A comparative study between collagen dressings and conventional dressings in wound healing

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ABSTRACT

BACKGROUND
Treatment of foot ulcer remains a major health-care issue; and especially diabetic foot ulcer which is the commonest cause of lower-extremity amputation. Although several investigations have examined topical collagen-based dressings, none have specifically looked in India. We, therefore, evaluated the effect of the collagen dressing on foot ulcer.

METHODS
A Hundred patients with foot ulcer were evaluated. A collagen or conventional dressings were applied, and the patients were followed as per standard post-application treatment protocol. Patients underwent dressing changes every 3 to 4 days until wound healing or for maximum period of 12 weeks. Changes in wound size were recorded when the dressing was removed; and at 4 and 12 weeks.

RESULTS
In 75 patients collagen dressing was applied, whereas conventional dressing in 25 patients. All the patients were prospectively available for evaluation. On enrollment, the median wound size was 33.5 cm^2 in collagen dressing group and 48 cm^2 in conventional dressing group. Healing time (4.02 ± 0.59 Vs 7.6 ±1.38), duration of antibiotic therapy (15.12±4.55 Vs 24.08± 6.5) and mean follow up period (2.40 ± 0.61 Vs 2.96 ± 1.2) were significantly less in collagen dressing group as compared to conventional dressing group ($P<0.001$). No adverse event was reported in both the groups.

CONCLUSIONS
Collagen dressing is safe and effective in the treatment of foot ulcer and significantly reduces healing time, duration of antibiotic therapy and follow up time.

Keywords: Collagen Dressings, Wound Healing, Skin grafts, Diabetic ulcers, Non healing wounds

INTRODUCTION

Chronic foot ulcers are defined as a slow or non-healing breakdown of epidermal and dermal tissue on the foot that last more than 6 weeks. The majority of the ulcers are associated with venous disease, peripheral arterial disease, mixed arterio-venous disease and diabetes. Ulcers in people with diabetes are caused by a variety of factors, in particular peripheral vascular disease and loss of sensation because of peripheral neuropathy [(1)] Furthermore, foot ulceration can promote more serious morbidity leading to eventual limb loss. In diabetes, effective treatment of ulceration is seen as key to the reduction in the number of amputations, as highlighted in the St Vincent Declaration. [(2)]

The burden of lower limb ulcers

Venous leg ulcers are thought to affect up to 3.5% of the general population [(3)] while 15% of all diabetic patients are affected by foot ulceration at some time. [(4)] Women suffer more than men from lower limb ulcers, outnumbering them by a ratio of more than 2:1. [(5)]

Regardless of etiology, foot ulcers cause considerable and prolonged distress for patients. Acute pain or continuous aching discomfort is usual, exacerbated with changes of dressings. Often, ulcers become secondarily and heavily infected, with the production of a foul-smelling slough and copious exudate that promote general unhappiness and increasing social isolation, ultimately reducing quality of life. Other issues for patients include restricted mobility, embarrassing dressings and inability to continue working. [(6)]

AIMS AND OBJECTIVES

PRIMARY:

- Rate of healing
- Control of infection
- Whether SSG was eventually required or not

SECONDARY:

- Pain felt by patient after application of dressings
- Appearance of granulation tissue

MATERIALS AND METHODS

STUDY DESIGN

This was a prospective comparative study. The study was carried out at Kasturba Medical College and Wenlock Government Hospital (WGH), Mangalore from July 2008 to September 2010.

Total hundred patients with **chronic foot ulcer** at Kasturba Medical College and Wenlock Government Hospital (WGH), Mangalore were studied.

STUDY METHODS

The study was conducted to achieve following objectives.

Primary Objective:

To study and compare the efficacy Collagen dressing with conventional dressing in patients with chronic foot ulcer.**Secondary Objectives:**

To assess the safety of Collagen as well as conventional dressings in patients with chronic foot ulcer.

End Points:

Primary Endpoints:

1. **Ulcer healing time:** Time required to completely heal ulcer after the initiation of the therapy with Collagen/Conventional dressings in patients with chronic foot ulcer.

Secondary Endpoints:

2. **Duration of antibiotic therapy: D**uration for which antibiotic therapy was continued to completely heal ulcer after the initiation of the therapy with Collagen/Conventional dressings in patients with chronic foot ulcer.**Follow up period: Duration** of follow up after the initiation of the therapy with Collagen/Conventional dressings in patients with chronic foot ulcer.Adverse events reported with Collagen/Conventional dressings in patients with chronic foot ulcer.**Eligibility criteria:**

The following eligibility (inclusion/exclusion) criteria were used for recruitment of patients in the study.

Inclusion Criteria:

1. Patients with chronic foot ulcer (diabetic/burn patients).
2. Patient willing to give informed consent
3. In case of diabetic patients- diabetes mellitus is defined as per World Health Organization (WHO) criteria of age and duration of therapy
   1. Age ≥35 years
   2. Absence of insulin requirement in the first 5 years after diagnosis.

Exclusion Criteria:

1. Critically ill patients
2. Patient refusal
3. Any evidence of underlying bone osteomyelitis
4. Malignancy

STUDY PROCEDURES

The study was conducted on total hundred patients with foot ulcer patients who reported at Kasturba Medical College and Wenlock Government Hospital (WGH), Mangalore. All foot ulcer

patients attending the Surgery Department were invited to participate in the study and written informed consent was taken. All patients underwent a standard clinical and laboratory evaluation. Briefly, information about age, known DM duration, smoking habits, arterial blood pressure, and anthropometric measurements was collected. Patients with chronic foot ulcer (diabetic/burn patients) who were willing to give informed consent were considered. Critically ill patients and patients who refused were excluded. In case of Type II diabetic patients, WHO criteria of age and duration of therapy (Age≥35 years & absence of insulin requirement in the first 5 years after diagnosis) were used.

In all patients, wound size was noted before treatment initiation. A collagen or conventional dressings were applied to would, and all patients were followed as per standard post-application treatment protocol. Patients underwent dressing changes every 3 to 4 days until wound healing or for maximum period of **12 weeks.** Changes in wound size were recorded when the dressing was removed; and at 4 and 12 weeks.

Healing time, duration of antibiotic therapy, follow up period were noted. All patients were also followed up for adverse events. All the data were captured in the pre-printed pro-forma (given below).

STATISTICAL ANALYSIS

- Demographic data were presented in number and %.
- Wound size, Healing time, duration of antibiotic therapy, follow up period are expressed as mean and SD.

1. ***'Chi-Square test' or 'Fisher exact test'*** was applied as appropriate for comparison of nominal data.

2. ***'t test'*** was applied for comparison of continuous data.

3. Additional exploratory (parametric as well as non-parametric) analysis of the data was performed as deemed essential by using appropriate statistical tests.

4. p value of 0.05 was considered as statistically significant.

RESULTS & 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. [7, 8] 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. [9, 10] A common characteristic of all chronic wounds is the elevation of the levels of matrix metalloproteinases, which results in increased proteolytic activity and inactivation of the growth factors involved in the wound-healing process. The use of collagen has been shown to specifically inhibit the action of these proteases without affecting the activity of the growth factors. Thus, Collagen is an advantageous alternative to the moistened gauze, which is the current standard of care.

This prospective study was undertaken with a main objective to evaluate the efficacy of collagen dressing as a topical wound dressing in 100 patients with chronic leg ulcer. Safety of the collagen dressing was the secondary objective. In this study, a chronic leg ulcer was defined as any break in the skin on the lower leg (below the knee) or on the foot, which had been present for more than 4 weeks. All the patients were prospectively available for evaluation. Patients underwent dressing change every 3 to 4 days until wound healing or for maximum period of 12 weeks. Changes in wound size were recorded when the dressing was removed; and at 4 and 12 weeks.

We found high number of male (75 %) had chronic leg ulcer as compared to female (25 %). However, the gender distribution was comparable same in both collagen and conventional dressing groups ($p>0.05$).

Since the study was not randomised we found unequal distribution of patients in both the groups. Collagen dressing was applied to 75 % patients, whereas conventional dressing to 25 % patients.

There is a clear association between age and chronic leg ulceration. Data suggest that the prevalence of leg ulceration progressively increases with increasing age. In our study, overall, the chronic leg ulcer was found more in older age. Mean age [conventional dressing group (50.58 ± 10.96 years) and collagen dressing group (46.13 ± 6.70 years)]. The finding is in the line with published literature.

Studies by Cornwall et al [25]; Callam et al [24]; Baker et al [23]; Baker and Stacey [11]; O'Brien et al [12] reported prevalence estimates in age bands and all show an increase in prevalence with each decade of life.

It is observed that the site and duration of ulcer is not consistent across the studies. In our study, all the patients were of leg ulcer with variable duration of ulcer. Patients receiving conventional dressing (5.75 ± 2.03 years) was significantly higher as compared to patients receiving collagen dressing (4.33 ± 1.38) ($p<0.05$).

The mean wound size was 6.49 ± 3.40cm in collagen dressing group and 8.63 ± 2.89 cm in conventional dressing group. Significantly high mean age, duration of ulcer and wound size in patients receiving conventional dressing could be because of chance, and partly because of non-randomized nature of the study.

The process by which leg ulcers develop is complex and largely dependent on the underlying vascular status of the patient's lower legs. Consequently, the pathophysiology of leg ulcers is normally considered according to four distinct types of ulcers: venous ulcers, arterial ulcers, mixed ulcers (since there is both a venous and arterial component to their development), and ulcers due to other, rarer causes. It is evident that the most common cause of a leg ulcer is venous disease (range 37% 76%), however this percentage will depend on how many of the other groups of ulcers have been included. Unlike the published literature, majority of the patients had diabetes ulcer followed by traumatic ulcer and then venous ulcer. The distribution was same in both the groups. We found high number of diabetic foot ulcer as compared to venous ulcer.

Baker et al [23] reported venous ulcer in 57 % of patients followed by arterial (22 %), diabetes (12 %). Callam et al [24] reported venous ulcer in 76 % of patients followed by arterial (22 %), diabetes (5 %). Cornwall et al [25] reported venous ulcer in 52 % of patients followed by arterial (9%), mixed ulcer (12 %). Nelzen et al reported venous ulcer in 54 % of patients followed by mixed ulcer (26 %) and diabetes (25 %). In one study, Nelzen et al [34] reported venous ulcer in 37 % of patients followed by mixed ulcer (13 %) and diabetes (12 %). The higher number of diabetic foot ulcer in our study could be because of chance factor.

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 ulcer. [13-15]
Collagen plays a relevant role in cutaneous tissue repair and represents a valid therapeutic option when used as a bioactive advanced dressing in chronic wound management. It improves fibroblast deposition in the dermal matrix and stimulates angiogenesis, granulation tissue formation, and reepithelization.[16] Fibroblasts mainly participate in the biosynthesis of collagen, which acts as a mold, precursor, plastic material, and cementing substance in the wound healing process.
In the present study, we have found an overall benefit of collagen on the rate of wound healing compared with moistened gauze. The healing time use was significantly lower in patients receiving collagen dressing (4.63±1.18 weeks) as compared to conventional dressing (7.79±1.61 weeks). The requirement of SSG use was also significantly lower in collagen dressing patients (64.47%) as compared to conventional dressing patients (100 %). Further, the follow up period was significantly lower in collagen dressing patients (2.13±1.11) days as compared to conventional dressing patients (2.92±1.41). We also found significantly less antibiotic use was in collagen treated patients (16.01± 5.74 days) as compared to patients receiving conventional dressing (21.79 ±7.31 days).
Our results showed that collagen dressing is effective in promoting complete wound healing in the studied patient population. The analysis indicated that collagen dressing was of greater benefit, compared with saline-moistened gauze, in treating foot ulcers with duration of less than 6 months. The results are in the line with published literature.
In a study by **Veves** in 276 patients with diabetic foot ulcer, after 12 weeks of treatment, 51 (37.0%) Promogran'-a collagen/oxidized regenerated cellulose dressing-treated patients had complete wound closure as compared to 39 (28.3%) patients of control group (moistened gauze), but this difference was not statistically significant (P=0.12). In this study, author found an overall benefit of collagen on the rate of wound healing compared with moistened gauze.
Donaghue compared the efficacy of a collagen-alginate topical wound dressing with that of regular gauze moistened with normal saline in 75 patients diabetic foot ulcers. The mean percent reduction of the wound area was 80.6% in the collagen-alginate dressing group and 61.1% in the gauze-dressing group. Complete healing was achieved in 48% of the collagen-alginate dressing group and 36% of the gauze-dressing group. [17]
Di Mauro found that lyophilized type I collagen (LC) significantly improves wound healing in the treatment of diabetic ulcers. The mean time for wound healing in the group treated with LC was 32.4 +/- 8.6 days, and in the group treated with hyaluronic acid medicated gauze was 49.0 +/- 11.0 days ($p < 0.001$).
Though, the role of collagen in promoting wound healing is well established, [18, 19] but it has not previously been tried extensively in the management of leg ulcers. The results of the present study are, therefore, encouraging. In addition, collagen dressing, unlike conventional dressing, is absorbed and does not have to be re-applied frequently. However, the ulcer should be debrided and cleaned before application. If there is evidence of infection, appropriate antibiotics should be administered.

The infection rate was comparable in patients receiving conventional dressing (100%) and patients receiving collagen dressing (89.47 %). The difference was not statistically significant. Patients receiving collagen dressing, 11.84 % had E. Coli; 5.26 % had E. Coli & Klebsiella; 6.58% had Klebsiella; 1.32 % had Klebsiella & Staphylococcus infection; 5.26 % had proteus

infection; 17.11 % had pseudomonas; 42.11 % had Staphylococcus infection and 10.53 % had no growth. Whereas patients receiving conventional dressing, 12.50 % had E.Coli; 4.17 % had E. Coli & Klebsiella; 4.17% had Klebsiella; 4.17 % had proteus infection; 29.17 % had pseudomonas and 45.83 % had Staphylococcus infection.

In this study, the collagen sponge proved to be efficacious in the promotion and stabilization of granulation tissue. The collagen available for this use comes in the form of soft sponges, which are lyophilized and sterilized. It has been proven that the material implanted, lysed by enzymatic digestion by leukocytic proteases, maintains intimate contact with the bottom of the lesion, is embedded into the granulation process, and forms plastic scaffolding over which fibroblast migration takes place followed by endogenous cell invasion.

The result is a physiological and natural tissue repair. Its spongy network contributes to exudate absorption and blocking of possible extensions of the wound, preventing bacterial growth that would delay the healing process. Moreover, the pores are neither so large as to favor dryness nor too small that they hinder granulation or gaseous exchange.

It would appear that aside from acting as a mechanical support and agent of fibroblast motility, heterologous collagen participates as a feeding substrate to the metabolic activity of the granulation tissue. The product acts locally without absorption and does not enter into the systemic structures of the body. Rather, it enters the fibroblastic cellular local metabolism, where it acts by stimulating the production of endogenous collagen, which is responsible for wound healing.

The wound healing process involves phenomena such as proliferation, migration, and cell differentiation—all of which are influenced by the presence of collagen. In the final stage of repair with a continuity tissue solution, the maturation of collagen takes place and collagen fibers create a bridge between the edges of the damaged tissues, going on to form or favor a scar with elasticity and mechanical strength.

Recently, variety of treatments methods are under clinical investigation or are available for the management of foot ulcers, including growth factors and living-skin equivalents. [17, 20-22] None of these treatments replace the role of wound dressing, but are used in combination with dressings. The use of newer dressings with collagen dressing may increase the wound-healing potentials of these new treatments, and further studies will be required to evaluate the effects of the combined treatments.

The present study has two limitations. First, the study was not randomized therefore unequal number of patients get enrolled in the groups. Significantly high mean age; duration of ulcer; and wound size in were observed in conventional dressing patients because of non-randomized nature of the study. Second, the sample size was less.

CONCLUSION

Collagen dressing increases the rate of wound healing as compared to m oistened gauze. It also reduces the requirement of SSG. Further, it also reduces the follow up period and antibiotic use significantly as compared to conventional dressing. Probably, its spongy network contributes to exudate absorption and blocking of possible extensions of the wound, preventing bacterial growth that would delay the healing process. Since the sample size

of study is not too large, further studies will be required to evaluate the effects of the collagen treatment.

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Table 1: Comparison of sex in both the groups

Parameter	Treatment	P value	Significance

	Collagen dressing		Conventional dressing			
Sex	N	%	N	%	0.78	NS
Female	20	26.32	6	20.83		
Male	55	73.68	19	79.17		
Total	75	75	25	25		

Chi Square test is applied. *P value is significant if <0.05,

Table 2: Comparison of age in both the groups

Parameter	Treatment				P value	Significance
	Collagen dressing		Conventional dressing			
	Mean	SD	Mean	SD	0.02	Significant
Age	46.13	6.70	50.58	10.96		

t test is applied. *P value is significant if <0.05,

Table 3: Comparison of etiology in both the groups

Parameter	Treatment				P value	Significance
	Collagen dressing		Conventional dressing			
Etiology	N	%	N	%		
Diabetes	55	73.68	17	70.83		
Traumatic ulcer	10	13.16	5	20.83		
Venous ulcer	10	13.16	3	8.33		
Total	75	75	25	25		

Chi Square test is applied. *P value is significant if <0.05,

Table 4: Comparison of Size of ulcer in both the groups

Parameter	Treatment				P value	Significance
	Collagen dressing		Conventional dressing			
	Mean	SD	Mean	SD	0.001	Significant
Size	6.49	3.40	8.63	2.89		

t test is applied. *P value is significant if <0.05,

Table 5: Comparison of healing time in both the groups

Parameter	Treatment				P value	Significance
	Collagen dressing		Conventional dressing			
	Mean	SD	Mean	SD	0.001	Significant
Healing time (Wks)	4.63	1.18	7.79	1.61		

t test is applied. *P value is significant if <0.05,

Table 6: Comparison of Requirement of SSG in both the groups

Parameter	Treatment				P value	Significance
	Collagen dressing		Conventional dressing			
Requirement of SSG	N	%	N	%	0.016	Significant
No	26	35.53	0	0.00		
Yes	49	64.47	25	100.00		
Total	75	75	25	25		

Chi Square test is applied. *P value is significant if <0.05,

COLLAGEN MATERIAL

RESULTS: COLLAGEN GROUP

DAY-0

3-WEEKS

6-WEEKS