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ORIGINAL RESEARCH

Study to Assess the Efficacy of Collagen Dressing in Diabetic Foot Ulcer Patients

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ABSTRACT

Introduction: Diabetic foot has become the common indication for hospital admissions among diabetics. The diabetic foot commonly begins as an ulcer. So rapid and extensive is the underlying damage that approximately 20% of these patients end up with amputation. The present study has been performed to compare the efficacy of collagen dressing with that of conventional dressing materials like silver sulfadiazine, nadifloxacin, povidone iodine.

Materials and Methods: Fifty patients (40 males and 10 females) were procured to be included to experimental group who were treated using collagen dressing and they form the study group. Control treatment was performed on 25 patients (21 males and 4 females) at the same period. All the quantitative values were noted as mean± standard deviations.

Results: 1. The final ulcer sizes (by the 3-week measurement) ranged between 0.2 and 4.2 cm^2 (mean, 1.11 ± 1.19 cm^2) in the experimental group, and ranged between 0.1 and 12.8 cm^2 (mean, 2.52 ± 2.61 cm^2) in the control group. It was found that all of 25 patients of the experimental group were reported with shrinkage of wound area and depth over 30% at the third week regardless of wound location, duration, and grade. In contrast, the improvement of only 5 ulcers in area over 30% at the third week was observed, and 6 in depth.

Conclusion: Collagen dressing also might also provide supplementary advantages of patients' comfort and compliance as well as maintenance of ideal healing environment. In order to confirm the usefulness and wound healing potential of collagen dressing in the management of diabetic foot ulcers, future research with longer follow-up periods should be conducted.

Keywords: Collagen Dressing, Diabetic, Foot Ulcer.

INTRODUCTION

Diabetic foot ulcer is due to the result of uncontrolled diabetes mellitus or as a result of long-term complication of diabetes mellitus. The healing process of diabetic foot ulcer is challenging due to the sustained inflammatory condition, extracellular matrix degradation and multiple numbers of bacteria presence. The presence of collagen components plays a fundamental role in effective wound healing and skin rejuvenation. Hence, collagen-containing dressings for the diabetic wound which aids in creating a scaffold matrix havebeen tried for the treatment of diabetic foot ulcer. But there is still no clear evidence for this whether the collagen dressing aids in diabetic wound management. This study examined the safety and effectiveness of new collagen dressing material for the effective treatment of diabetic foot ulcer.[1]

In the past decades, various new dressing materials have been developed such as calcium alginate, hydro-colloid membranes and fine mesh gauze. These have anobserved disadvantage in that they become much more permeable to bacteria. On the contrary, biological dressings like collagen would create the most physiological interface between the wound surface and environment which are observed impermeable to bacteria. Collagen dressings have various advantages with respect to its ease of application and being natural, non-immunogenic, non-pyrogenic, hypo-allergenic and pain-free when compared to the conventional dressings. The present study has been performed to compare the efficacy of collagen dressing with that of conventional dressing materials like silver sulfadiazine, nadifloxacin, povidone iodine.[2,3]

Recently, various new treatment protocols have been developed in order to stimulate wound healing in the diabetic foot ulcers. These are reported to be having topical growth factors, extra cellular matrix products, bioengineered human skin, hyperbaric oxygen therapy, granulocytes macrophage colony stimulating factors and collagen granules. As stated in the literature, collagen is a main structural protein component of connective tissue. There is a growing interest of knowledge about the biochemical aspects of collagen and its significant role in wound healing.[4,5] Collagen is commercially available as spherical hydrophilic particles of collagen with 0. 1 to 0. 3 mm in diameter. It is available as 5, 10, 15 mL packets.[6,7]

MATERIALS AND METHODS

This study is designed to bea randomized and controlled study where the patients were reported with diabetic foot ulcer reporting to Department of General Surgery, G. S. Medical College and Hospital, Pilkhuwa, Hapur, Uttar Pradesh, India. Colladerm (Bioland Corp. Korea) was applied for analysing treatment results of diabetic foot ulcer patients. Colladerm is a porous spongy formed collagen dressing material that primarily composed of high purity heterogenic type - 1 collagen derived from porcine skin. All the patients were provided with an informed consent and the study was started out after getting prior approval from the institutional ethical committee.

Fifty patients (40 males and 10 females) were procured to be included to experimental group who were treated using collagen dressing andthey form the study group. Control treatment

was performed on 25 patients (21 males and 4 females) at the same period. All patients were randomly belonged to experimental or control group according to priority and they did not be aware of allocation of which group since the study was single-blinded. The inclusion criteria of patients who were eligible for enrolment in the study arethose patients with type 1 or type 2 diabetes, a foot ulcer with a size >1.0 cm^2 that did not show signs of healing for at least 6 weeks, a Wagner grade II, more than one intact foot arterial flow at Doppler-ultrasound test or transcutaneous oxygen pressure ≥30 mmHg. A total of 50 patients with ulcers were included in an intention-to-treat analysis of the study and were analysed effectively. Of the 50 ulcers analysed, 25 were aligned to the experimental group and 25 to the control group. Patient's demographic details with some clinical laboratory parameters were noted.

Follow-up evaluations were routinely called on a weekly basis fora total 3 weeks. Single investigator evaluated and recorded the following observations which are the condition of the study wound and the effect of primary dressing, the compliance of the use of adequate off-loading device, the presence or absence of any adverse events, changes in medication and the number of dressing changes since the study start. The study wound was photographed for record purpose followed by compared and measured weekly as described above after removal of the primary dressing and sharp debridement. Final evaluations were carried out at the third week after first application of the Colladerm.

All the quantitative values were noted as mean± standard deviations. Statistical comparisons for the degree of wound reduction in terms of the area and depth and the degree of increment of granulation tissue area were conducted using the 'Mann-Whitney U-test'. Statistical significance was accepted at the 5% confidence level.

RESULTS

Patient's demographic details with some clinical laboratory parameters were noted (table 1). Clinical characteristics of ulcers at baseline in both groups are presented in table 2. The final ulcer sizes (by the 3-week measurement) ranged between 0.2 and 4.2 cm^2 (mean, 1.11 ± 1.19 cm^2) in the experimental group, and ranged between 0.1 and 12.8 cm^2 (mean, 2.52 ± 2.61 cm^2) in the control group. The percentage of reduction of wound area and depth relative to the baseline planimetry wound was calculated each week. By the end of week 3, the mean percentage of reduction of wound area was 74.2 ± 17.77% in the experimental group and 44.2 ± 36.21% in the control group (P=0.094). Also, the mean percentage of reduction of wound depth was 73.2 ± 17.72% in the experimental group and 51.8 ± 38.82% in the control group (P=0.762) as stated in table - 3. There were no noticeable statistical significances. The mean percentage of increment of healthy granulation tissue area was 62.3 ± 37.42% in the experimental group and 49.8 ± 42.32% in the control group (P=0.352) as proposed in table - 3. Statistical significance was also not proven.

It was found that all of 25 patients of the experimental group were reported with shrinkage of wound area and depth over 30% at the third week regardless of wound location, duration, and grade. In contrast, the improvement of only 5 ulcers in area over 30% at the third week was observed, and 6 in depth. It was inconsistent. The safety and tolerability were excellent. During the study period, nonserious adverse events like dermatitis were present in 5 patient (10%) in the Colladerm group and 10 (20%) in the control group. Allevyn used as a

secondary dressing material, not Colladerm, might be reported with dermatitis. Clinically overt infections did not occur in both groups. No clinically meaningful changes occurred from the baselines of the clinical laboratory parameters, including serum chemistry, haematology, and urinalysis, or vital signs for any of the patients.

Table 1: Patient characteristics for the Colladerm-treated and the control groups

Parameters	**Experimental group (n=25)**	**Control group (n=25)**
Age (years)	61.2 ± 11.18	61.5 ± 12.19
Type-1:Type-2	0: 25	1: 25
Male:Female	18: 7	18: 7
HbA1c (%)	7.58 ± 0.72	7.19 ± 0.72
Hb (g/dL)	10.34 ± 2.02	10.92 ± 0.87
Albumin (g/dL)	3.39 ± 0.41	3.69 ± 0.39
WBC (x10^3/mL)	6.72 ± 2.89	7.74 ± 2.72
CRP (mg/L)	17.12 ± 36.88	18.81 ± 28.49

Table -2: Clinical characteristics of the ulcers at baseline

Parameters	**Experimental group (n=25)**	**Control group (n=25)**
Ulcer size (cm^3)	4.31 ± 3.88	3.49 ± 3.76
Depth of ulcer (mm)	18.8 ± 9.68	11.8 ± 8.11
Granulation tissue (%)	26.22 ± 33.83	17.5 ± 26.31
Ulcer duration (months)	17.1 ± 7.61	15.9 ± 5.48
Ulcer location		
Dorsal	12	17
Plantar	13	8

Table – 3: Comparisons of final data between experimental and control patients

Parameters	**Experimental group (n=25)**	**Control group (n=25)**	**P – value**
Final ulcer size(cm^2)	1.11 ± 1.19	2.52 ± 2.61	
Final depth (mm)	3.4 ± 3.01	9.9 ± 12.82	
Final granulation tissue (%)	87.4 ± 33.75	66.52 ± 41.13	
Wound area reduction (%)	74.2 ± 17.77	44.2 ± 36.21	0.094
Wound depth reduction (%)	73.2 ± 17.72	51.8 ± 38.82	0.762
Granulation tissue area increment (%)	62.3 ± 37.42	49.8 ± 42.32	0.352

$P < 0.05$, statistically significant

DISCUSSION

It has been for a very long time that the importance of collagen in wound healing has been known widely that the ultimate result of most wound repair is the formation of scar tissue predominantly comprised of collagen fibres. But the collagen mightinterfere with the normal wound healing not only at its final stage, but also at the very early stages.[6] Collagen is known to be a very efficient haemostatic agent due to the adherence of platelets to collagen causing

them to swell and release substances that might initiate haemostasis.[7,8] In this due process, collagen dressing can be used as an effective method of haemostasis through platelet agglomeration. Granulation tissue comprised of an array of macrophages, fibroblastsand neo-vasculature which are embedded in a matrix of collagen, fibronectin and hyaluronic acid.[9] Collagen accentuates the development of granulation tissue and vascularization. Moreover, collagen effectively enhances the fibroblastic activity.[10] Activity of fibroblast normally governs the restoration of tissue continuity and strengthening of the tissue to be repaired. Fibroblast known to possess various membrane receptors with specific binding sites for collagen which could efficiently agglutinates with collagen. Hence, collagen is involved in one of the major events of the wound healing process which is the migration of fibroblast.[11,12] Collagen also variably sustains the differentiation and migration of epidermal cells and may also play a role in re-epithelialisation due of its ability to bind with fibronectin.[13]Lastly, collagen tend to reduce the scar size efficiently. It was observed that collagen has an ability to control collagenase activity and extracellular matrix decomposition by accentuating the growth and differentiation of keratinocyte.[14]Thereby, collagen is thought to be responsible for a reduced scar size.[15] Studies have been claimed that collagen dressing has scientifically established to be effective exogenously in acute wound such as major burn, postoperative wound as a substrate and viable biomaterial. Marc GJ et al[16] and Mian M et al[17] concluded that heterologous collagen accentuated that epidermal regeneration and locally enhances the growth factor concentrations in acute wounds of animal models. Yang et al[18]observed that collagen dressing in treating patients with deep second-degree burns displayed shorten re-epithelialization period. Additionally, Steven el at[8] used a bovine collagen matrix in post-operative wound and observed more faster wound healing rate than traditional second intention healing at all post-operative sites. But there has been a lot of controversy about whether the collagen has same effects in the chronic wound and not in the acute wound. Thus, this study was conducted to effectively compare the efficacy of collagen dressing with that of conventional dressing in the treatment of diabetic foot ulcers.

Diabetic foot ulcer is vicious chronic wound that is stuck in the inflammatory phase and stop the epidermal growth or migration over the wound surface.[1] One key characteristic of all chronic wounds is an elevated level of MMPsresults in an increased proteolytic activity and inactivation of numerous growth factors that could actively promote cellular migration, proliferation, production of new connective tissue matrix and collagen deposition.[2-4]With the knowledge available in literature, collagen dressing is opted to act as a ‘sacrificial substrate’ in chronic wound against the elevated levels of MMPs. Moreover, collagen breakdown products are chemo-attractive for variety of cells required for the wound healing process.[10-12] However, we couldn’t prove that collagen dressing leads to an accelerated wound healing rate than conventional dressing materials in diabetic foot ulcers. Damaged cellular components are considered as a cause. Diabetes alters glucose homeostasis and persistent hyperglycemia leads to advanced glycation end products (AGEs) which are primarily responsible for the damage of cells which have a slow turn over. The metabolic hyperglycemic complication affects these cell lines associated with wound healing, so the cellular maturity does not occur, and this can result into poor quality of wound healing which may manifest either in poor capillary bed formation by endothelial cell, weak reticular network laid by fibroblast and abnormal epithelial cell migration. The other cellular component like macrophages and

lymphocytes may also become weak and could result into wound infection readily.[19] In other words, although collagen can inhibit the action of MMPs and attract cells such as fibroblasts, keratinocytes which are associated with wound healing, damaged cells and their products may not lead to accelerate the wound healing process.

The ideal dressing should be maintaining a moist wound environment, eliminate dead space, absorb excess exudates, and protect bacterial propagation. Collagen dressing has these essential factors that should be kept in ideal dressing. Authors and patients experienced that Colladerm was easier to apply and to remove without pain. And it was more likely to keep the wound moistened and to be comfortable. Collagen dressing containing antibiotics such as gentamycin or amikacin also acts as an effective physical barrier to infection and reduces the number of living bacterial cells in the infected tissue almost to zero,[20] although the present study did not design in this manner. Collagen treatment is also considerably less expensive and inconvenient compared with other new treatments. Therefore, it may be applied as an independent treatment choice or combined with other treatment in managing diabetic foot ulcer patients. The present study has a few limitations. First, this study was based on the findings of a small number of patients and short follow-up periods of only four weeks. Second, our patients had different wound sites and pressure off-loading methods including footwear with cushioning insoles, crutches, and wheelchairs. Third, more information is needed regarding the frequency of changes of the collagen dressing. In our trial, dressing changes of three times a week was used for two groups; more or lesser frequent application might have the advantages of stimulating cells located within wound and accelerating the wound closure. It is not known which is the standardized option for promoting the wound healing process. Lastly, the present study was designed to focus on gross findings as reduction of wound size and depth, increment of healthy granulation tissue. In other words, quantitative measurements of the reduction of MMPs and the increment of cellular components like cytokines, growth factors were impossible to be a evaluation method in human models. Gross findings were inevitably replaced as evaluation criteria. Therefore, the further randomized controlled standard studies that examine these particular issues should be performed.

CONCLUSION

No significant better results with respect tocomplete healing of chronic wounds, especially diabetic foot ulcers comparing the collagen dressing and conventional dressing were observed. But many studies have established that collagen dressing has a potential to accentuate the wound healing process. Collagen dressing also might also provide supplementary advantages of patients' comfort and compliance as well as maintenance of ideal healing environment. In order to confirm the usefulness and wound healing potential of collagen dressing in the management of diabetic foot ulcers, futureresearch with longer follow-up periods should be conducted.

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