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COMPARATIVE STUDY OF COLLAGEN BASED DRESSING AND STANDARD DRESSING IN DIABETIC FOOT ULCER

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ABSTRACT: 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. Numerous dressings have been introduced that could help or hasten the healing process in foot ulcers. In this study, we have compared the efficacy of collagen granules in diabetic foot ulcers. 50 patients were divided into 2 groups of 25 patients each. One group received collagen dressing and the other group received standard saline dressings. The wound was reviewed on weekly basis for the maximum period of 12 weeks or till the wound healed spontaneously (whichever was earlier). We found collagen dressing to have statistically significant impact on the ultimate outcome (healing) in diabetic foot ulcers.

KEYWORDS: Ulcer, collagen, diabetic.

INTRODUCTION: Diabetes mellitus is characterized by chronic hyperglycemia and disturbances of carbohydrate, fat and protein metabolism associated with absolute or relative deficiency in insulin secretion and/ or insulin action. It is known for its micro and macro vascular complications like retinopathy, neuropathy, nephropathy, cardio vascular and peripheral vascular disease.

A diabetic foot is a foot that exhibits any pathology that results directly from diabetes mellitus or any long-term (or "chronic") complication of diabetes mellitus. The most serious foot complications in diabetes are Ulceration, Infection and Neuropathic osteo arthropathy. Foot ulceration precedes the majority of amputations in diabetics. Prevention and early treatment of foot ulcers requires multidisciplinary teamwork. The diabetic foot is mainly because of peripheral neuropathy, arteriopathy and superimposed infection.

Peripheral neuropathy^[1] in diabetics is typically symmetrical characterized by loss of pain, light touch and vibration perception and absent ankle reflexes. Wasting of the small muscles of the foot as a result of motor neuropathy may cause deformities such as claw or hammer toes. Sympathetic neuropathy causes dryness and vasodilation of the skin, making it more susceptible to infection. The neuropathic foot is therefore, vulnerable to heat, chemical and mechanical trauma.

Peripheral vascular disease^[2] in diabetics is common and occurs in parallel with coronary, renovascular and cerebrovascular disease. It affects all vessels and is characterized by early onset, multi segmental disease, greater involvement of collateral vessels and a significant exacerbation associated with smoking. Small vessel disease particularly affecting the mid- tarsal and digital arteries is also common and can cause diagnostic confusion when it occurs in isolation.

Poor wound healing results from a combination of neuropathy, ischemia and prolonged hyperglycemia. It provides an enriched growth medium for bacteria. The leukocyte function becomes abnormal. There is reduced phagocytosis and chemotaxis.

The most common location for foot ulcers is the plantar surface of forefoot. These ulcers are

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often caused by repetitive mechanical stress that is not recognized by patients because of peripheral neuropathy and loss of protective sensation.^[1]

Among people with diabetes, 15% will experience foot ulcers in their life time.^[3] Foot ulcers are a major predictor of future lower extremity amputation in patients with diabetes; about 14- 24% of patients with foot ulcers will require an amputation.^{[4][5]} Thus appropriate techniques for wound care that can reduce amputation rates are an essential prevention strategy.

In recent years, several new treatment strategies have been developed to stimulate wound healing in the diabetic foot ulcers. These are topical growth factors, extra cellular matrix products, bioengineered human skin, hyperbaric oxygen therapy, granulocytes macrophage colony stimulating factors and collagen granules.

New 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 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.^{[6],[7]}

Collagen is available as spherical hydrophilic particles of collagen, 0. 1 to 0. 3 mm in diameter. It is available as 5, 10, 15 ml packets.

MATERIAL & METHODS: A total 50 patients suffering from chronic foot ulcers in type II diabetes mellitus were selected for the study. After explaining the procedure and motto of the study, written informed consent was taken prior to enrolment in the study.

Diabetes was diagnosed according to American Diabetes Association (ADA) revised criteria.

1. Fasting blood glucose level greater or equal to 126 mg/dl (7. 0 mmol/L) on two separate occasions.
2. A random plasma glucose level of 200mg/ dl (11. 10 mmol/L) or more.
3. A blood glucose level of 200 mg/dl (11. 10 mmol/L) or more two hours after ingestion of 75 gm glucose.

Exclusion Criteria:

1. A condition that may have interfered with wound healing (e. g carcinoma, connective tissues disease or an immune system disorder).
2. Current treatment with dialysis, corticosteroids, immunosuppressive agents, radiation therapy, chemotherapy.
3. Known hyper sensitivity to any of the dressing components.
4. Those who have not completed three months follow up and dropped out.

Inclusion Criteria:

1. 18 years or above, with a diabetic foot ulcer of at least 30 days duration.
2. An Area of at least 1 cm².
3. Patient with adequate peripheral pulses of limbs.
4. A wound that was debrided of necrotic / non-viable tissue at enrolment.

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Appropriate investigations were undertaken which included apart from the routine hemogram (Hb, TLC and DLC), blood sugar levels (random, fasting, postprandial) and urinary sugar and ketones to known the diabetic status. Serum albumin were done wound swab were taken from all wounds at the time of admission and repeated as frequently as required to culture the infecting organism and find out its sensitivity to the available antibiotics. X-ray foot was done in all cases to see the bony deformities and to rule out osteomyelitis.

The target wounds greatest length, width and depth were measured at baseline. The target wound was assessed before and after cleaning and / or debridement for local infection and for wound condition (improving, stable or deteriorating). The wound area was determined by means of planimetry (the greatest width x the greatest length, measured in centimeters).

Eligible patients were grouped in two, alternatively. In treatment group, where appropriate, collagen was applied as primary dressing. It was covered with gauge and bandage and tape and no other chemical was used. In control group, isotonic sodium chloride solution and betadine moistened gauge was applied as primary dressing over wound area covered with gauge and bandage and tapes.

The frequency of dressing change was once a day. If soakage was high then dressing was done twice a day. Treatment was given for 12 consecutive weeks or until ulcer closure, whichever occurred first.

EVALUATION OF RESPONSE: The 2 longest perpendicular dimensions of the ulcers were recorded at baseline and weekly thereafter on weeks 1, 2, 3, 5 and 12. Any untoward effects like local pain, local pruritus and bony aches were recorded every week.

Primary study Endpoints: At the end of the study period of 12 weeks, patients were categorized as:

1. Complete Responders: Complete healing of leg ulcers.
2. Partial Responders: 50% or greater reduction in product of the 2 longest perpendicular diameters from baseline.
3. Non-complete Responders: Less than 50% reduction in the product of the 2 longest perpendicular diameters from baseline.
4. Non- responders: No reduction in ulcer area or increase in ulcer area over baseline.

Two groups were compared; Analysis of variance was calculated for the ulcer size in sq. cm. Post treatment comparisons were made using 't' test and critical ranges were calculated.

RESULTS:

1. Age/ Sex: The mean age of the study group was 55. 68 years with a range of 35-75 years, whereas in control group the mean age was 54. 60 with a range of 32-80 years. There were 16 and 21 males in study and control group respectively.
2. Other variables: Baseline characteristics were comparable in both study and control group (Table 1).

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Variable	Study	Control	p-value	Significance
Age	55. 68 + 10. 16	54. 60 + 11. 94	>. 10	NS
Sex: Male Female	16 (25) 4 (16)	21 (84) 4 (16)	>. 10	NS
Duration of DM (years)	9. 52 + 4. 11	9. 68 + 4. 10	>. 10	NS
Systolic BP (mmHg)	144. 80 + 10. 95	142. 96 + 10. 35	>. 10	NS
Diastolic BP (mmHg)	90. 08 + 7. 60	90. 72 + 7. 44	>. 10	NS
FBS (mg%)	213. 60 + 73. 17	223. 20 + 63. 55	>. 10	NS
Ulcer Size (cm ²)	8. 68 + 5. 65	10. 00 + 5. 42	>. 10	NS

Table 1: Study of different variables

3. Healing response at the end of 1st week: After one week of treatment, in the study group complete responders (CR) were 2, partial responders (PR) were 12 and non-complete responders (NCP) were 11. In control group, there were 6 partial responders and 19 non-complete responders (Table 2).

Healing Response	Study (n = 25)	Control (n =25)	z-value	p-value
CR	2 (8)	0 (0)	1. 44	>. 10 NS
PR	12 (48)	6 (24)	1. 77	<. 10
NCP	11 (44)	19 (76)	2. 31	<. 05
NR	0 (0)	0 (0)	--	--

Table 2: Distribution according to healing response of 1st week

4. Healing response at the end of 2nd week: After 2nd week of treatment, in the study group complete responders (CR) were 4 and partial responders (PR) were 21. In control group, there were 2 complete responders, 7 partial responders and 16 non-complete responders (Table 3).

Healing Response	Study (n =25)	Control (n =25)	z-value	p-value
CR	4 (16)	2 (8)	0. 87	>. 10 NS
PR	21 (84)	7 (28)	3. 99	<. 01
NCP	0 (0)	16 (64)	4. 85	<. 01
NR	0 (0)	0 (0)	--	--

Table 3: Distribution according to healing response of 2nd week

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5. Healing response at the end of 3 weeks: After three weeks of treatment 15 patients were complete responders and 10 were partial responders in study group while in control group 2 patients were complete responders, 15 patients were partial responders and 8 patients were non-complete responders. Complete responders were statistically significant (p value < 0.01) in study group at 3rd week. (Table 4).

Healing Response	Study (n =25)	Control (n =25)	z-value	p-value
CR	15 (60)	2 (8)	3.88	$< .01$
PR	10 (40)	15 (60)	1.41	$> .10$ NS
NCP	0 (0)	8 (32)	3.09	$< .01$
NR	0 (0)	0 (0)	--	--

Table 4: Distribution according to healing response of 3rd week

6. Healing response at the end of 5 weeks: In the study group, complete and partial responders were 15 and 10 in number respectively, while in control group complete responders, partial responders and non-complete responders were 3, 20 and 2 in numbers respectively. Complete response was significantly higher in treatment group (p value < 0.01) at 3rd week. (Table 5) Partial response was significantly higher in control group (p value < 0.01) in control group.

Healing Response	Study (n =25)	Control (n =25)	z-value	p-value
CR	15 (60)	3 (12)	3.54	$< .01$
PR	10 (40)	20 (80)	2.89	$< .01$
NCP	0 (0)	2 (8)	1.44	$> .10$ NS
NR	0 (0)	0 (0)	--	--

Table 5: Distribution according to healing response of 5th week

7. Healing response at the end of 12 weeks: In the study group, there were 21 complete responders and 4 partial responders. In control group, there were 7 complete responders and 18 partial responders. Complete response was statistically significant ($p < 0.01$) in study group while it was significant in control group in partial responders ($p < 0.01$) Table 6.

Healing Response	Study (n =25)	Control (n =25)	z-value	p-value
CR	21 (84)	7 (28)	3.99	$< .01$
PR	4 (16)	18 (72)	3.99	$< .01$
NCP	0 (0)	0 (0)	--	--
NR	0 (0)	0 (0)	--	--

Table 6: Distribution according to healing response of 12th week



Fig. 1: Collagen granules in available packing

DISCUSSION: Foot problems are the most common indication for hospital admission in diabetes. They account for approximately 20% of all hospital admissions in diabetics.^{[8] [9]} Approximately 50% of all non-traumatic amputations are in diabetics.^[10] Most hospital beds are occupied with diabetic patients with foot problems than all other causes associated with the disease.

Of the many complications of diabetes, those involving the foot lead not only to pain and suffering, but take months to heal. It leads to loss of working hours, hospitalization and great expense both to the patient and the community.^{[11],[12]}

Different modalities of treatment have been used time to time to treat the diabetic foot ulcers such as debridement, different anti- infective wound dressing, antibiotics according to culture sensitivity, skin grafting etc.^[13]

Even after various modes of treatment, treatment failure rate is very high. Hence we planned to use the collagen dressing for the treatment of diabetic foot ulcer. There is a large body of evidence that suggest collagen is a common denominator in all stages of wound healing. Collagen serves as the key extracellular component for repair and remodeling of skin tissue.

The exogenous collagen functions as a substrate for hemostasis and is chemotactic to cellular elements of healing such as granulocytes, macrophages and fibroblasts. The materials promote wound maturation by providing a scaffold for more rapid transition.^[14] Biomaterials are resistant to degradation and provide a template for cellular attachment, migration and proliferation.

As a biomaterial, collagen offers several advantages over traditional dressings, growth hormones and biological coverings.

For this purpose, we selected 50 diabetic foot ulcer patients.

We included only chronic ulcers of at least 30 days duration. We excluded those patients who were having neoplastic disease, pre-existing cardiovascular, pulmonary or immunological disease.

We did collagen dressing in 25 patients, in remaining patients standard dressing was used. We also followed standard treatment of diabetic foot that includes good glycemic control, control of infection by appropriate antibiotics according to culture sensitivity and debridement if needed in all patients.

After 12 weeks of collagen treatment, there were 21 patients who achieved complete healing and 4 patients achieved partial healing, while in control group, only 7 patients achieved complete healing and 18 patients had partial healing.

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In our study complete response at 1st and 2nd weeks in both study as well as control groups were statistically at par but after 2 weeks complete response was significantly higher in study group. Partial response was significantly higher in study group except at 3rd week as compared to control group.

In diabetic foot ulcers, no such studies are available for comparison except some case reports. Manu Shankar, Chentamani^[15] and in their case reports observed that there was significant improvement in diabetic foot ulcer patients by collagen dressing.

Duration of ulcer also have effect on healing response, if ulcer was of prolonged duration, healing was delayed in both groups, but healing was better in study group as compared to control group.

Collagen dressings have very good results in our study. Collagen favors the outcome because of increased defense mechanisms by stimulating and differentiation of early and late granulocytes, erythroids and megakaryocyte precursors cells.^[16] Side effects of collagen are generally infrequent and mild and can be well tolerated by the patients.^[17]

No doubt till today, collagen is costly affair in our country, but if we consider the cost of hospitalization and if we prevent amputation, then this therapy seems to be logical. Hence, collagen can be good option for chronic non-healing diabetic ulcers. No doubt this study has its own limitations as small cohort and cost of treatment. To confirm our results, more studies in large cohort are required.

CONCLUSIONS: Our study is a hospital based case control prospective study done in 50 patients of chronic diabetic foot ulcers. There was statistically significant difference between the results of collagen and saline dressings as collagen dressings had better healing response rate as compared to placebo when given along with standard treatment of diabetic foot ulcer.

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