



PROSPECTIVE STUDY ON ROLE OF COLLAGEN GRANULES IN MANAGEMENT OF CHRONIC NON HEALING ULCERS

General Surgery

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ABSTRACT

Background: Ulcers over the foot, ankle, and leg are the common problems faced by the surgeons. Leg ulceration has been a recognized public health problem for centuries. Present day hospital statistics in days of hospitalization for ulcers are similar to those in 1800s. Average length of hospital stay for ulcer patients is higher than patients admitted for other conditions and range between 18 and 121 days. (1, 2,3) what has changed over last two centuries is age distribution of ulcer patients suggesting difference in underlying aetiology for leg ulcer. (4) chronic wounds are wounds that have failed to proceed through an orderly and timely reparative process to produce anatomic and functional integrity over a period of 3 months. (5) The development of ulcer in a leg is a complex process and dependent mainly on underlying circulatory status of patient's lower limbs. Many studies have been conducted to assess the percentage of ulcer patients with each ulcer type. (1,6-30).

Wound healing is a complex process involving a number of chemical and biological events. Collagen serves as the key extra cellular component for repair and remodeling of skin tissue. As a biomaterial, collagen offers several advantages over traditional dressings, growth hormones and biological coverings (13). The use of collagen as a drug delivery system is very comprehensive and diverse. Due to its excellent biocompatibility and safety, the use of collagen in biomedical application has been rapidly growing and widely expanding to bioengineering area.

Objective: To compare the rate of healing process in non healing ulcers using collagen particles with those of conventional methods.

To compare the bacterial growth in wounds with collagen particle dressing to that of wounds with conventional method of dressing.

Results: In this study it was observed that mean Wound Bed Score at the end of 4 weeks was 14.88 in collagen group against 11.86 in control group with significant statistical difference $p < 0.0001$. There was significant statistical difference $p < 0.0001$ in the mean Time of wound healing in Collagen group 22.5 days, where as in control group it was 31.4 days

Conclusion: Collagen based dressing showed better results like faster healing, less antibiotic usage and less pain and discomfort

KEYWORDS

Collagen dressing, Wound healing, conventional dressing, Wound Bed Score

1) INTRODUCTION :

Wound healing is a complex process involving a number of chemical and biological events. Collagen serves as the key extra cellular component for repair and remodeling of skin tissue. As a biomaterial, collagen offers several advantages over traditional dressings, growth hormones and biological coverings (13). The use of collagen as a drug delivery system is very comprehensive and diverse. Collagen can be extracted into an aqueous solution and molded into various forms of delivery systems. Due to its excellent biocompatibility and safety, the use of collagen in biomedical application has been rapidly growing and widely expanding to bioengineering area.

Collagens are Proline-rich proteins that are fibrous with long, stiff, triple stranded helical structure comprising of three α -chains. Collagens function as structural proteins of extracellular matrix that are synthesized by fibroblasts. The vertebrate family of collagens contain more than 40 genes each encoding different α -chains that forms a minimum of 28 different collagen molecules. (14,15) Even though there are many types of collagen those important in wound repair are types I and III. The role of collagen in improving wound healing is by stimulating fibroblast activity. (16) The important function of fibroblasts is to synthesize and deposit extracellular matrix components. (17) the fibrous connective tissue components are collagen, elastin, and reticulin, while the non fibrous part consists of basic substances like water, salts, and glycosaminoglycans.

Collagenase and other proteolytic enzymes are synthesized during the phase of inflammation and continued in the proliferative phase with the help of fibroplasia regulators. (18) The goals of wound healing during

this phase is to fill the wound defect with fresh tissue and hence restoring the skin integrity. (19) Dressings composed of collagen matrix are available with main considerations of bio security in the clinical application. The application of equine collagen to the wound not only provides haemostatic activity, but also promotes fibroblast and keratinocyte migration leading to effective wound healing.

"Comupimet" is a combination of collagen granules with mupirocin and metronidazole. Mupirocin, which was isolated from pseudomonas fluorescence, is active against staphylococcus including MRSA, streptococcus and inactive against many anaerobic organisms. Metronidazole, which is active against anaerobic is added to this combination, which covers the spectrum.

2) Methodology :

This was a prospective study conducted on a total of 120 patients with chronic non-healing ulcer attending the General Surgery Out Patient Department of Katuri Medical College and Hospital, during the period of October 2015 to October 2017. The allocation of patients into test and control group was done randomly. Patients in test group were treated with Collagen dressings and control group were treated with conventional dressings. Groups were done randomly. Followup was done until the wound healed completely. Statistical analysis of the data was done using student t test All chronic non healing ulcers: Non specific ulcers; (including ulcers with slough) Traumatic ulcers, Arterial ulcers, Venous ulcers, Diabetic ulcers, Bed sores, Trophic ulcers were included in this study. Ulcers having exposed bone without granulation tissue and ulcers with proven malignancy were excluded from the study.

3)RESULTS :

Table 1 : Age Distribution :-

Age	Collagen (n=60)	Cases (n=60)	Total
35 & below	3 (5%)	2 (3.3%)	5 (4.2%)
36 – 45	11 (18.3%)	12 (20%)	23 (19.1%)
46 – 55	21 (35%)	20 (33.3%)	41 (34.1%)
56 – 65	17 (28.3%)	17 (28.3%)	34 (26.6%)
65 & above	8 (1.33%)	9 (15%)	17 (14.1 %)
Total	60	60	120

Observation : The majority of the study population i.e.,total of 75 patients are of the age group between 46 – 65 yrs of age comprising of more than half of the patients i.e.60.7%. As the age increases the prevalence of ulcers especially leg ulcers progressively increased in this study.

Table 2 : Comparing the Decrease in Wound Area :-

GROUP	N	Mean	S.D	Mean Difference	Percentage change	T - statistic	p- valve
Collagen: Initial	60	73.2	53.87	41.56	56.77%	11.612	<0.0001
Final	60	31.6	30.33				
Controls Initial	60	64.91	47.83	16.88	26%		
Final	60	48.03	35.57				

Observation : The decrease in wound size from initial area to final area with mean difference of 41.56 was observed in the test group when compared to 16.88 in control group, and the percentage change of wound area was 56.77 % in test group when compared to control group having 26 % percentage change,with p value < 0.0001

Table 3 :Comparison of Wound Bed Score (WBS) :-

GROUP	N	Mean	S.D	Mean Difference	Percentage Change	T - Statistic	P -value
Collagen Initial	60	7.81	1.51	7.07	90.5%	47.086	<0.0001
Final	60	14.88	1.29				
Controls Initial	60	64.91	47.83	16.88	26%		
Final	60	48.03	35.57				

Observation :

We observed that mean wound scoring initial of (7.81) and mean wound scoring final (14.88) with a difference of (7.07) and a percentage change of 90 % , when compared to that of control group mean wound scoring initial of (8.06) and mean wound scoring final (11.86) with a difference of (3.8) and a percentage change of 47 %.(p value<0.0001)

Table 4 : Comparison of Final WBS :-

Group	Mean Final WBS	S.D	T- Statistic	P –value
Collagen	14.88	1.29	10.88	<0.0001
Controls	11.66	1.72		

Table 5 : Comparison of number of Dressings :-

Group	N	Min	Max	Mean	S.D	T- Statistic	P-value
Collagen	60	5	14	9.33	2.52	14.464	<0.0001
Controls	60	14	29	18.46	4.19		

Observation : The number of dressings required in collagen treated patients is significantly low with a mean of (9.33 ±2.52) in comparison to conventional treated patients with a mean of (18.46 ± 4.19),with significant p value less than 0.0001

Table 6: Comparing the number of Debridements :-

Group	N	Min	Max	Mean	S.D	T- Statistic	P-value
Collagen	60	0	3	1.33	0.96	5.030	<0.0001
Controls	60	1	4	2.18	0.89		

Observation : the number of debridements required in collagen treated patients is significantly low with a mean of (1.33 ±0.96) in comparison to conventional treated patients with a mean of (2.18 ±0.89)

Table 7 : Comparing the Time(in days) to get Nil Cultures :-

Group	N	Mean	S.D	T- Statistic	P-value
Collagen	60	8.86	3.20	6.729	<0.0001
Control	60	12.81	3.23		

Observation : The average time for the wound to grow nil cultures in test group was 8.8 ±3.2days compared to 12.8 ± 3.23 days in control group.(p-value<0.0001)

Table 8 : Time (in days) for Ulcer to Heal Completely :-

Group	N	Mean	S.D	T- Statistic	P-value
Collagen	60	22.5	5.78	6.729	<0.0001
Control	60	31.4	6.85		

Observation : The mean time for healing in study group undergoing collagen dressing is 22.51 ± 5.78, when compared to control group where mean time for healing is 31.4 ± 6.85 days,with p-value < 0.0001.

Table 9 : Mode of Wound Healing :-

Healed by	Collagen (n=60)	Controls (n=60)	Total
Secondary Intention	45 (75%)	36 (60%)	81
SSTG	15 (25%)	24 (40%)	39
Total	60	60	120

Wound healing by secondary intention, without the need for skin graft was 75 % in test group and 60% in the control group, and the difference was found to be statistically significant (p<0.01)

DISCUSSION :

Wound healing involves a timely expression of various growth factors that promotes cellular proliferation and migration, collagen deposition and formation of new connective tissue matrix. (20, 21) Chronic diabetic ulcers are trapped in inflammatory phase of wound healing as there is termination of epidermal growth or migration on wound surface. (22, 23) The common feature of all chronic wounds is elevated levels of matrix metalloproteinases, resulting in increased proteolytic activity and decreased activity of growth factors that are integral part of wound healing process. Collagen has a role during this phase as it specifically inhibits the function of proteases without any influence on activity of growth factors. Thus collagen is effective compared to regular moistened gauze dressing.

This study has been undertaken with a main aim to evaluate the efficacy of antibiotic impregnated collagen particles as a topical wound dressing in 120 patients with chronic non healing ulcers. In our study all kinds of ulcers have been included like, venous ulcers, arterial ulcers, diabetic foot ulcers, bedsores, traumatic ulcers. Patients underwent change of dressing initially every day followed by alternate days and later every 3–4 days until wound healing. Changes in wound size were recorded periodically when the dressing was removed.

In the present prospective study, the number of male patients in experimental group is 66.6% and in control group 71.6%.The majority of the study population are with age group between 46 - 55 yrs both in experimental and control group as 35% and 33.3 % respectively . As the age increases the prevalence of ulcers especially leg ulcers progressively increases. The studies conducted by Baker et al (13); Callam et al (24); Cornwall et al (25); Nelzen et al (26, 27, 13); O'Brien et al (23); Margolis et al (28) all have reported that prevalence of leg ulcers increases with each decade of life.

The duration of ulcer, site of ulcer and the type of ulcer is not consistent in this study but the observation was that diabetic ulcers are more in number with experimental group of 36.6% and control group of 45% , with a total consisting of 40.8% ,which is nearly half of the study population . This helped in decreasing the variation between types of ulcers in this study, thereby achieving better results. In the present study collagen particle dressing has been tried on all types of ulcers. Good improvement in wound contraction due to granulation tissue has been noted in stump ulcers and bed sores, with little improvement in arterial ulcer after a 2 weeks of application.

Control of infection, appropriate off loading of the foot, extensive debridement and lower extremity revascularization are the cornerstones in the management of chronic leg ulcers. (29, 30) Collagen plays an important role in cutaneous tissue repair mechanism when used as a bioactive advanced dressing in chronic ulcers. Collagen helps in fibroblast deposition at wound site mainly in the dermal matrix that enhances angiogenesis, granulation tissue formation and as well as re-epithelisation. (31) In this present study patients who undergone Split Skin Grafting (SSG) following collagen dressing are less of 25 % when compared to 40% with conventional dressings.

In a study done by Veves et al in 276 patients with diabetic ulcer of foot, 51 (37%) of promogram(a collagen/ oxidized regenerated cellulose dressing) based treatment patients had a complete healing of wound as compared to 39(28.3%) in control group treated with moist gauze dressing. The difference was not statistically significant as the p value is 0.12. So in the above mentioned study, author found an overall benefit in rate of wound healing in collagen based dressing compared to moistened gauze. (32)

The present study also found that the antibiotic usage in collagen treated patients is less when compared with the conventional group. This is because the culture from the wound on subsequent dressings showed no bacterial growth in 43% of study group as compared to 3% in control group by the end of first week of application. This was a better result when compared with results of other collagen studies. This result attained was thought to be due to addition of antibiotic to the collagen particles i.e, Metronidazole and Mupirocin which acted very effectively on gram negative organisms and by the average time for the wound to grow nil cultures in control group was 8.8 days, when compared to control group which is 12.8 days. Out of the organisms cultured from the wounds, proteus was cultured more common in 18% of the study population and klebsiella the next common 16.6 % , followed by staphylococcus aureus, pseudomonas and streptococcus. In the experimental group pseudomonas and staphylococcus aureus were isolated from the wounds 18.6 % of the study population followed by klebsiella, and proteus in their order 16.6% ,15 % respectively.

In this present study a decrease in wound size from initial area to final area with mean difference of 41.56 was observed in experimental group when compared to 16.88, and the percentage change of 56.77 % when compared to control group having 26 % percentage change, with p value < 0.0001 that is highly significant. In this present study, the mean time for healing in study group undergoing collagen dressing is 22.51 days with a standard deviation of 5.78, when compared to control group where mean time for healing is 31.4 days with standard deviation of 6.85 days. The present study has got the similar results comparable with their study with a significant p value less than 0.0001. So the mean time in wound healing is also low in collagen treated patients when compared to conventional dressing patients.

In this present study we also observed that the number of debridements required in collagen treated patients is significantly low with a mean of (1.33) and standard deviation of (0.96) in comparison to conventional treated patients with a mean of (2.18) and a standard deviation of (0.89). By this study we are able to see that the pain during the time of dressings can be decreased by collagen based dressings, as many debridements needed anaesthesia and post procedure analgesics. The number of dressings required in collagen treated patients is significantly low with a mean of (9.33) and standard deviation of (2.52) in comparison to conventional treated patients with a mean of (18.46) and a standard deviation of (4.19), with significant p value less than 0.0001, showing that the stay in hospital and the time for healing is low in the collagen based dressings. Also we can tally the cost effectiveness which is the main barrier in the collagen group, as the number of dressings is low in collagen group. Although the role of collagen in wound healing is well established, it has not been tried extensively in the management of chronic non healing ulcers. (33,34) The results from the present study are encouraging that, collagen particles unlike regular dressing are absorbed at the wound bed and need not be re-applied very frequently, unlike regular conventional dressings which needed to be changed very frequently.

To assess the components in wound healing several tools have been developed of which Wound Bed Score - WBS has been used in this present study which has a published record of validity and reliability. A new classification system that scores the following parameters: healing edges (wound edge effect), presence of eschar, greatest wound depth/granulation tissue, amount of exudate amount, edema, peri-wound dermatitis, peri-wound callus and or fibrosis, and a pink/red wound bed. Each parameter receives a score from 0 (worst score) to 2 (best score), and all the parameter scores are added for a total score. Each wound can have a maximum score of 16 (the best score possible), to a minimum score of 0 (the worst score possible). We observed that mean wound scoring initial of (7.81) and mean wound scoring final (14.88) with a difference of (7.07) and a percentage change of 90 % , when compared to that of control group mean wound scoring initial of (8.06) and mean wound scoring final (11.86) with a difference of (3.8)

and a percentage change of 47 % that is highly significant with a p value of < 0.001. Similar study based on collagen dressing was conducted recently in 2015 by Shankar N et al in Kims, Bangalore on deep wounds achieved similar results proving the use of new dressing modalities with use of collagen particles can increase the potentials in wound healing but further studies are needed to prove the efficacy. The present study has following limitations the first was that it was not a randomized study, so equality in type of ulcer and size of ulcer was not maintained. Second was that sample size was less where we included only 60 patients in each group. Third one being cost factor as collagen dressing in this present study is not very cost effective.

Limitations :

- It was a randomized study, allocation of patients into test and control group was done randomly
- The wound was studied in only two dimensions .
- There was a chance of observer bias .
- Third one being cost factor as collagen dressing in this present study is not very cost effective.

CONCLUSION :

Collagen particles hasten the formation of granulation tissue and wound contraction, thereby accelerating the healing process. Collagen dressings can be changed once in 2-3 days depending on the wound burden and the bacterial load also has been reduced on subsequent dressings with antibiotic impregnated collagen as compared with conventional betadine dressing. Hence, the number of debridements and dressings can be reduced, subjecting the patients to far lesser discomfort and decreased hospital stay



Fig 1 : showing the venous ulcer in diabetic over left leg (initial)



Fig 2 :Application of collagen granules over the ulcer & showing the same ulcer in fig 1 after 3 weeks

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