliance and the symptoms resolved. Another patient reported mild to moderate pain during the first 4 days of tretinoin therapy. He discontinued the treatment for several days and subsequently resumed application for the rest of the 4-week treatment period, without experiencing pain. One patient in the control group experienced mild to moderate pain with application of his study solution. He stopped the application for several days during weeks 2 and 4 of the 4-week treatment period; he reported milder pain with this decreased frequency of application, and his pain had resolved by the fifth week of the study. No significant erythema or edema was noted in the area surrounding the ulcers in patients in the tretinoin group. One patient in the control group had mild surrounding erythema and edema at the start of the study, both of which were gone by week 4. None of the wounds demonstrated purulence or necrotic tissue during the study period. No significant systemic effects were reported by either group.

COMMENT

This study demonstrated improvement in the healing of diabetic foot ulcers when topical tretinoin was added to standard therapy. It showed an increase in the number of ulcers healed as well as a decrease in ulcer size, with mild adverse effects.

Normal wound healing proceeds through a sequence of overlapping processes: hemostasis, inflammation and debridement, proliferation, wound contraction, epithelialization, and remodeling.^{7,8} Patients with diabetes have multiple disturbances in wound healing, independent of their increased likelihood of developing peripheral vas-

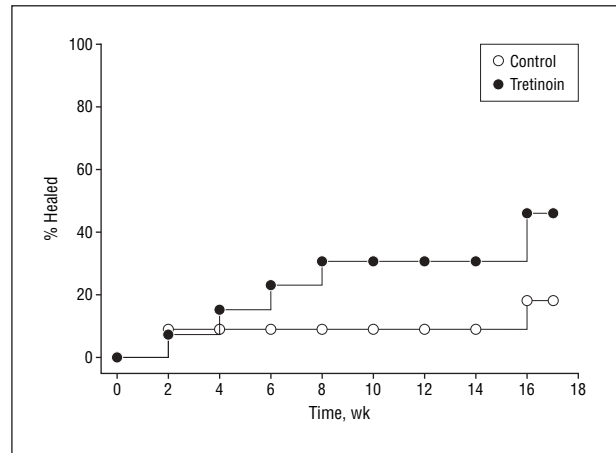


Figure 2. Time to complete healing. The control group consisted of 11 foot ulcers (in 10 patients); the tretinoin group, 13 ulcers (in 12 patients). $P = .03$ when the 2 groups were compared.

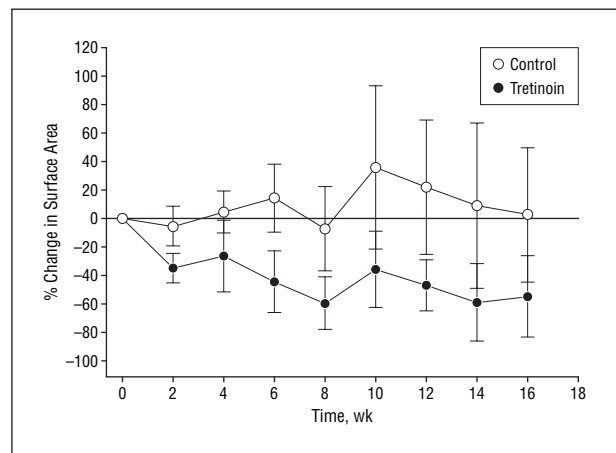


Figure 3. Change in surface area with time. Surface area was measured by means of computerized planimetry analysis of photographs. $P < .01$ when the 2 groups were compared.

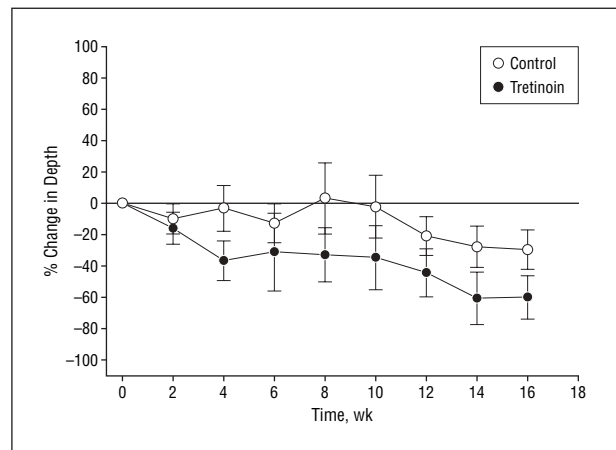


Figure 4. Change in depth with time. Ulcer depth was measured with a probe at the deepest part of the wound. $P = .02$ when the 2 groups were compared.

cular disease. These disturbances include prolonged inflammation, impaired neovascularization, decreased collagen synthesis, an abnormal pattern of synthesis of extracellular matrix protein, and decreased fibroblast pro-

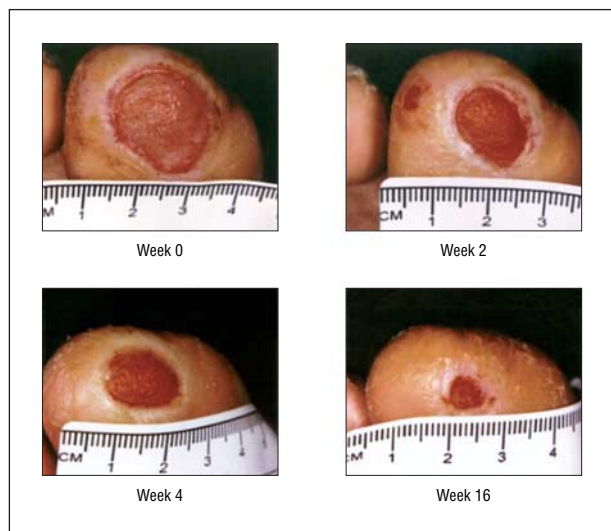


Figure 5. Improved healing and formation of granulation tissue in a representative patient treated with topical 0.05% tretinoin solution.

liferation.^{1,9} Current techniques of treatment include off-loading to avoid mechanical stress on the wound, debridement to remove devitalized tissue, and improvement of oxygenation and glycemic control.¹⁰

As a retinoid, tretinoin may enhance wound healing by its effect on cell division and differentiation. The use of tretinoin increases epidermal thickness and cell turnover, which may lead to faster reepithelialization. It also stimulates angiogenesis in the superficial dermis.^{11,12} This neovascularization allows delivery of oxygen and nutrients, and the endothelial cells secrete biologically active substances, including growth factors.⁴ The use of retinoids also increases granulation tissue formation by increasing mucopolysaccharide, collagen, and fibronectin synthesis.¹² Therefore, tretinoin has been studied as an agent that can potentially help the process of healing.

Topical tretinoin therapy has been found to improve healing of partial- and full-thickness wounds when applied before wounding. In human patients, it has been found to accelerate healing when used as pretreatment before the administration of trichloroacetic acid peels on actinically damaged skin of the face and arms,³ dermabrasion of the face,¹³ and electroepilation of the axillae and groin.¹⁴ Reepithelialization occurred faster in full-thickness wounds in actinically damaged skin that was first treated with topical tretinoin for 16 weeks.⁴ Application on already open wounds, however, has yielded varying results. In some animal models, tretinoin therapy has been found to enhance healing^{4,15,16}; in others, it has been shown to have no effect¹⁷ or to cause inflammation and excessive granulation without reepithelialization.^{5,18} It has been suggested that tretinoin may be too irritating when applied after wounding has occurred, especially to the surrounding skin.^{4,5} Recently Paquette et al⁶ introduced the use of short-contact daily application of topical tretinoin and found that it improved the healing of chronic leg ulcers in 5 patients who were using immunosuppressive agents for systemic illnesses. Short-contact application still stimulated increased granula-

tion tissue, new vascular tissue, and new collagen formation on histologic examination.

The present study aimed to see if short-contact application of topical tretinoin would improve the healing of foot ulcers in patients with diabetes in a randomized, placebo-controlled trial. More ulcers healed in the tretinoin-treated group over the 16-week study period. Planimetry showed quicker decrease in the surface area and depth of ulcers, suggesting faster wound contraction. Improved formation of granulation tissue was also seen in patients treated with tretinoin (**Figure 5**).

Patients were entirely randomized to their treatment group (tretinoin or placebo). It should be noted that patients in the tretinoin group generally presented with slightly smaller and less chronic ulcers; although this difference was not statistically significant, some of the measured improvement could be attributed to this tendency. Larger studies are needed to confirm efficacy.

As mentioned, irritation caused by topical tretinoin therapy is often a concern. In our study, short-contact application of tretinoin caused mild to moderate pain and irritation in several patients in the initial period of treatment, but either the symptoms self-resolved or the treatment was able to be restarted after several days without application. No significant surrounding erythema or edema was noted with tretinoin. Short-contact application appeared to be well-tolerated, as in the report by Paquette et al.⁶ Additional factors that allowed tolerance of topical tretinoin on open wounds included instruction to avoid application to the surrounding intact skin to reduce irritation to the surrounding area. Peripheral neuropathy associated with diabetes, while making the patient more prone to injury or trauma to cause or worsen foot ulcers,¹ may also limit the sensation of pain due to topical tretinoin. Most of the diabetic foot ulcers were located on the plantar surface, which has a thicker epidermis and less sensitivity to pain.

In conclusion, this pilot study found that short-contact application of topical tretinoin can improve the healing of foot ulcers in patients with diabetes. It suggests that topical tretinoin therapy may be a good addition to the already established methods of treating diabetic foot ulcers. Larger randomized, controlled trials are needed to further delineate the efficacy and effects of its use.

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REFERENCES

1. American Diabetes Association. Consensus Development Conference on Diabetic Foot Wound Care: 7-8 April 1999, Boston, Massachusetts. *Diabetes Care*. 1999;22:1354-1360.
2. Vileikyte L. Diabetic foot ulcers: a quality of life issue. *Diabetes Metab Res Rev*. 2001;17:246-249.
3. Hevia O, Nemeth AJ, Taylor JR. Tretinoin accelerates healing after trichloroacetic acid chemical peel. *Arch Dermatol*. 1991;127:678-682.
4. Popp C, Kligman AM, Stoudemayer TJ. Pretreatment of photoaged forearm skin with topical tretinoin accelerates healing of full-thickness wounds. *Br J Dermatol*. 1995;132:46-53.
5. Hung VC, Lee JY, Zitelli JA, Hebda PA. Topical tretinoin and epithelial wound healing. *Arch Dermatol*. 1989;125:65-69.
6. Paquette D, Badiavas E, Falanga V. Short-contact topical tretinoin therapy to stimulate granulation tissue in chronic wounds. *J Am Acad Dermatol*. 2001;45:382-386.
7. Brissett AE, Hom DB. The effects of tissue sealants, platelet gels, and growth factors on wound healing. *Curr Opin Otolaryngol Head Neck Surg*. 2003;11:245-250.
8. Hess CL, Howard MA, Attinger CE. A review of mechanical adjuncts in wound healing: hydrotherapy, ultrasound, negative pressure therapy, hyperbaric oxygen, and electrostimulation. *Ann Plast Surg*. 2003;51:210-218.
9. Martin A, Komada MR, Sane DC. Abnormal angiogenesis in diabetes mellitus. *Med Res Rev*. 2003;23:117-145.
10. Mekkes JR, Loots MA, Van Der Wal AC, Bos JD. Causes, investigation and treatment of leg ulceration. *Br J Dermatol*. 2003;148:388-401.
11. Bhawan J. Short- and long-term histologic effects of topical tretinoin on photodamaged skin. *Int J Dermatol*. 1998;37:286-292.
12. Elson ML. The role of retinoids in wound healing. *J Am Acad Dermatol*. 1998;39: S79-S81.
13. Mandy SH. Tretinoin in the preoperative and postoperative management of dermabrasion. *J Am Acad Dermatol*. 1986;15:878-879, 888-889.
14. Anthony J, Miller L, Dinehart SM. Topical tretinoin decreases healing times of electroepilation-induced wounds. *Dermatologica*. 1991;183:129-131.
15. Basak PY, Eroglu E, Altuntas I, Agalar F, Basak K, Sutcu R. Comparison of the effects of tretinoin, adapalene and collagenase in an experimental model of wound healing. *Eur J Dermatol*. 2002;12:145-148.
16. Hunt TK, Ehrlich HP, Garcia JA, Dunphy JE. Effect of vitamin A on reversing the inhibitory effect of cortisone on healing of open wounds in animals and man. *Ann Surg*. 1969;170:633-641.
17. Otley CC, Gayner SM, Ahmed I, Moore EJ, Roenigk RK, Sherris DA. Preoperative and postoperative topical tretinoin on high-tension excisional wounds and full-thickness skin grafts in a porcine model: a pilot study. *Dermatol Surg*. 1999;25:716-721.
18. Watcher MA, Wheeland RG. The role of topical agents in the healing of full-thickness wounds. *J Dermatol Surg Oncol*. 1989;15:1188-1195.

Announcement

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As a member of the International Committee of Medical Journal Editors (ICMJE), *Archives of Dermatology* will require, as a condition of consideration for publication, registration of all trials in a public trials registry (such as <http://ClinicalTrials.gov>). Trials must be registered at or before the onset of patient enrollment. This policy applies to any clinical trial starting enrollment after July 1, 2005. For trials that began enrollment before this date, registration will be required by September 13, 2005, before considering the trial for publication. The trial registration number should be supplied at the time of submission.

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