Clinical Investigation

Multicenter Trial of Cadexomer Iodine to Treat Venous Stasis Ulcer

G. ALLEN HOLLOWAY, Jr, MD, *Phoenix;* KAJ H. JOHANSEN, MD, PhD, *Seattle;*
ROBERT W. BARNES, MD, *Little Rock, Arkansas; and* GEORGE E. PIERCE, MD, *Kansas City, Kansas*

In a crossover study designed to judge the efficacy of the topical polymeric starch iodophore, cadexomer iodine, in accelerating the healing of venous stasis ulcers, 75 patients were prospectively randomly assigned to receive either cadexomer iodine or standard treatment. The control treatment consisted of a standard saline wet-to-dry compressive dressing. The patients improved with either treatment: ulcers healed more than twice as rapidly using cadexomer iodine (n = 38) as with standard therapy (n = 37) (P = .0025). Ulcers treated with cadexomer iodine showed trends toward less pain, exudate, pus, and debris, and a more rapid development of granulation tissue. Twelve patients crossed over from control treatment to the use of cadexomer iodine because of a failure to heal, but no patients switched to control therapy from the use of cadexomer iodine (P = .01). Except for occasional mild local burning in wounds treated with cadexomer iodine, no adverse effects were noted with either regimen.

(Holloway GA Jr, Johansen KH, Barnes RW, et al: Multicenter trial of cadexomer iodine to treat venous stasis ulcer. West J Med 1989 Jul; 151:35-38)

Venous disorders are the most common ailments involving the vascular system. It is estimated that 250,000 new cases of deep venous thrombosis occur each year in the United States.[1] Many such patients go on to have the postthrombotic syndrome; more than 1% of all adults in Scotland[2] and in Switzerland[3] have been affected by venous ulceration, and perhaps as many as 500,000 stasis ulcers are treated annually in this country.[1]

Venous stasis ulcers are difficult and time-consuming to heal and commonly recur many times. While these lesions are rarely lethal, they exact an extraordinary toll in patient inconvenience, frustration, disfigurement, pain, and incapacitation. The economic cost of venous stasis ulcers in terms of time lost from work and the use of medical resources is staggering.[1-3]

Neither an optimal prophylaxis against deep venous thrombosis nor a curative treatment of chronic venous insufficiency has been identified. Thus, the current management is restricted to palliating the long-term complications of the postthrombotic syndrome. Prolonged bed rest with leg elevation will heal nearly all venous stasis ulcers, but this is costly and must be reserved for selected refractory cases, as is also true for surgical ulcer excision and grafting. Multiple topical treatments—compresses of salicylic acid; enzymes to accelerate ulcer debridement; the application of synthetic or preserved xenogeneic wound dressings; the use of steroids, antibiotics, antiseptics, or silver salts—have been found, at best, only minimally effective in controlled trials: none have been demonstrably better than the classic wet-to-dry saline compress approach.

Recently hydrophilic dextran polymer beads (dextranomer [Debrisan]) have been used topically on venous stasis ulcers, on the principle that the hygroscopic removal of wound secretions might retard surface infection and thereby accelerate wound healing and epithelialization.[4] By this process the wound surface is kept clean, but a culture medium theoretically remains in the bead interstices. Cadexomer iodine (Iodosorb [Perstorp Carbotec, Perstorp, Sweden]), a starch polymer bead similar to dextranomer but with iodide (0.9% weight per weight) bonded to the polymer, extends this principle. When fluid contacts the beads, substantial amounts of fluid—as much as 6 ml per gram of cadexomer iodine—are absorbed, as well as bacteria within the fluid. In addition, bonded iodide becomes bactericidal in this milieu. Treatment with cadexomer iodine should theoretically result in a wound that contains both less secretions and fewer bacteria, thereby promoting wound healing. We evaluated the use of cadexomer iodine in the management of venous stasis ulcers by means of a prospective, randomized crossover trial in which the use of this agent was compared with that of a standard treatment approach at three university hospitals.

Patients and Methods

In all, 75 outpatients, 55 men and 20 women, were entered into the trial at three sites—Richmond, Virginia; Kansas City, Kansas; and Seattle, Washington. Their ages

From the Departments of Surgery, Harborview Medical Center, University of Washington School of Medicine, Seattle (Drs Holloway and Johansen), Virginia Commonwealth University School of Medicine, Richmond (Dr Barnes), and University of Kansas Medical Center School of Medicine, Kansas City (Dr Pierce).

Dr Holloway is currently with the Maricopa Medical Center, Phoenix, and Dr Barnes is with the University of Arkansas College of Medicine, Little Rock.

Technical assistance was provided by Molly Zaccardi, Glenn Turley, Linda Klein, RN, ET, and Paul Cunningham.

This study was funded by a grant from T.I.L. (Medical) Ltd, Toronto, Canada.

Reprint requests to Kaj H. Johansen, MD, PhD, Department of Surgery, Harborview Medical Center, 325 9th Ave, Seattle, WA 98104.

ranged from 31 to 93 years. Informed consent, approved by each site's institutional review board, was obtained from each patient. Inclusion criteria required a patient to be in good health and to have had a venous stasis ulcer present for a minimum of three months. Initially patients with ulcers less than 2 cm in maximum diameter were excluded, but this criterion was relaxed partway through the trial. Potential subjects were excluded if there was a suspected or proven nonvenous cause of the ulcer, an inability to comply with the treatment regimen, major medical disorders, an iodine allergy, or clinically significant arterial disease.

The initial patient evaluation included a relevant history, a physical examination, and laboratory studies, with an emphasis on blood, kidney, liver, and thyroid profiles. The ulcer size was measured planimetrically on transparent tracings. Ulcers were graded as "very superficial" (through skin), "superficial" (through subcutaneous tissue), or "deep" (into or through muscle, near bone). Surface characteristics of the ulcer—quantity of exudate, pus, debris, amount and quality of granulation tissue, degree of edema, and erythema—and pain were all recorded on an analog scale, and a color photograph of the ulcer, taken at a standard distance and under controlled lighting, was obtained. Swabs of the ulcer bed for aerobic and anaerobic culture, using Stuart's transport medium modified to neutralize the iodine during subsequent treatment, were taken for bacteriologic purposes. Noninvasive arterial and venous studies, carried out to confirm the underlying venous pathophysiology, included arterial and venous Doppler, venous outflow strain-gauge plethysmography, and photoplethysmography.

After the initial studies were done, patients were randomly assigned to either the standard or cadexomer iodine treatment groups. Standard treatment consisted of wet-to-dry dressings with saline-soaked sterile 4-in by 4-in gauze pads changed by the patient once a day. In the cadexomer iodine-treated patients, the ulcer was irrigated with a saline solution, the medication was sprinkled onto the ulcer, and the wound was covered with a dry gauze dressing. This treatment was repeated on a daily basis by the patient. In both groups the dressing was held in place by a toe-to-knee elastic compression bandage.

Follow-up was at two-week intervals for the first eight weeks and then at monthly intervals. Each ulcer was evaluated serially by the same person at each medical center. Patients were removed from the study when their ulcer healed or if it was felt by the attending physician that, due to worsening of the ulcer, more intensive therapy—that is, operative excision and grafting—was needed. At each visit a bacteriologic swab was taken, the ulcer was measured and traced, and a photograph taken. Ulcer healing was expressed in square centimeters per week and in square centimeters per week per centimeter of baseline ulcer circumference. At 12 weeks, the physical examination and the general laboratory studies were repeated. Also, if the ulcer was not healed at this time, the patient was offered the opportunity to switch to the alternate therapy group. Patients were questioned about compliance at each visit.

When an ulcer was healed, or at the end of 24 weeks, the patient was reexamined, laboratory tests were done, and the ulcer was reevaluated in the vascular laboratory in the same manner as at the beginning of the study.

Data from all patients were serially collated for statistical analysis. The Student's *t* test was used for comparing pretrial baseline studies and laboratory studies. An analysis of covariance was used for assessing differences in the healing rate. Statistical significance was assumed for *P* values of less than .05.

Results

Of the 75 patients starting the trial, 15 did not complete the study for reasons other than healing of the ulcer. Four failed to respond to one or both treatments and required more aggressive treatment. Two died during the study of causes unrelated to their ulcers, and nine dropped out or failed to return. An additional six patients were excluded from the statistical analysis. Two of these were felt in retrospect to have been inappropriately entered into the study because their ulcers were too small. The other four lacked adequate follow-up information. Subjects failed to complete the study or were excluded from analysis in equivalent proportions from the control and cadexomer iodine-treated groups, and noninclusion did not appear to influence the study's analysis or conclusions. A total of 54 patients remained from whom data were available for statistical analysis.

The two treatment groups were similar in all baseline characteristics, although the mean ulcer duration before treatment was considerably greater in the cadexomer iodine-treated group than in the control group (Table 1). The mean ulcer area was substantially—although not significantly: $P = .11$—greater in the cadexomer iodine-treated group, primarily due to randomization to this group of two patients with giant ulcers measuring 136.2 cm^2 and 127.3 cm^2, respectively.

Ulcer healing was significantly ($P < .0001$) different from zero in both the control and the cadexomer iodine treatment groups at all three centers. The healing rate for patients undergoing standard treatment was 0.41 cm^2 per week, compared with 0.95 cm^2 per week in those treated with cadexomer iodine ($P = .0025$; Table 2). This healing advantage achieved statistical significance both in the overall group and at two of the three individual centers; the *P* value at the third center was .09. Healing as a proportion of the baseline ulcer circumference approached statistical significance in the cadexomer iodine-treated group ($P = .072$). Overall, treatment with cadexomer iodine accelerated healing 1.5 to 2.5 times compared with standard treatment. A trend toward improvement in terms of enhanced granulation and diminished

TABLE 1.—*Patient Characteristics*

Patient and Ulcer Characteristics	*Ulcer Treatment*	
	Standard (n=37)	*Cadexomer Iodine (n=38)*
Male, No.	27	28
Female, No.	10	10
Age* (range), yr	61.5±12.7 (31-84)	63.0±0.8 (34-93)
Duration of ulcer, mo*	11.4±21.8	29.5±59.1
Median (range)	4.5 (3-130)	7.5 (3-240)
Area of ulcer, cm^2		
Mean	11.20	20.05
Median (range)	9.75 (3.0-37.0)	10.70 (0.6-136.0)
Depth of ulcer†		
Deep	13	18
Superficial	17	15
Very superficial	7	5

*Plus or minus standard error of the mean.
†See text (Methods section) for description of depth.

edema, pain, exudate, pus, and debris was also noted with the use of cadexomer iodine; this trend did not achieve statistical significance (Table 3).

As expected, numerous bacterial species were isolated from the ulcers. Neither treatment was superior in causing a reduction in bacterial numbers on a semiquantitative (categorized as profuse, moderate, or sparse) basis. A persistence of pathogenic organisms, even at levels often associated with invasive infection,[5] was frequently associated with rapid healing. On the other hand, the presence of β-hemolytic streptococci was almost invariably associated with a failure to heal[6]; only one patient with cultures positive for streptococci had ulcer healing.

A total of 12 patients switched treatments during the trial: all 12 crossed over from the control treatment to using cadexomer iodine because of a failure of healing, but no patient switched to control therapy from cadexomer iodine (P = .01, Fisher's exact test). Of the 12 patients, 5 did not benefit from the crossover, and the other 7 showed healing of their ulcers.

Only minimal adverse effects were noted with cadexomer iodine treatment and none with the control treatment. Six patients had mild transient burning, pain, or itching associated with using cadexomer iodine. No other symptoms could be related to the experimental treatment.

Although there were insignificant changes in serum chemistry values in both study groups, no specific patterns or correlations with treatment were seen. Of specific interest, no significant changes in thyroid function were seen in either group.

Discussion

Browse and Burnand have proposed that venous stasis ulcers occur when the pathologically altered venous hemodynamics of the postthrombotic syndrome result in the interstitial deposition of fibrinogen, with subsequent fibrosis, cutaneous ischemia, skin breakdown, and ulcer formation.[7] Ideally, venous function might be improved to allow healing of venous stasis ulcers, but this is usually not possible or, at least, not feasible, and clinicians are left to deal with the chronic ulcerative complications of the postthrombotic syndrome.

TABLE 2.—*Response to Treatment and Ulcer Healing*

Treatment Response	Treatment*		Difference Between Treatments, P Value
	Standard	Cadexomer Iodine	
Ulcer healing, cm²/wk	0.41±0.13	0.95±0.12	.0025
Ulcer healing vs baseline circumference, cm²/wk/cm²	0.03±0.01	0.04±0.01	.0720

*The numbers show the mean rate of change plus or minus the standard error of the mean.

TABLE 3.—*Response to Treatment*

Ulcer Characteristics	Treatment*		Difference Between Treatments, P Value
	Standard	Cadexomer Iodine	
Granulation	2.75±0.4	3.43±0.3	.16
Edema	−1.40±0.2	−1.60±0.2	.53
Pain	−2.44±0.4	−2.47±0.3	.96
Exudate	−2.51±0.3	−3.11±0.3	.20
Pus and debris	−2.43±0.3	−2.68±0.3	.55
Erythema	−1.86±0.3	−1.14±0.3	.06

*The numbers show the mean rate of change plus or minus the standard error of the mean.

We evaluated the ability of a starch polymer iodophore, cadexomer iodine, to accelerate the healing of venous stasis ulcers. The results of a three-center randomized crossover trial indicate that both standard saline wet-to-dry and cadexomer iodine treatments are effective in reducing ulcer size and promoting healing. Treatment with cadexomer iodine healed ulcers significantly more rapidly than standard treatment, a finding in accordance with two previous European trials.[8,9] In our study, the mean ulcer healing rate was more than twice as great with the use of cadexomer iodine as with the control treatment.

The cleansing action of the two treatments was evaluated on visual analog scales that assessed the amount of exudate, pus, and debris at the ulcer surface. Both treatments appeared to be highly effective in improving wound appearance: cadexomer iodine appeared to be more effective, although not at the level of statistical significance. Removing exudate and dead tissue, both of which provide an excellent bacterial culture medium, presumably results in a better environment for epithelialization and healing. Pain and edema were also substantially reduced by both treatments, again with a trend favoring the use of topical cadexomer iodine.

Bacteriologic studies showed that in both treatment groups the number of organisms decreased during the study, with neither showing superiority. It is unclear, however, whether this represents a response to the topical treatment or, alternatively, a response to an improved healing process. A decrease in the number of organisms was commonly associated with healing. On the other hand, ulcers often healed despite the persistent presence or even profuse growth of pathogenic organisms. This apparently occurs because most such bacteria primarily colonize the superficial exudate and debris of the venous stasis ulcer. The presence of β-hemolytic streptococci, however, was associated with a failure to heal in all but one patient. This is in keeping with previous experience[6] and presumably occurs because this organism is tissue-invasive. These results support the systemic use of antibiotics in patients having β-hemolytic streptococci on venous stasis ulcer culture.

No significant adverse effects were noted during the trial other than mild transient local burning noted by a few of the cadexomer iodine-treated patients. This has been reported in other trials using iodine-containing compounds but has not been associated with other or more severe effects. None of the laboratory safety monitoring—hematology, clinical chemistry, urinalysis, or thyroid function—showed any consistent changes that could be related to the treatment.

This trial shows that both standard wet-to-dry dressings and the topical use of cadexomer iodine promote the healing of venous stasis ulcers. In this study, the latter was more than twice as effective (P = .0025) in promoting healing. Both treatment methods appear to improve the environment for healing by cleaning the ulcer surface and thereby accelerating the development of ulcer granulation tissue and epithelialization. Comparing the use of cadexomer iodine with other recently introduced topical agents or treatments might further delineate the means by which venous stasis ulcers heal. Topical cadexomer iodine may be a useful addition to

the therapeutic armamentarium of clinicians treating patients with venous stasis ulcers.

REFERENCES

1. Coon WW, Willis PW, Keller JB: Venous thromboembolism and other venous disease in the Tecumseh Community Health Study. Circulation 1973; 48:839-847

2. Ruckley CV, Dale JJ, Callam MJ, et al: Causes of chronic leg ulcers (Letter). Lancet 1982; 2:615-616

3. Widmer LK, Mall T, Martin H: Epidemiological and sociomedical importance of peripheral vascular disease, *In* Hobbs JT (Ed): The Treatment of Venous Disorders, Vol 1. Lancaster, England, MTP Press, 1977, pp 3-12

4. Jacobsson S, Rothman U, Arthurson G, et al: A new principle for the cleansing of infected wounds. Scand J Plast Reconstr Surg 1976; 10:65-67

5. Krizek TJ, Robson MJ: Evolution of quantitative bacteriology in wound management. Am J Surg 1975; 130:579-584

6. Robson MC, Heggers JP: Surgical infection—II. The β-hemolytic streptococcus. J Surg Res 1969; 9:289-292

7. Browse NL, Burnand KG: The postphlebitic syndromes: A new look, chap 25, *In* Bergan JJ, Yao JST (Eds): Venous Problems. Chicago, Year Book Medical, 1978, pp 395-404

8. Skog E, Arnesjö B, Troëng T, et al: A randomized trial comparing cadexomer iodine and standard treatment in the out-patient management of chronic venous ulcers. Br J Dermatol 1983; 109:77-83

9. Ormiston MC, Seymour MTJ, Venn GE, et al: Controlled trial of Iodosorb in chronic venous ulcers. Br Med J [Clin Res] 1985; 291:308-310

Pupil Response

IN NONTRAUMATIC COMA, excluding drug-induced coma, one can perhaps make some prognostication on the best recovery at one year by noting the presence or absence of the pupil response, corneal reflex, or caloric response at the time the patient is admitted. If two or more of these are absent, only 1% of these patients at one year will have moderate disability to good recovery. Of these patients 99% will either have no recovery—they've died—vegetative state, or perhaps severe disability.

In comatose head-injured patients one can perhaps "predict" the mortality rate at 6 months by noting the pupillary response. In one study, if both pupils were reactive, the mortality rate at 6 months was 37%; if only one pupil was reactive at the time of admission, the mortality rate increased to 57%; and if both pupils were unreactive, the mortality rate increased to 83%.

The hallmark of metabolic coma is preserved pupil response despite substantial respiratory depression, absent caloric response, or decerebrate posturing.

Atropine, glutethimide, and barbiturates . . . will alter the pupil and may mimic structural-induced coma.

The pupil from pontine lesions will be a pinpoint pupil, but the pupil will still be reactive if one were to use a hand-held magnifier to examine the pupil reflex.

—LENWORTH N. JOHNSON, MD

Extracted from *Audio-Digest Ophthalmology,* Vol. 29, No. 09, in the Audio-Digest Foundation's series of tape-recorded programs. For subscription information: 1577 E Chevy Chase Dr, Glendale, CA 91206