Chronic wounds are estimated to affect about 3% of people over 60 years of age. Among chronic wounds, diabetic foot ulcers (DFUs), venous leg ulcers (VLUs), and pressure ulcers (PUs) are common. These account for high morbidity and also cause a drain on already limited health care resources, especially in developing countries. Despite availability of advanced therapies, chronic wounds are often difficult to treat, and there is no single line of effective therapy for chronic wounds. Therefore, new means and modalities are continuously explored.

Infection control has been recognized as a basic requirement in chronic wound treatment. However, there is no reliable evidence to recommend routine use of systemic antibiotics for the treatment of chronic wounds. In contrast, currently available literature gives credence to the use of topical preparations. Several topical products are available with potential advantages and disadvantages. Among those, iodine-based preparations, when in contact with wound exudate, are known to release free iodine that acts as an antiseptic and controls the infection, thereby promoting wound healing. However, controversies, particularly those related to its effects on systemic absorption, impact on metabolic function, and wound healing, continue to daunt clinicians. With the emergence of multidrug-resistant strains of organisms and a better understanding of the dynamics of wound healing, there has been a resurgence of interest in topical use of iodine in wound care.

Among the iodine preparations, povidone-iodine was first introduced in the 1960s and cadexomer iodine in the 1980s. Though the majority of studies show the efficacy of povidone-iodine in reducing the bacterial load in chronic wounds, there is a lack of evidence to determine if there is a positive or negative effect on wound healing when there is no infection. On the other hand, cadexomer iodine has a positive impact on healing in the chronic wound environment. It is a hydrophilic starch polymer bead, containing 0.9% w/w iodine. Pharmacodynamic study has shown that when in contact with wound exudates, cadexomer iodine releases free iodine (an antiseptic), which reduces the bacterial count. It also absorbs fluid (as much as 6 mL/g of cadexomer iodine), removes pus.
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and debris, and facilitates desloughing.\(^8\) In addition, cadexomer iodine maintains a moist environment to promote the healing of chronic skin ulcers. Keeping these factors in view, the clinical safety and efficacy of cadexomer iodine was tested on Indian patients with chronic wounds in a randomized, multicenter, controlled study.

**MATERIALS AND METHODS**

**Patient selection**

People aged between 18 and 65 years, with a single VLU, DFU, or PU with adequate arterial blood supply as assessed by color Doppler, ultrasonography, and ankle-brachial index were enrolled in the study. Chronic ulcers were of at least 4 weeks’ duration and between 2 cm\(^2\) to 10 cm\(^2\). Patients were excluded if they had diabetes (uncontrolled glycemia, HbA\(_1c\) ≥ 9%), renal failure (serum creatinine > 3.0 mg/dL), poor nutritional status (serum albumin < 3.0 g/dL or total protein < 6.5 g/dL), or a history of thyroid disorder. Further, patients on corticosteroids, immunosuppressive agents, and anti-cancer chemotherapy were excluded. Study procedures were explained to each participant and written, informed consent was obtained prior to study enrollment.

**Study design**

This prospective, randomized, open-label, multicenter study was conducted in accordance with the principles under the 1964 Declaration of Helsinki and later revisions at 15 centers across 8 Indian cities from March 2016 to March 2017. The study was initiated after obtaining approval from the Drugs Controller General of India and the institutional ethical committees at their respective centers. The trial was registered in Clinical Trial Registry, India (CTRI/2016/03/006779).

**Treatment regimen**

Eligible and consenting patients were randomized using a simple randomization technique based on computer-generated random numbers in the ratio of 1:1:1 to receive 1 of 3 treatments: 0.9% cadexomer iodine ointment plus standard care, 0.9% cadexomer iodine powder plus standard care, or standard care therapy alone. Standard care varied depending on the nature of the wound; for example, compression bandages were applied to VLU and offloading procedures (ie, bed rest, wheelchairs, crutches, cast walkers, and orthopedic shoes) were offered to patients with DFUs. In general, standard care consisted of cleaning the wound with sterile saline, debridement (if required), and frequent applications of saline over the nonadherent absorbent cotton and gauze wound dressing so that it was not allowed to dry. In addition, metabolic control and treatment of comorbidities, including infection, were considered.

As part of standard care, saline solution was topically applied to the wound, depending on the exudate, once daily for the first 4 weeks. Saline dressings were changed every 3 days from weeks 5 to 12 or until complete wound healing, whichever occurred first. However, if the exudate was found to be inadequate during weeks 5 to 12, saline solution was re-applied at more frequent intervals to maintain a moist wound bed. Patients were educated on proper wound care, including the treatment and dressing procedures at the center, in order for them to continue their specified treatment at

<table>
<thead>
<tr>
<th>Table 1. Demographic data and target ulcer characteristics of patients in 3 treatment groups</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age (y) (a)</strong></td>
</tr>
<tr>
<td>Male; n (%)</td>
</tr>
<tr>
<td>Female; n (%)</td>
</tr>
<tr>
<td><strong>Height (cm) (a)</strong></td>
</tr>
<tr>
<td><strong>Weight (kg) (a)</strong></td>
</tr>
<tr>
<td><strong>Ulcer size (cm(^2)) (a)</strong></td>
</tr>
<tr>
<td><strong>ABPI (a)</strong></td>
</tr>
<tr>
<td><strong>Ankle-systolic pressure (mmHg) (a)</strong></td>
</tr>
<tr>
<td><strong>Ulcer duration (wk) (a)</strong></td>
</tr>
<tr>
<td><strong>Ulcer type</strong></td>
</tr>
<tr>
<td>Pressure; n (%)</td>
</tr>
<tr>
<td>Diabetic; n (%)</td>
</tr>
<tr>
<td>Venous; n (%)</td>
</tr>
</tbody>
</table>

\(a\) Mean ± standard deviation

**ABPI:** ankle-brachial pressure index
Patients were given a diary to record treatment compliance and incidence of adverse events throughout the study period. Two (ointment and powder) formulations of cadexomer iodine, containing 0.9% w/w iodine, were tested. Cadexomer iodine ointment was provided in 10-g tubes; the powder form was supplied in 3-g sachets. The cadexomer iodine products were applied to the wound, depending on the wound exudate, once daily for the first 4 weeks and then every 3 days from weeks 5 to 12 or until complete wound healing, whichever occurred first. The ointment was applied and the powder was sprinkled on the wound surface as per the contour of the ulcer to a minimum depth of 3 mm. If a wound was not responding to treatment in the standard care group, on ethical grounds, patients were allowed to apply povidone-iodine preparation to the wound at the discretion of the investigator.

Assessment of efficacy

The primary endpoint was percentage of reduction in ulcer size from baseline to 12 weeks. Ulcer size was measured at each of the 9 visits and calculated systematically by multiplying the greatest width by length. The secondary endpoints were mean change in ulcer size from baseline to 12 weeks, percentage of patients with complete ulcer healing within 12 weeks (complete healing was defined as 100% epithelialization or skin closure without drainage), and mean change in total wound evaluation score from baseline to 12 weeks. The wound evaluation score was assessed based on 5 wound parameters (edema, pain, exudate, erythema, and pus) and measured on a scale of 0 to 3 (0 = absent; 1 = mild; 2 = moderate; 3 = severe). Based on the score of each parameter, the total wound score was derived by summing up the score for each individual parameter.

Sample size

Published studies reported 34% reduction in ulcer size from baseline at 12 weeks with standard care alone, whereas cadexomer iodine ointment application had been shown to produce 62% reduction in ulcer size at 12 weeks. Therefore, considering 95% confidence interval and 80% power, the required sample size was calculated to be 93 (31/treatment). Expecting 15% attrition, the required sample size was 108 (36/group).

Statistical analysis

Data analysis was performed on intent-to-treat (ITT) population, which was defined as all randomized patients (n = 124) who received at least 1 dose of study medication and had at least 1 post baseline assessment. Standard descriptive summary statistics were calculated for continuous variables. Categorical data were presented in frequency tables using counts and percentages. Individual patient changes (vital signs, laboratory values) were analyzed over time by treatment. Primary and secondary outcomes were analyzed by using 1-way analysis of variance (ANOVA) with post hoc comparison and chi-square tests. All analyses were performed using SPSS version 19.0 (IBM Corporation, Armonk, NY).

RESULTS

Demographics

A total of 145 patients were screened for the study, and 124 met the study criteria. Among the 124 patients enrolled, 79 (63.7%) were men and 45 (36.3%) were women. The age of the patients ranged from 19 to 65 years (mean, 47.6 ± 11.7 years). The demographic and target ulcer characteristics of patients in the 3 treatment groups were similar at baseline (Table 1).

Patients were enrolled randomly to receive 1 of the 3 treatments: cadexomer iodine ointment (n = 41), cadexomer iodine powder (n = 43), and standard therapy (n = 40). The disposition of patients is presented in Figure 1. While 116 (93.5%) patients completed the study as per the stipulated protocol, 8 (6.5%) patients discontinued from the study. Among those patients, 5 (62.5%) were unwilling to continue the treatment, 2 (25.0%) were lost to follow-up, and 1 (12.5%) had treatment interruption and study withdrawal due to a nontreatment-related adverse event.

Primary efficacy

The primary efficacy outcome was the percentage of reduction in ulcer size from

![Figure 1. Disposition of patients.](image_url)

HIV: human immunodeficiency virus
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Results analyzed by ANOVA showed there was a significantly ($P < .0001$) higher percentage of reduction in ulcer size with both formulations of cadexomer iodine compared with standard therapy (Figure 2).

Secondary efficacy variables

The mean change in ulcer size from baseline to 12 weeks was significantly ($P < .01$) higher with both cadexomer iodine ointment (5.19 cm$^2$ ± 2.28 cm$^2$) and powder (5.19 cm$^2$ ± 2.28 cm$^2$) compared with standard care (3.94 cm$^2$ ± 1.44 cm$^2$).

Twenty-seven patients (65.9%) with cadexomer iodine ointment, 25 (58.1%) with cadexomer iodine powder, and 8 (20.0%) with standard therapy achieved complete wound healing at 12 weeks. The number of patients achieving complete wound healing was statistically ($P < .001$) higher in both formulations of cadexomer iodine treatment compared with those in standard care.

There was a gradual reduction in total wound evaluation score in all 3 treatment groups from baseline to 12 weeks. The total wound evaluation scores were significantly lower with cadexomer iodine treatment than with standard care from week 1 to week 8 (Figure 3).

Safety

There were no significant differences in the vitals measured during different visits.

Similarly, there were no significant differences in hematological and biochemical parameters, including thyroid function, from baseline to 12 weeks.

Side effects

Among the 124 patients who received study medications, 17 (13.7%) reported 27 adverse events (Table 2). With cadexomer iodine ointment, 8 adverse events were reported by 7 (17.1%) patients. There were 7 adverse events reported by 3 (7.0%) patients in the cadexomer iodine powder group. In standard therapy, 7 (17.5%) patients reported 12 adverse events. All reported adverse events were mild to moderate in severity and only 1 event with cadexomer iodine ointment was categorized as serious because the patient required hospitalization for fever and chills; this was not a treatment-related adverse event. Only 1 patient (from the ointment group) discontinued treatment due to an adverse event. All patients with adverse events recovered without sequelae.

DISCUSSION

Literature is available on the therapeutic benefits of cadexomer iodine in the treatment of chronic wounds, particularly in VLUs.\(^7\) However, limited studies exist on its role in the treatment of DFUs\(^11,13\) and PUs.\(^13\) Its cost effectiveness in the treatment of cavity foot ulcers of patients with diabetes also has been documented.\(^16\) Based on this positive evidence from these clinical trials,\(^5,11-13\) the present study was undertaken to compare the safety and efficacy of 2 formulations (ointment and powder) of cadexomer iodine with that of standard care for chronic wounds. In this multicenter, open-label, parallel-group, comparative, randomized study conducted in 8 cities across 15 institutions in India, a total of 145 patients were screened and 124 eligible patients were enrolled.

The baseline demographic and ulcer characteristics of all patients in the 3 groups were similar, thereby validating randomization of patients into 3 treatment groups. It also allowed comparison of primary and secondary endpoints between the 3 treatment groups. There were no significant changes in laboratory parameters of hematology and clinical chemistry either at baseline or at 12 weeks. Further, though cadexomer iodine is an iodine formulation, it had no adverse impact on thyroid function in any of the treated patients. Literature also has reported that apart from being effective in reducing the ulcer size, cadexomer iodine has minimal side effects unrelated to thyroid function.\(^2,8\)

From all 3 groups, a total of 27 adverse events were reported by 17 patients (Table 2). Major events included burning pain (44.4%) and irritation and itching (18.5%). Only 1 patient developed chills and rigors.
In this study, the percentage of reduction in ulcer size from baseline to 12 weeks, a primary endpoint, was significantly (P < .001) higher in patients treated with both formulations of cadexomer iodine compared with standard treatment. Besides, the percentage of patients with complete wound healing at the end of 12 weeks, a secondary endpoint, was significantly (P < .01) higher with both cadexomer iodine formulations. Similar efficacy values observed in this trial for these 2 parameters also were reported in the literature for cadexomer iodine. However, some of these studies were conducted for only 6 weeks and 8 weeks, which might be responsible for the lower efficacy values reported.

The mean change in ulcer size, another secondary endpoint, was significantly (P < .01) higher with both cadexomer iodine formulations. Similar efficacy values observed in this trial for these 2 parameters also were reported in the literature for cadexomer iodine. However, some of these studies were conducted for only 6 weeks and 8 weeks, which might be responsible for the lower efficacy values reported.

The total wound evaluation scores, based on the presence of erythema, edema, pain, and exudates, were significantly lower in the cadexomer iodine-treated groups than in the standard care group from week 1 to week 8. Similar effects of cadexomer iodine on the reduction of pain and erythema as well as the removal of pus and exudates were reported leading to increased formation granulation tissue. In the present study, bacteriologic examination of wounds was not performed; nonetheless, systemic antibiotics were prescribed to 24 patients with clinically evident infective ulcers in all 3 treatment groups. A higher percentage (32%) of patients in the standard care group required systemic antibiotics to control wound infection compared with the cadexomer iodine ointment (12.2%) and cadexomer iodine powder (13.9%) groups, which indicates better cleansing action of cadexomer iodine on wounds. Cadexomer iodine is known to remove the barrier and desloughing properties. The broad-spectrum antimicrobial action is provided by the sustained release of iodine, and the desloughing action is provided by the unique cadexomer matrix. Experimental studies conducted using a porcine wound model also show cadexomer iodine not only reduces the number of pathogens but increases epidermal regeneration.

A moist wound bed plays an important role in wound healing. Since gauze dressings are not as effective as modern dressings in maintaining moisture, every effort was made to ensure a moist wound by reapplying saline over the nonadherent absorbent cotton and gauze wound dressing that was used. If the exudate was insufficient, saline also was more frequently applied over the gauze dressing to ensure a moist wound environment. Although cadexomer iodine has a better moisture-retention ability (as much as 6 mL/g of cadexomer iodine), the superior efficacy of cadexomer iodine over saline dressings cannot entirely be attributed to differences in moisture retention of the dressing materials used. In an experimental study, cadexomer iodine ointment had been shown to produce significantly more epithelization than wounds treated with either cadexomer or saline alone. In addition, the epidermis of wounds treated with cadexomer iodine showed more epithelial cell layers. If the iodine in cadexomer iodine had no role, there would have been similar epithelization in wounds either treated with cadexomer iodine or cadexomer.

Thus, these results demonstrate the superior efficacy of the combination of cadexomer and iodine over cadexomer alone due to its dual action of antimicrobial and desloughing properties. Both cadexomer formulations, in comparison with standard care, showed consistently positive effects on wound healing. Yet, there were no significant differences in any of the efficacy parameters between the 2 formulations (ie, ointment and powder). However, the application of cadexomer iodine ointment was found to be easier for the patient as compared with sprinkling the powder on the wound.

LIMITATIONS
Placebo effects and vehicle effects are known to influence evaluation of wound care. Therefore, instead of an open-label study, a double-blind study along with inclusion of 2 vehicle groups, namely, the ointment or cadexomer (hydrophilic

Table 2. Number of adverse events

<table>
<thead>
<tr>
<th>ADVERSE EVENTS</th>
<th>TOTAL</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pain</td>
<td>12 (44.4%)</td>
</tr>
<tr>
<td>Irritation/itching</td>
<td>5 (18.5%)</td>
</tr>
<tr>
<td>Redness</td>
<td>3 (11.1%)</td>
</tr>
<tr>
<td>Swelling</td>
<td>1 (3.7%)</td>
</tr>
<tr>
<td>Fever</td>
<td>3 (11.1%)</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>1 (3.7%)</td>
</tr>
<tr>
<td>Headache</td>
<td>1 (3.7%)</td>
</tr>
<tr>
<td>Chills</td>
<td>1 (3.7%)</td>
</tr>
<tr>
<td><strong>Total number of adverse events</strong></td>
<td><strong>27 (100%)</strong></td>
</tr>
<tr>
<td><strong>Total number of patients</strong></td>
<td><strong>17 (13.7%)</strong></td>
</tr>
</tbody>
</table>
Efficacy of Cadexomer Iodine in Chronic Ulcers

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REFERENCES


starch polymer bead without 0.9% w/w iodine) would have enhanced the quality of this study.

CONCLUSIONS

The results of this study show that both formulations of cadexomer iodine (ointment and powder) are safe and effective in the treatment of chronic ulcers, which may lead to improved patient quality of life and reduction in health care costs. With these potential benefits, cadexomer iodine is yet another therapeutic option available to physicians treating patients with chronic ulcers.  

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