

A Randomized, Controlled Trial of Promogran (a Collagen/Oxidized Regenerated Cellulose Dressing) vs Standard Treatment in the Management of Diabetic Foot Ulcers

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Hypothesis: Promogran, a wound dressing consisting of collagen and oxidized regenerated cellulose, is more effective than standard care in treating chronic diabetic plantar ulcers.

Design: Randomized, prospective, controlled multicenter trial.

Setting: University teaching hospitals and primary care centers.

Patients: A total of 276 patients from 11 centers were enrolled in the study. The mean age of the patients was 58.3 years (range, 23-85 years). All patients had at least 1 diabetic foot ulcer.

Interventions: Patients were randomized to receive Promogran (n=138) or moistened gauze (control group; n=138) and a secondary dressing. Dressings were changed when clinically required. The maximum follow-up for each patient was 12 weeks.

Main Outcome Measure: Complete healing of the study ulcer (wound).

Results: After 12 weeks of treatment, 51 (37.0%) Promogran-treated patients had complete wound closure

compared with 39 (28.3%) control patients, but this difference was not statistically significant ($P=.12$). The difference in healing between treatment groups achieved borderline significance in the subgroup of patients with wounds of less than 6 months' duration. In patients with ulcers of less than 6 months' duration, 43 (45%) of 95 Promogran-treated patients healed compared with 29 (33%) of 89 controls ($P=.056$). In the group with wounds of at least 6 months' duration, similar numbers of patients healed in the control (10/49 [20%]) and the Promogran (8/43 [19%]; $P=.83$) groups. No differences were seen in the safety measurements between groups. Patients and investigators expressed a strong preference for Promogran compared with moistened gauze.

Conclusions: Promogran was comparable to moistened gauze in promoting wound healing in diabetic foot ulcers. It showed an additional efficacy for ulcers of less than 6 months' duration that was of marginal statistical significance. Furthermore, Promogran had a safety profile that was similar to that of moistened gauze, with greater user satisfaction. Therefore, Promogran may be a useful adjunct in the management of diabetic foot ulceration, especially in ulcers of less than 6 months' duration.

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DIABETIC FOOT ULCERS and the related excess morbidity and mortality as a consequence of foot problems in people with diabetes represent a major public health challenge.¹ The most frequent cause of hospitalization of diabetic patients is serious foot or lower extremity problems. Furthermore, 40% to 70% of all nontraumatic major (lower limb) amputations are performed on patients with diabetes.² The resulting burden to society in terms of costly health care cannot be underestimated. A 1998 study identified the total cost of treatment of a lower extremity ulcer for working-age adults (18-64 years old) as \$4595 per

episode.³ Other recent reviews suggest that the total costs of treating a diabetic foot ulcer range from \$10 000 to nearly \$60 000, depending on the severity of the ulcer and the clinical outcome.⁴⁻⁶

The treatment of diabetic ulcers is complex. Even when properly managed, the wounds may not heal as well as expected; when they do heal, the closure is often temporary and difficult to maintain. Medical intervention to prevent ulcer formation and subsequent amputation is imperative to reduce health care costs and to improve the quality of life of diabetic patients. Several methods of off-loading that reduce the mechanical stress on the foot have been recommended for the treatment of diabetic ul-

PATIENTS AND METHODS

PATIENTS

Patients were eligible for enrollment in the study if they met the following inclusion criteria: 18 years or older with a diabetic foot ulcer of at least 30 days' duration, Wagner grade 1 to 2, and an area of at least 1 cm² (greatest length × greatest width). Patients had adequate circulation with an oscillometer reading of the limb that had the target wound of at least 1 U and a wound that was debrided of necrotic/nonviable tissue at enrollment. The main exclusion criteria included the following: clinical signs of infection; a target wound that had exposed bone; a concurrent illness or a condition that may have interfered with wound healing (eg, carcinoma, vasculitis, connective tissue disease, or an immune system disorder); known current abuse of alcohol or other drugs or treatment with dialysis, corticosteroids, immunosuppressive agents, radiation therapy, or chemotherapy at a dose that might have interfered with wound healing within the last 30 days before study enrollment; known hypersensitivity to any of the dressing components; unwillingness or inability of an ambulatory patient to be fitted with appropriate shoe gear or an off-loading device; and multiple diabetic ulcers on the same foot. The clinical study protocol and the informed consent were approved by the appropriate institutional review boards for each participating center.

PROTOCOL

Baseline Evaluation

The protocol was designed according to the fundamental treatment principles of the Expert Panel of the American Diabetes Association Consensus Development Conference on Diabetic Foot Wound Care.⁹ It was also submitted and approved by the US Food and Drug Administration before the study initiation. At the baseline/initial visit, a full medical history and assessment of the patient's present conditions were obtained and recorded. Concomitant medications and their indications for use were also recorded. The diabetic status of the patient, including duration, type, and management, was noted with current activity level, ambulatory status, and history of ulceration or amputations. Blood test results included levels of glycosylated hemoglobin, glucose, albumin, creatinine, serum urea nitrogen, and alkaline phosphatase; liver function; and human chorionic gonadotropin levels in women of reproductive age. Oscillometry was also performed to assess the vascular status. One

investigator in each center was responsible for the assessment and management of the ulcer condition.

The target wound's greatest length, width, and depth were measured at baseline. The target wound was photographed. The perimeter of the wound was traced using an acetate film and a fine-tipped permanent black ink marker. The target wound was assessed before and after cleansing and/or debridement for local infection and for wound condition (improving, stable, or deteriorating). Wound bed characteristics, the periwound skin, and the presence or absence of undermining or tunneling were also assessed. The wound was photographed again after cleansing and/or debridement.

Surgical debridement of healthy tissue was performed in the studied ulcer during the initial and all follow-up visits when necessary. The debridement technique was standardized during an initial meeting of the investigators, at which all investigators were instructed to debride the wound until healthy granulating tissue or healthy bleeding tissue was reached.

Test Article Use

The wound area was determined by means of planimetry (the greatest length × the greatest width, measured in centimeters). Eligible patients were stratified in 2 groups, ie, patients with a wound area of less than or of at least 10 cm². A stratified randomization was used in assigning treatments to patients on the basis of their wound area. The following standard procedures were observed at all study visits: When deemed to be appropriate, only sharp/surgical debridement was used. After debridement, the wound was cleaned and irrigated with isotonic sodium chloride solution, where necessary. The surrounding tissue was carefully dried to avoid tissue damage. In the treatment group, where appropriate, the Promogran was cut to the wound size and applied as the primary dressing. It was then covered with gauze, a bandage (Sof-Kling Conforming Bandage; Johnson & Johnson), and tape as the secondary dressing. In the control group, isotonic sodium chloride solution-moistened gauze was applied as the primary dressing over the wound and covered with gauze, a bandage (Sof-Kling Conforming Bandage), and tape as the secondary dressing.

The frequency of dressing changes varied according to the condition of the wound and the amount of drainage. If the wound was evaluated by the investigator as having a high level of drainage (serosanguineous), then the investigator instructed the patient to change the dressing

Continued on next page

cers. These include bed rest, crutches, walking casts and splints, prefabricated walkers and splints, patellar tendon-bearing braces, foam pads, cutout sandals, and healing footwear.⁷ In granulating wounds, the topical application of wet-to-dry gauze has traditionally been used and acknowledged as a standard of care.^{8,9} The fundamentals of caring for diabetic foot ulcers are off-loading, frequent debriding, and moist wound healing.

New advanced topical dressings are emerging that may improve wound care. Such dressings are designed to modulate levels of biological molecules, such as growth factors, that may promote wound healing. Collagen and

oxidized regenerated cellulose composite materials are undergoing studies for such properties. Promogran (Johnson & Johnson Wound Management, Somerville, NJ) is a new topical dressing in a ratio of collagen to oxidized regenerated collagen of approximately 55:45. Collagen is a main structural protein component of connective tissue. There is a growing body of knowledge about the biochemical aspects of collagen and its role in wound healing.^{10,11} Studies have shown that purified lyophilized sponges of native bovine-tendon collagen can act as a mechanical support, and this lattice may serve as a stimulus to the migration of fibroblasts and to enhance

twice a day. If the wound was evaluated as having no maceration and mild drainage, the dressing change was performed once a day. If the wound was evaluated to be well granulating with minimal drainage, the dressing was changed every 2 or 3 days.

Dressings were changed when good clinical practice dictated (eg, a high level of exudate, the presence of soiling, wound treatment and assessment, dry primary dressing [if gauze], ability of the patient to bathe, etc). The wounds were cleansed with isotonic sodium chloride solution at the time of the dressing change. The patient and/or health care provider were instructed on dressing change procedures. Written instructions detailing these procedures were also provided to assist with dressing changes between clinic visits. In addition, a diary card, with instructions for completion, was also provided to the patient or the caregiver to record the number of dressing changes between study visits.

FOLLOW-UP EVALUATIONS

Follow-up evaluations were completed on a weekly basis. At each clinic visit, the investigator assessed and recorded the following: the condition of the primary dressing and the study wound, compliance with dressing use and change, the use of foot gear and/or off-loading, changes in medication, the presence or absence of any adverse events, and the number of dressing changes since the previous clinic visit. After removal of the primary dressing and wound debridement, the study wound was photographed and measured as described previously. For the purpose of this study, complete wound healing was described as 100% reepithelialization of the wound surface with the absence of drainage, in accordance with the definition by the Wound Healing Society. The course of healing was based on these criteria and was determined by the direct observations of the investigators, with the photographs serving as a backup.

FINAL EVALUATION

At the last clinic visit (week 12 for completion of the study or sooner if the patient discontinued the study or the wound healed), an exit form was completed by the investigator. Details of the patient's exit from the study were recorded (together with reasons for termination if the patient exited the study early). In addition, the patient completed a questionnaire evaluating the primary dressing (ease of removal and application, healing progress, and overall performance). An evaluation of the study dressing was also completed by the investigator (ie, conformability/malleability to wound area/cavity, ease of removal and

application, and maintenance of a moist wound bed). In addition, the investigator provided an assessment of the degree to which the dressing met healing expectations, patient satisfaction with the dressing, the likelihood of using the dressing again, and the likelihood of recommending the dressing for treatment of diabetic ulcers. A blood sample was also drawn for measurement of glycosylated hemoglobin levels to provide an assessment of the patient's diabetes management during the study.

OFF-LOADING

The same technique of off-loading was performed in each center for both the controls and the Promogran-treated patients. However, the choice of the off-loading technique was left to the individual investigator. Familiarity with the technique was believed to be more important than use of the same technique in all participating centers. All patients were instructed to limit weight bearing, ambulating only for necessary activities.

STATISTICAL ANALYSIS

Data were entered and verification/validation programs were run on an ACCESS 97 database (Microsoft Corp, Redmond, Wash). Statistical analysis was performed using the SAS System Release 6.12 (SAS Institute Inc, Cary, NC). Linear logistic regression analysis was used to compare the proportion of patients whose target ulcers had healed by the end of the study in terms of odds ratio, between the 2 treatment groups. Percentage of wound area reduction was compared using a random-effects mixed model implemented by means of PROC MIXED (SAS Institute Inc) for repeated-measures data. Time to complete ulcer healing was measured as the number of days from the start of treatment to the date that a patient achieved complete wound healing (wound closure). The analyses of time to healing between treatment groups are presented in the following 2 steps: incidence of healed wounds over time using life-table survival estimates and a regression analysis of time to healing using the Cox proportional hazards model adjusted for treatment, center, and any influential/confounding factors. The Cox proportional hazards model analysis was performed using PROC PHREG (SAS Institute Inc). The life-table estimates were used instead of the Kaplan-Meier product limit, as the exact healing times were not known for each individual. Wound healing was observed on a weekly basis, and the life-table analysis assumes that the probability of healing remains constant through the intervals between weekly visits. Unless otherwise indicated, data are given as mean±SD.

the metabolic activity of granulation tissue and massively bound fibronectin.^{12,13}

The composite material also provides a combination of the wound-healing properties of the individual components. In vitro and ex vivo studies of fluids in chronic human wounds have indicated that treatment with Promogran reduces the protease activity of the fluids and protects growth factors from degradation.¹⁴ As the diabetic foot ulcer is stuck in the inflammatory phase that is characterized by increased matrix metalloproteinase activity, treatment with Promogran could help to promote wound healing in such patients.

The main objective of the present study was to evaluate healing rates of diabetic foot ulcers during a 12-week period in patients treated with Promogran compared with standard therapy consisting of saline-moistened gauze.

RESULTS

A total of 276 patients from 11 centers were enrolled in the study and randomized to moistened gauze or Promogran. One hundred thirty-eight patients (50.0%) patients were enrolled in each group, and all patients received study therapy according to their randomization.

Baseline Characteristics*

	Promogran Group (n = 138)	Control Group (n = 138)
Age, mean (range), y	58 (23-85)	59 (37-83)
Sex, No. (%) M/F†	95 (68.8)/43 (31.2)	108 (78.3)/30 (21.7)
Race, No. (%)		
African American	15 (10.9)	12 (8.7)
Native American	16 (11.6)	16 (11.6)
White	85 (61.6)	88 (63.8)
Hispanic	22 (15.9)	22 (15.9)
HbA _{1c} level, (range), %	8.6 (5.3-14.0)	8.5 (4.9-13.1)
Oscillometry, mean (range), U	4.4 (0.9-13.0)	4.3 (0.9-12.0)
Wound area, mean (range), cm ²	2.5 (0.2-27.4)	3.1 (0.1-42.4)
Wound duration, median (range), mo	3 (1-84)	3 (1-144)

*Promogran is a proprietary name for a wound dressing consisting of collagen and oxidized regenerated cellulose. Study groups are described in the "Protocol" subsection of the "Patients and Methods" section. HbA_{1c} indicates glycosylated hemoglobin.

†Percentages have been rounded and may not sum 100.

The center recruiting the lowest number of patients had 5 (1.8%), compared with 49 (17.8%) at the center with highest recruitment. One hundred eighty-eight patients completed the study (104 in the Promogran group and 84 in the control group), and ulcers in 98 of these (53 in the Promogran group and 45 in the control group) did not heal. Patients were stratified on the basis of the area of their target wound (<10 or ≥10 cm²) before randomization. Confirmation of wound area using planimetry assigned 259 patients to the stratum of less than 10 cm² and 13 to the stratum of at least 10 cm² (4 patients did not have tracings available for planimetry). Baseline characteristics are described in the **Table**. A history of foot ulceration was present in 98 Promogran-treated patients (71.0%) and 88 controls (63.8%) ($P = .20$).

EFFICACY ASSESSMENT

By the 12-week measurements, 51 (37.0%) and 39 patients (28.3%) in the Promogran and control groups, respectively, had achieved complete wound closure ($P = .12$) (**Figure 1**). The percentage of reduction relative to the baseline planimetry wound area was calculated each week. By week 12, the mean percentage of reduction was similar in both groups, 64.5% in the Promogran group and 63.8% for the control group. Figure 1 shows the time to complete healing based on a life-table estimate. A mean time to complete healing was also calculated from the raw data. The mean time to healing for those Promogran-treated patients with complete healing was 7.0 ± 0.4 weeks; in the control group, 5.8 ± 0.4 weeks.

Results of post hoc analysis showed that the difference between treatments in healing was greater in the group with wounds of less than 6 months' duration. In this group 43 (45.3%) of 95 patients in the Promogran group healed compared with 29 (32.6%) of 89 in the control group, but this difference was of marginal significance ($P = .056$) (**Figure 2**). The mean time to complete healing for those in the Promogran group was 6.9 ± 0.4 weeks; in the con-

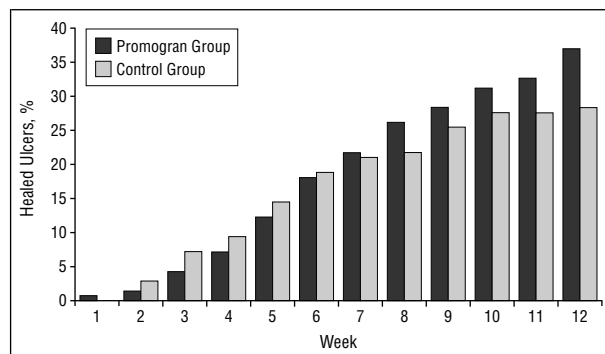


Figure 1. Cumulative proportion of healed ulcers during the 12-week study. Complete wound healing tended to be higher in patients treated with Promogran, a wound dressing consisting of collagen and oxidized regenerated cellulose (37.0%), than in gauze-treated patients (28.3%) (control group), but this difference failed to reach statistical significance ($P = .12$). Study dressings are described in the "Protocol" subsection of the "Patients and Methods" section.

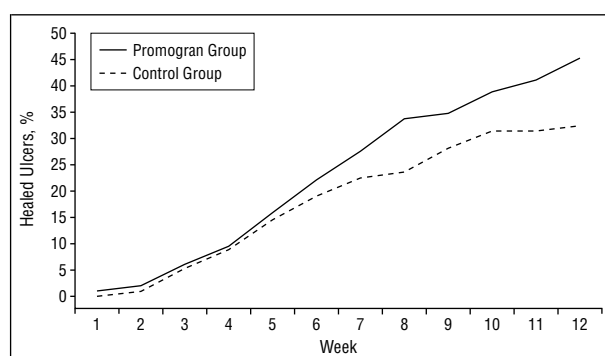


Figure 2. Life-table estimate for the time to complete wound healing in patients with an ulcer of a duration less than 6 months. Complete wound healing tended to be higher in patients treated with Promogran, a wound dressing consisting of collagen and oxidized regenerated cellulose (45.3%), than in gauze-treated patients (32.6%) (control group), but this difference marginally failed to reach statistical significance ($P = .056$). Study dressings are described in the "Protocol" subsection of the "Patients and Methods" section.

control group, 6.3 ± 0.4 weeks. The treatment effect was significantly associated with albumin level and associated with diabetes duration, ie, the proportion of healed wounds in the Promogran group compared with that of the control group was not consistent across the levels of the covariates. Finally, the proportion of healed wounds of less than 6 months' duration varied considerably across centers ($P = .07$). The percentage of healed wounds observed ranged from 14.3% of patients in one center to 66.7% of patients in another center.

In the group with wounds of greater than 6 months' duration, a similar number of wounds healed in the control (10/49 [20.4%]) and the Promogran (8/43 [18.6%]) groups ($P = .83$). Overall, more wounds in the Promogran group with Wagner grade 1 ulcers healed than in the control group (25/56 [44.6%] vs 20/63 [31.7%]; $P = .15$). The Promogran group also had a larger number of patients with Wagner grade 2 ulcers that healed (27/82 [32.9%] vs 19/75 [25.3%]; $P = .30$). No differences were observed between patients with an ulcer of at least 10 cm² and those with an ulcer smaller than 10 cm².

The average number of dressing changes across the treatment groups was similar (Promogran group, 10.1 per

week per patient; control group, 11.2 per week per patient), but a significant variation between centers was found ($P=.03$). The average number of dressing changes each week in each treatment group remained constant throughout the study. Fewer patients in the Promogran group than in the control group had suspected infection reported at any time (17 vs 26; $P=.14$). At least 80% of patients in both groups had no exudate or a small amount reported at each week. Only 12 patients in the Promogran group and 14 in the control group did not achieve a 100% granulated wound base during the study. Seventeen and 25 patients in the Promogran and control groups, respectively, were reported to have no evidence of reepithelialized tissue at any time during their study participation. Compliance with treatment and dressing changes exceeded 90% in both groups.

The patients' rating of the dressing in the Promogran group was significantly higher than that in the control group (8.6 ± 0.1 vs 7.6 ± 0.2 , $P=.01$). The clinician ratings of dressings were also higher for the Promogran dressing compared with gauze (9.3 ± 0.1 vs 7.4 ± 0.2 ; $P<.05$).

SAFETY EVALUATION

We found no differences in the safety measurements between groups. Thus, nonserious adverse events were present in 37 patients (26.8%) in the Promogran group and 34 (24.6%) in the control group. Serious adverse events were reported by 25 patients (18.1%) in the Promogran group and 35 (25.4%) in the control group. None of these events were described as related to the study dressings. Deaths were reported as adverse events for 2 patients (1.4%) in the Promogran group and 6 (4.3%) in the control group. All deaths were unrelated to study dressings.

COMMENT

The main objective of the present study was to evaluate the efficacy and safety of Promogran, a combination of collagen and oxidized regenerated cellulose, as a topical wound dressing in diabetic foot ulcers. Our results showed that Promogran was at least equally effective in promoting complete wound healing in the studied patient population. The multivariate analysis indicated that Promogran was of marginally greater benefit, compared with saline-moistened gauze, in treating diabetic foot ulcers with a duration of less than 6 months. Promogran-treated patients had a similar number of adverse events compared with the controls. Furthermore, the participating physicians and patients in the study rated Promogran higher than regular gauze in regard to its ease of removal and application.

Wound healing is a complex process that involves the timely expression of numerous growth factors that promote cellular migration and proliferation, production of new connective tissue matrix, and collagen deposition.^{15,16} In addition, diabetic foot ulcers are chronic wounds that are stuck in the inflammation phase and show a cessation of epidermal growth or migration over the wound surface.¹⁷⁻¹⁹ A common characteristic of all chronic wounds is the elevation of the levels of matrix metallo-

proteinases, which results in increased proteolytic activity and inactivation of the growth factors involved in the wound-healing process. The combined use of collagen and oxidized regenerated cellulose has been shown to specifically inhibit the action of these proteases without affecting the activity of the growth factors. Thus, theoretically, Promogran may be an advantageous alternative to the moistened gauze that is the current standard of care.

In the present study, we have not found an overall benefit of Promogran on the rate of wound healing compared with moistened gauze. Nevertheless, the new treatment was found to be marginally more effective in ulcers with a duration of less than 6 months, whereas the gauze was equally effective in ulcers with a duration of more than 6 months. The reasons for this discrepancy are not clear, but the large number of patients whose wounds did not heal by the end of the 12-week treatment in this study suggests that the observation period may not have been long enough. Closer examination of the healing data demonstrates a separation between groups in favor of Promogran from week 8 onward. Extrapolation of the data suggests that had the study continued beyond 12 weeks, this trend would have continued, with increased numbers of wounds healed in Promogran-treated patients. However, this remains speculation and can be tested only by a study with longer follow-up. In addition, the data indicate that the study was not powered adequately to examine the effect of Promogran separately in patients with ulcers of less than 6 months' duration. Further studies will be needed toward this direction.

A successful wound dressing should keep the wound moist and be devoid of any adverse reactions such as infection, maceration, and allergic reaction. To this end, the present study has shown that Promogran has a safety profile that is comparable to that of moistened gauze. Furthermore, patients and clinicians reported that Promogran was easier to remove and to apply and that it was more likely to keep the wound moistened and to be comfortable.

A variety of treatment methods are under clinical investigation or are available for the management of diabetic foot ulcers, including growth factors and living-skin equivalents.²⁰⁻²³ None of these treatments replace the role of wound dressing, but are used in combination with dressings. The use of newer dressings may increase the wound-healing potentials of these new treatments, and further studies will be required to evaluate the effects of the combined treatments.

Extensive debridement, control of infection, adequate off-loading of the ulcerated foot, and lower extremity revascularization when required are the cornerstones of treatment for the diabetic ulcer.^{8,9,24} Special emphasis was given in the present study to all of these principles. This emphasis is reflected in the healing rate in the control group, which was within the range that would be expected from meta-analysis studies of previous major clinical trials.²⁵ Therefore, Promogran should be considered as an adjunct to, not a substitute for, these principles.

The present study has limitations. The off-loading technique was not the same among the centers, and the

Promogran Diabetic Foot Ulcer Study Investigators

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frequency of changes of the dressing was left to the discretion of the investigators. The study design was chosen as the best way to reflect the different practices that are used at present. Therefore, although the protocol was not strictly standardized, it has the advantage of being representative of the present clinical practices and of being more generalizable. This also accounts for the considerable differences in the complete wound healing rate that was observed among the participating centers, as such differences also exist in real clinical practice. Finally, as the price of Promogran has not yet been determined, no comments can be made on the cost-benefit ratio of this product. Further studies that examine this particular issue will be required. However, Promogran treatment is considerably less expensive compared with other new treatments and therefore may be an initial choice in treating patients with nonhealing ulcers.

CONCLUSIONS

In the present study, we have shown that Promogran, a wound dressing consisting of collagen and oxidized regenerated cellulose, was as effective as moistened gauze in promoting wound healing in diabetic foot ulcers, with a benefit of marginal significance to ulcers with a duration of less than 6 months. Furthermore, Promogran had a safety profile that was comparable to that of moistened gauze. The above results indicate that Promogran may be a useful adjunct in the management of diabetic foot ulceration, especially in ulcers with a duration of less than 6 months.

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