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(Accepted 9 May 1985)

Controlled trial of Iodosorb in chronic venous ulcers

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Abstract

Cadexomer iodine (Iodosorb) is a hydrophilic starch powder containing iodine, which is a suitable dressing for granulating wounds such as venous ulcers. A total of 61 outpatients with chronic venous ulcers participated in a randomised optional crossover trial using cadexomer iodine or a standard dressing for their ulcers. The trial lasted for 24 weeks or until the ulcer had healed. Two patients withdrew during the course of the trial. Both treatments were highly effective, but the epithelium of ulcers dressed with cadexomer iodine grew again significantly faster ($p < 0.001$). At the midpoint of the trial (12th week) 13 of 30 patients receiving standard treatment were changed to cadexomer iodine, while only three of 29 receiving cadexomer iodine changed to the standard dressing ($p < 0.02$). In most cases ulcers were dressed and rebanded daily by the patients themselves after instruction and supervision. This may be better than having dressings and bandages applied by professionals less regularly.

Introduction

Chronic venous ulcers occur in 1-3% of the population¹ and present a relapsing or intractable problem that places a heavy demand on nursing and medical resources. A well applied compression bandage is the mainstay of treatment in ambulant patients. Though numerous local dressings are available, there have been few controlled trials that compare them.²⁻⁴

Cadexomer iodine (Iodosorb, Perstorp AB and Stuart Pharmaceuticals Ltd) is a strongly hydrophilic starch polymer

powder with iodine incorporated within its matrix. It absorbs exudate and particulate matter from the surface of granulating wounds. As it becomes moist the iodine is released. Thus it is designed to clean the wound and, at the same time, exert a bactericidal action. Furthermore, it can be washed off without disturbing delicate new epithelium when the wound is dressed. Once saturated it is no longer effective, so wounds must be redressed regularly.

In an international multicentre study cadexomer iodine was compared with various local favourite dressings in treating chronic venous ulcers.³ The preliminary results of the study carried out in this hospital have already been presented,⁵ and we now analyse the results in 61 patients.

Patients and methods

Outpatients with chronic venous ulcers that had not healed for at least three months were asked to participate in the study. In all cases a medical history was taken and a physical examination, including Doppler ankle pressure index, performed. A full blood count, erythrocyte sedimentation rate, Wasserman reaction, blood glucose concentration, tests of liver function, and analysis of urine were carried out. Almost all patients selected were capable of dressing and bandaging their own ulcers. In the few exceptional cases a relative or nurse was available to dress the ulcer. Patients were excluded from the study if there was clinical or laboratory evidence that their ulcer was of non-venous aetiology. Particular care was taken not to include patients with peripheral vascular disease suggested by examination or a pressure index of the dorsalis pedis or posterior tibial to brachial artery of less than 0.70. Patients in whom compliance was expected to be poor due to concomitant physical or mental disability or travelling problems were also excluded from the study.

At the first visit the size and appearance of the ulcer were recorded by outline tracing, planimetry, and photography. Bacterial culture swabs were taken. Subjective criteria including pain, oedema, erythema, exudate, slough, and the proportion of the surface of the ulcer covered by granulation tissue were recorded on linear scales (0-100). Pain was assessed by the patient and the other criteria by the same observer at each visit. Patients were then allocated a code number according to the sequence of selection for the trial. For each number there was a double sealed envelope that contained a paper stating which treatment the patient should receive. The sequence of treatments was randomised, and the code of randomisation was not available to the investigators. The comparative treatments were cadexomer iodine or a standard

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dressing, which in this study was gentian violet and Polyfax (polymyxin and bacitracin) ointment.

The ulcer was cleaned with saline and dressed. Cadexomer iodine powder was sprinkled on to the ulcer in a layer 0.3-0.5 cm deep. Polyfax ointment was applied in a generous layer after painting on gentian violet. Each dressing was covered with a similar sized pad to keep it in place. Pilot studies showed a gauze pad to be most suitable for cadexomer iodine while a non-adherent (Melolin) pad was best for the standard dressing. The legs were then bandaged identically to below the knee with a crepe bandage followed by a cotton crepe (STD) compression bandage.

A nurse specially attached to the study taught the patients how to dress and bandage their ulcers, supervising them by visiting their homes until she was satisfied that they had mastered the technique. At first under her instruction and subsequently on their own patients in each stage of the study redressed and bandaged their ulcers every day. They were reassessed at regular intervals until the ulcer had healed or for up to 24 weeks. On each occasion the variables of ulcers described above were measured. At the 12th week each case was reviewed by a clinician not associated with the routine assessment of the ulcer to see whether it was healing satisfactorily. If it was the patient continued with the dressing originally allocated, if not he or she was changed to the alternative treatment.

At the end of the study the blood tests were repeated. Patients whose ulcers had healed were given a tailored support stocking to help prevent relapse and were considered for definitive treatment of the underlying venous problem.

Analysis of covariance was used to assess differences in the rate of healing and the linear scale variables. This statistical analysis applied only to the first 12 weeks of the trial as thereafter the populations were conditional on the optional crossover. Student's *t* test, Fisher's exact test, or the χ^2 test was used for all other calculations. Based on pilot studies and assuming variability of estimates of healing slopes as ≤ 0.35 and difference between treatments as ≥ 0.25 , on a two tailed test for $\alpha = 0.05$ and $1 - \beta = 0.9$, $n = 29$ per group.

Results

Sixty one patients entered this study. One patient receiving cadexomer iodine was admitted to hospital for routine surgery and his ulcer was dressed inappropriately. He was withdrawn from the trial. This left 30 in each group. Two patients, both receiving cadexomer iodine, failed to complete the study. One died of a perforated ulcer and the other had difficulty removing the cadexomer iodine from the ulcer. The data on these two patients were included in the analysis. The groups receiving cadexomer iodine and standard treatment were reasonably matched for age, sex, and size of ulcer (table I). Ulcers in the group receiving cadexomer iodine had not healed for a mean of 46 months, compared with 16 months for the standard group. This discrepancy was largely because the ulcers of

TABLE I—Summary of group comparability

	Standard treatment (n = 30)	Cadexomer iodine (n = 30)
Mean (SD) age (years)	70.3 (13.3)	67.3 (9.7)
Range	44-92	49-86
No of men	8	13
No of women	22	17
Mean (SD) duration of ulcer (months)	15.9 (19.5)	45.9 (105.9)
Median duration of ulcer (months)	6	8.5
Range	3-96	3-517
10th-90th percentile	4-36	3-144
Mean (SD) size of ulcer (cm ²)	10.2 (8.7)	12.1 (13.9)

TABLE II—Response to treatment over 12 weeks. (Values are means (SEM))

	Standard treatment (n = 30)		Cadexomer iodine (n = 30)		Difference between treatments (p value)
	Change/week	Change from baseline (p value)	Change/week	Change from baseline (p value)	
Healing rate (cm ²)	0.46 (0.1)	0.0001	0.89 (0.1)	0.0001	0.0001
Healing rate (cm ²)/cm of circumference	0.03 (0.004)	0.0001	0.06 (0.005)	0.0001	0.0001
Granulation	2.5 (0.4)	0.0001	3.3 (0.4)	0.0001	NS
Oedema	1.8 (0.3)	0.0001	2.1 (0.3)	0.0001	NS
Pain	0.9 (0.3)	0.0006	1.2 (0.3)	0.0001	NS
Exudate	2.6 (0.3)	0.0001	3.0 (0.4)	0.0001	NS
Pus and debris	2.5 (0.3)	0.0001	3.3 (0.4)	0.0001	NS
Erythema	0.9 (0.3)	0.0077	1.4 (0.3)	0.0001	NS

TABLE III—Results at crossover

	Standard treatment (n = 30)	Cadexomer iodine (n = 30)
No who withdrew before crossover		1
No who changed treatment	13	3
No who did not change treatment	17	26

$p < 0.02$, χ^2 test with Yates's correction.

four patients in the group receiving cadexomer iodine had been present for over 10 years.

During the first 12 weeks 12 of the ulcers treated with cadexomer iodine and seven with the standard dressing healed completely (not significant). Overall, however, ulcers in the group receiving cadexomer iodine healed significantly faster during this time as judged by both planimetry and change in area as a function of circumference ($p < 0.001$, table II). The responses of men and women were similar. The optional crossover figures at the 12th week were also in favour of cadexomer iodine ($p < 0.02$, table III). The ulcers of 10 out of 13 patients who changed from standard treatment to cadexomer iodine had healed or had almost healed after 12 weeks, and only one failed to reduce in area by more than 50%. One patient died from a perforated duodenal ulcer 11 days after changing treatments. Among the remaining 12 the mean reduction of area after 12 weeks was 87%. For the three patients who crossed from cadexomer iodine to standard treatment the area of two ulcers decreased by roughly 50% and one increased. The mean reduction of area of ulcers after 12 weeks in these three patients was 35%.

An obvious improvement in granulation, oedema, exudate, pus and debris, and erythema was seen after both treatments ($p < 0.001$), but, although trends favoured cadexomer iodine, the difference between the two groups was not significant in these subjective variables (table II). Bacterial cultures grew a wide and changing variety of organisms, and there was no consistent trend towards eradicating particular pathogens irrespective of the treatment or response of the ulcer.

Two patients had difficulty removing the cadexomer iodine from the ulcer. Three patients complained of stinging or itching when cadexomer iodine was applied, but this was not severe enough to make them withdraw from the study. Two patients receiving standard treatment and five receiving cadexomer iodine developed eczema, pruritus, or rashes. These all resolved despite continued treatment. Beclomethasone dipropionate (Propaderm) ointment was applied to the eczematous skin in two of the patients receiving cadexomer iodine. All repeat blood tests were normal.

Discussion

In this study both cadexomer iodine and the standard dressing proved to be highly effective. Ulcers treated with cadexomer iodine healed nearly twice as quickly during the first 12 weeks of the study, a finding in keeping with other reported trials of cadexomer iodine.³⁻⁶ Side effects attributable to cadexomer iodine were not frequent or serious, and it has been shown not to affect thyroid function, although iodine concentrations bound with protein can increase.⁶

This trial was designed as an optional crossover study so that patients whose ulcers did not respond well would not be obliged to continue with an ineffective treatment for 24 weeks. As the results of planimetry were not immediately available the decision whether to cross over had to be made on clinical criteria and

visual assessment of the tracings and photographic records. On reviewing the planimetry the reasons for deciding whether or not to change were unclear in four cases. Furthermore, traces of the dressing could often be seen, and the decision was thus not "blind." The crossover figures must, therefore, be viewed critically. It is noteworthy that when the four cases mentioned were excluded from the analysis the results still favoured cadexomer iodine ($p < 0.05$).

Contrary to the findings of Skog *et al*³ we did not observe any significant effect on bacterial colonisation. Studies using a simulated wound model, however, have shown that although cadexomer iodine may not eliminate organisms, it does suppress growth for almost 18 hours and thereby significantly reduces bacterial mass.⁷ The action of bacteria in inhibiting the healing of wounds may relate to the production of cytotoxic chemicals,^{8, 9} and reduction of bacterial mass for a substantial proportion of the day may be one of the mechanisms by which cadexomer iodine accelerates regrowth of the epithelium.

Ulcers in both groups healed well. This study shows that selected patients (average age 68 years) can manage their own ulcers effectively. Patient compliance was remarkably good.

Our former opinion, in common with that of many others, was that weekly dressing and bandaging provides adequate support for ulcers with minimal disturbance of new epithelium. On the basis of this study we suggest that daily bandaging and renewal of a non-adherent dressing may have distinct advantages over less demanding regimens. Bandages reapplied daily probably provide better support than those changed less regularly. Furthermore, many of our patients remarked how much the reduction in odour had improved their social lives. Although it takes time and patience to teach patients how to

dress and bandage their ulcers—that is, five two hour sessions—this seems to be repaid in terms of both healing of ulcers and, eventually, a reduction in demands on the doctor and nurse. Cadexomer iodine seems to be useful in this context.

We thank Mrs P Crisp and Mrs J Woods for supervising the teaching of dressings and nursing assistance; Dr P Sanderson, department of bacteriology, Edgware General Hospital, for bacteriological studies; Dr M Flynn of TIL (Medical) Ltd for study design and interpretation; Mr J Bailey, neuropsychiatry unit, Epsom; Dr M Rubison, Marion Laboratories Inc, Kansas City, for statistical analysis; and Perstorp AB for providing the cadexomer iodine.

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(Accepted 11 June 1985)

SHORT REPORTS

Gastric emptying in chronic renal failure

Gastrointestinal symptoms almost invariably accompany advanced chronic renal failure, but little is known about the mechanisms responsible. Abdominal distension and nausea occur in patients with reflux oesophagitis, a condition known to be associated with delayed gastric emptying.¹ As there have been few investigations into the effect of uraemia on gastric motility we compared gastric emptying in patients with uraemia with that in healthy controls.

Patients, methods, and results

We studied 14 patients with uraemia (eight women), whose ages ranged from 21 to 61 (mean age 37). All had a glomerular filtration rate of less than 5 ml/min, and serum creatinine concentrations ranged from 690 to 1560 $\mu\text{mol/l}$ (7.8 to 17.6 mg/100 ml). Four patients had started regular haemodialysis six to 12 months previously; the 10 others were studied shortly before joining the haemodialysis programme. The patients not undergoing dialysis were receiving a diet containing 20 g protein, and those undergoing dialysis consumed 60 g protein daily. All patients experienced intermittent nausea and vomiting, although these symptoms were less severe in the four undergoing haemodialysis. Barium meal studies in all patients showed no evidence of peptic ulceration. No patient took any drug likely to influence gastric motility—for example, metoclopramide or cimetidine—within 72 hours of the study.

Eleven healthy volunteers (seven women) aged 22-69 (mean age 44) were also studied.

After a six hour fast each subject ate a meal consisting of 30 g instant porridge, 8 g sugar, and 150 ml warm milk, to which 11.1 MBq (300 μCi) technetium-99m tin colloid had been added.² Each study began at 1500, and the four patients undergoing haemodialysis were studied on the day before a dialysis session. After eating the meal the subjects lay supine beneath a gammacamera linked to an on line computer. Successive 90 second images obtained over a 90 minute period were stored on magnetic discs. The gastric

images were then delineated, and the total counts within this area were calculated for each of the 60 images. A curve showing gastric emptying was produced after adjustment for radioactive decay. Counts were expressed as a percentage of the maximum count.

No control subject experienced nausea or vomiting during the study, and no patient with renal failure vomited, although most described mild nausea and abdominal fullness.

The patients with uraemia showed significantly greater retention of isotope in the stomach as judged by counts at 30 minutes ($p < 0.01$), 60 minutes, and 90 minutes ($p < 0.05$) (Mann-Whitney U test). Three of the four patients undergoing dialysis had normal gastric emptying patterns. When the four

Mean (SD) proportion of radioisotope label left in stomach in patients with uraemia not receiving dialysis (●—●) and control subjects (---○---).