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RESEARCH ARTICLE

COLLAGEN SPONGE DRESSINGS IN DIABETIC FOOT ULCERS

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ABSTRACT

Diabetic Foot Ulcers (DFU) are therapeutic challenge to the surgeon. While many dressing options and materials are in vogue, Collagen sponge dressings stand out as a reasonably good choice in accelerating the healing of DFU. In this study collagen sponge dressings were tried in 25 patients against control with conventional dressings in equal number of patients. Average age is 58 years with majority falling between 39 to 78 years. Males were three times more. Mean ulcer size is 14.1 and 15.6 ^{cms}² in test and control groups respectively; duration being 60.5 days. At the end of 12 weeks ulcers treated with collagen sponge healed in 53.9 days against 69.1 in control group i.e. 22% reduction (P=<0.0001). The number of dressings required are also decreased in collagen group 6.3vs8.8 (P-<0.0001).

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INTRODUCTION

Diabetic Foot Ulcer (DFU) is a therapeutic challenge to the surgeon. In spite of treatment of primary causes, diabetic ulcers once formed, take a considerable time to heal. Local ulcer care in the form of antiseptics and dressing has been in use for decades with an idea to provide the ulcers an optimum environment to heal. In recent years, numerous synthetic and biological dressings have been developed based on scientific principles of wound healing mechanism. In this quest for an ideal wound dressing, the options are many, each of the material has a short coming; leading us to a situation of poverty amongst plenty. Micro angiopathy characterised by thickening of basement of small vessels and vasa vasora of large vessels significantly interferes with transfer of oxygen and nutrients to tissues, impairing wound healing. It also decrease the migration of leucocytes to areas of tissues, impairing resistance to infection. In diabetes, there exists a hyper coagulable state, Which is related to changes in platelets, red cells and fibrinogens. There is an increased tendency to thrombosis, which increases the rate of occlusion of large vessels while sludging and poor blood flow accentuates the affects of micro angiopathy

Current categories of dressings: (Hess, Cathy Thomas, 2000; Ladin, Daniel 1998)

1. Impregnated dressings: Povidone-iodine, silver, bismuth, scarlet red and acemannan aloe vera, xeroform
2. Transparent films
3. Foams
4. Hydrogels
5. Xerogels—dextranomers, alginates
6. Hydrocolloides
7. Biological dressings: (Brem, Harold et al., 2000; Hansborough, 1998; Lynch, William, 1987; Perri et al., 1994; Piacquadio, 1994; Sanana, 1987) – combinations and formulations of collagen, elastin
8. Allografts—fresh frozen lyophilised skin from family members, Amniotic membranes.
9. Auto skin graft
10. Collagen dressings (Hess, Cathy Thomas 2000; Perri et al., 1994) –collagen sheets, membranes, granules, gels, sponges
11. Bioengineered skin: (Hansborough, 1998; Lynch, William 1987; Perri et al., Piacquadio, 1994)

Collagen dressings are one of these new developments. The efficacy of collagen in partial thickness skin loss (superficial burns, skin grafts donor sites) is well proven (Gupta et al., 1978; Gupta et al., 1985). As collagen is an integral part of wound healing process, provision of a collagen scaffold in the form of a dressing is shown to hasten the wound healing by

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promoting granulation, providing growth factors like EGF and epithelialisation (Abramo and Viola, 1992).

MATERIALS AND METHODS

Fifty patients with diabetic ulcers were selected and allocated in two groups twenty five in each. One group is treated with collagen sponge dressing and other group with conventional dressings. Patients are explained about both the types dressings available for the treatment and it is left to the discretion of patient to choose type of dressing they want. Informed consent is obtained from all the patients.

Inclusion criteria

- Type 1 or 2 diabetes
- 18 years or older with a diabetic foot ulcer of at least 30 days' duration.
- Culture and sensitivity of ulcer floor - sterile.
- An area of 1 cm² to 50 cm² (greatest length x greatest width).
- Glycemic control HbA_{1c} between 6 and 12%.
- All patients are also required to have good volume dorsalispedis and posterior tibial arterial pulsations that are audible by Doppler using Toshiba Nemio XG & Philips Envisor C Ultrasound machines.

Exclusion criteria

- Clinical signs of infection
- Target wound that had exposed bone
- 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.

Wound bed characteristics, the peri-wound skin, and the presence or absence of undermining or tunnelling were also assessed. 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 until healthy granulating tissue or healthy bleeding tissue was reached. Surgical debridement using scissors or scalpel blade was done and wound taken down to healthy tissue. After debridement, the wound was cleaned and irrigated with isotonic sodium chloride solution. The surrounding tissue was carefully dried to avoid tissue damage. Haemostasis was always ensured. The target wound's greatest length and width were measured at baseline. The target wound was photographed. Further treatment was dependent upon whether patient belongs to the collagen group or conventional group

Collagen group

In this group, patients received collagen dressings after debridement. Collagen dressing used in this study was lyophilized type 1 collagen in sponge form extracted from fish source with a non-denaturation process (KOLSPON –

Eucare pharmaceuticals -chennai). The manufactures claim that a particular proprietary extraction and purification procedure ensures that the product is free of bacterial, viral and mycotic contaminants and protein such as albumin, fibronectin and fibrinogen, which may be allergenic.

The product used was in 5 x 5 cm sponges, sterilized by gamma rays at 2.5 Mrad and supplied in transparent blister packs.

At study day 0, collagen sponge was applied using a sterile technique. The ulcer was debrided and irrigated with saline before collagen sponge was placed directly over the ulcer site. Any excess edge was trimmed to fit the ulcer. After the collagen sponge was applied, the site was covered with a layer of saline-moistened sterile gauze, completely covering the ulcer and extending to the normal surrounding skin. Hypoallergenic tape was used to secure the gauze to normal skin. The wound was then covered with a layer of dry sterile bandage. These bandages are applied with moderate pressure to ensure adequate contact of collagen sponge with the wound.

After initial application of collagen sponge, the first assessment of lesion was done after 24 hrs. In presence of any discharge from ulcer the sponge was completely removed and a new sponge was reapplied. In absence of such signs the collagen that has melted out from ulcer bed was replaced by a new piece of collagen sponge. If the wound was evaluated to be well granulating with minimal drainage, the dressing was changed every 2 or 3 days. The wounds were cleansed with isotonic sodium chloride solution at the time of the dressing change. The patients were instructed on dressing change procedures. Written instructions detailing these procedures were also provided to assist with dressing changes between hospital visits. In addition, a card was also provided to the patient or the caregiver to record the number of dressing changes between study visits.

The process of reapplication of collagen was continued until collagen was adherent to the whole wound and no further lysis occurred. The wound was termed as completely healed once collagen separated from the wound leaving a completely formed scar.

Conventional group

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 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 having a high level of drainage (sero sanguineous), then the patient is instructed to change the dressing twice a day.

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] etc). The wounds were cleansed with isotonic sodium

chloride solution at the time of the dressing change. Written instructions detailing these procedures were also provided to assist with dressing changes between clinic visits. In addition, a card, with instructions was also provided to the patient or the caregiver to record the number of dressing changes between study visits.

Follow-up evaluation

Follow-up evaluations were completed on a weekly basis. At each hospital visit, the assessed and recorded the following: the condition of the primary dressing and the study wound, compliance with dressing use and change, changes in medication, the presence or absence of any adverse events, and the number of dressing changes since the previous hospital 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% re-epithelization 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.

At the last hospital visit (week 12 for completion of the study or sooner if the patient discontinued the study or the wound healed), details of the patient's exit from the study were recorded (together with reasons for termination if the patient exited the study early). An evaluation of the study dressing was also completed (ie, conformability/malleability to wound area/cavity, ease of removal and application, and maintenance of a moist wound bed). 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.

Follow up

Once the ulcer was completely healed, patients were regularly followed up for a period of one year to assess re-modeling of scar and detect formation of hypertrophic scars or keloids, if any. Advise regarding foot care and proper footwear were always given and reinforced regularly.

Statistical analysis

Data was collected and maintained throughout the protocol. The observations in the collagen and conventional groups were then compared using students T-test for ascertaining their statistical significance.

OBSERVATION AND RESULTS

Average age in this study is 58 years (15-80 years), majority falling in 39 to 78 year bracket. Males are three times more than females

Size of ulcer

Size Collagen Conventional

1-10 cm ²	11	10
11-20 cm ²	7	8
21-40 cm ²	4	3
41-50 cm ²	3	4
Average	14.1 cm ²	15.6 cm ²

36 ulcer (80%) were less than 20 cm². There was no significant difference in ulcer size in both the groups.

Duration of ulcers

Duration Collagen Conventional

30-60 days	11	10
61-90 days	8	9
91-120 days	4	5
>121 days	2	1
median	60 days	61 days

Thirty eight patients in the study present before ninety days of onset of ulceration. Only twelve patients had ulcers more than ninety days duration. Average duration of ulcer in study is sixty years in collagen, sixty one years in conventional group.

Healing time

Collagen group 53.9 days; Conventional group 69.1 days a reduction by 22%. $P < 0.0001$ significant. Average number of dressings per patient per week : Collagen group 6.3 where as in conventional group 8.8. $P < 0.0001$. significant. Number of healed ulcers at the end of 12 wks of study period: Collagen group-20 (80%); conventional group 15 (60%).

DISCUSSION

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. (Spence, 1997; Singer and Clark, 1999) 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. (Loots *et al.*, 1998; Loots *et al.*, 1999) A common characteristic of all chronic wounds is the elevation of the levels of matrix metalloproteinase, which results in increased proteolytic activity and inactivation of the growth factors involved in the wound-healing process. The use of collagen sponge dressing has been shown to specifically inhibit the action of these proteases without affecting the activity of the growth factors. Thus, theoretically, collagen sponge dressing may be an advantageous alternative to the moistened gauze that is the current standard of care.

The Average healing time in collagen group was 53.9 days whereas it was 69.1 days in conventional group and p value < 0.001 being highly significant. This has a lot of impact on patient's life. Once healing time is reduced, Patient can go back to work. Another factor in collagen group, which was satisfying to the patients, was that, once collagen was completely adherent to their wound

and no more lysing, they could go back to work and resume normal activities. Their hospital visits were then reduced to once per week for follow up. Hence the quality of life was significantly better in this group. Other studies and comparison with them is as shown below: Table 1 & Table 2

Table 1. Comparison with Veves et al. (2002) and Rai et al. (1984)

	Collagen dressing		Conventional dressing	
	Veves et al. This study		Veves et al. This study	
No.of Pts	138	25	138	25
Mean age	58 yrs	58 yrs	58 yrs	59 yrs
Sex ratio	2.2:1	2.6:1	3.6:1	3.1:1
Wound area	2.5 cm ²	14.1 cm ²	3.1 cm ²	15.6 cm ²
Wound duration	90 days	60 days	90 days	61 days
Healing time	7+/-0.4	53.9	5.8 +/- 0.4	69.1
	weeks	days	weeks	days
Dressings/ week/pt	10.1.	6.3	11.2	8.

Table 2. Comparison with Rai et al.

	Collagen dressing		Conventional dressing	
	Rai et al. This study		Rai et al. This study	
No.of Pts	25	25	138	25
Mean age	42	58	58	59
Sex ratio	4:1	2.6:1	3.6:1	3.1:1
Wound duration	68 days	60 days	54 days	61 days
Healing time	39 days	53.9 days	64 days	69.1 days

The study by Veves et al. from Joslin Beth Israel Deaconess Foot Center, Boston, Mass and the Diabetes Foot and Ankle Center, Hospital for Joint Diseases Orthopaedic Institute, New York and the study by Rai et al. from department of surgery, Armed Forces Medical College, Pune are some of the studies done comparing collagen with conventional dressings.

The present study contains same number patients per group as in study of Rai et al. with age sex ratio being comparable in both. The average duration of ulcers in this study is sixty days and in Veve et al. and Rai et al. are ninety and sixty eight days respectively. Healing time in this study is higher than two studies due to the average wound area in this study is much larger than Veves et al. study and the number of dressing per week per patient is also higher in Veves et al. study. Healing time is well comparable in all the three studies. This highlights the fact that whatever may be the primary cause of ulcer, if its well-controlled, good local ulcer care produces consistent healing of wound.

Conclusion

By applying collagen dressings for small and medium size non healing diabetic ulcers showed much better and significant healing rates in terms of duration and quality of healing when compared to conventional dressings. Though the cost factor does come into consideration while applying collagen dressings it is worthwhile when viewed in terms of less duration of wound healing and early return to work and above all the psychological moral up lift the patient under goes by this method of treatment.

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