IOSR Journal of Dental and Medical Sciences (IOSR-JDMS)
e-ISSN: 2279-0853, p-ISSN: 2279-0861.Volume 18, Issue 3 Ser. 2 (March. 2019), PP 66-72
www.iosrjournals.org

A Comparative Study between Conventional Dressing (With Betadine, Antibiotic Ointment, Eusol and Normal Saline) of Ulcer and Dressing with Triple Helical Collagen

Dr. Mukesh Bagari[1], Dr. Sami Anwar Khan[2], Dr. Shalu gupta[3], Dr. Brijesh Mathur[4], Dr. Ashok Meghwal[5]

[1] Former Asst. Professor, [2]Former Resident, [3]Professor & Unit head - Department of General Surgery, SMS medical college and attached hospitals, Jaipur-302001, Rajasthan, India.
[1]Divisional Medical Officer (Surgery), railway hospital, Ajmer, Rajasthan, India.
[4]Former Professor, [5]Former Asso. Professor- Department of General Surgery, JLN medical college, Ajmer, Rajasthan, India.
Corresponding Author: Dr. Sami Anwar Khan

Abstract
BACKGROUND: Skin is the natural covering of the human body and is the largest organ by virtue of its extensive surface area. It serves a variety of functions ranging from protection of the underlying tissue to the maintenance of haemostasis. The skin is subjected to a variety of insults ranging from external trauma, infectious disease, noxious stimuli, and internal metabolic disorder. Ulcers are defined simply as a break in the continuity of the covering epithelium, mucous membrane or skin. In recent years several new treatment strategies emerge to stimulate wound healing. There are topical growth factors, extracellular matrix products, bioengineered skin and granulocytes macrophages colony stimulating factors. New advanced topical dressings are emerging that improve wound care. Such dressings are designed to modulate levels of biological molecules such as growth factors that may promote wound healing. Important examples of such dressing are collagen granules, hyaluronic acid cream, PDGF cream feracrrylum gel etc.
PATIENTS AND METHOD: This is prospective study conducted on 100 cases of symptomatic ulcer cases admitted in Surgical Wards of J.L.N. Medical College, Ajmer. All patients will be divided in two groups of 50 patients each. First group will undergo dressing with lyphophillized triple helical bovine collagen; second group will undergo conventional dressing with betadine, antibiotic ointment, EUSOL and normal saline. Further the healing process and results were analyzed.
RESULTS AND CONCLUSION: Most of the patients were males, with age group ranging from 41-60yrs; most common site was foot, with diabetes being the main culprit followed by the infective etiology. At the end of 1st week, 50% shows complete or near complete healing in collagen group as compared to 8% in control group, this further observed to be 74% & 24% after 2nd week, 82% & 44% after 4th week and 94% & 64% after 6th week. There was significant difference in the result of collagen granules and conventional dressing. Collagen granules had better healing response rate and occasionally dramatic response. We conclude that collagen granules are a useful topical agent to be applied locally to all types of ulcers except malignant ulcers. Collagen granules enhances the healing process, as evident by early appearance of red granulation tissue and epithelization, smaller lag period in healing and early completion of healing of ulcers.

Keywords*: wound healing, collagen granules, ulcer*

Date of Submission: 20-02-2019 Date of acceptance: 06-03-2019

I. Introduction

Skin is the natural covering of the human body and is the largest organ by virtue of its extensive surface area. It serves a variety of functions ranging from protection of the underlying tissue to the maintenance of haemostasis. The skin is subjected to a variety of insults ranging from external trauma, infectious disease, noxious stimuli, and internal metabolic disorder. Ulcers are defined simply as a Breach in the continuity of the covering epithelium, mucous membrane or skin. Delayed healing is generally a result of compromised wound physiology and typically occurs with venous stasis, diabetes, prolonged local pressure, malnourishment, anaemia and peripheral vascular disease.

MECHANISM OF WOUND HEALING

Wound healing/repair is not a simple linear process where growth factors released by physiological events trigger parenchymal cell growth. Rather, it is an integration of dynamic interactive processes involving soluble mediators, formed blood elements, extracellular matrix (ECM) and parenchymal cells. Unencumbered, follow a specific time sequence. These wound repair events can be temporarily grouped into inflammation, tissue formation, and tissue remodeling. These phases of wound repair are not mutually exclusive and overlap in time.

The regulatory factors that affect healing of wounds include:

1. Cell-Cell Interactions
2. Cell Matrix Interaction
3. Growth Factors

i. Transforming growth factors-a (TGA-a) → Re-epithelialization
ii. Platelet derived growth factor (PDGF) → Fibroblast chemotaxis proliferation and contraction
iii. Fibroblast growth factor (FGF)→ Fibroblast and epidermal cells proliferation and angiogenesis
iv. Transforming growth factor-b (TGF-b) → Fibroblasts chemotaxis, ECM, and protease inhibitor production.

Factor affecting the wound healing are:

1. Infection
2. Protein nutrition and wound tensile strength
3. Vitamin 'C'
4. Anemia and blood loss
5. Oxygen tension
6. Effect of stress and steroid hormone
7. Effect of commonly used drugs
8. Zinc and wound healing
9. Tissue anoxia
10. Environmental temperature
11. Necrotic tissue, foreign body, seroma and dead space
12. Antiseptic and bactericidal agents
13. Effect of edema and external pressure
14. Type of tissue
15. Site of wound
16. Type of dressing

Topical antibiotics reduces the wound healing power (Richard and Eiseman, 1973)[42].

When there is a wound anywhere in the skin, body heals itself because it is preprogrammed to respond with a series of complex sequential cellular and vascular activities. So to improve the life, treatment of the ulcer is necessary. The treatment of ulcer posses a significant challenge to clinicians.

Ulcers present difficulties in management due to a variety of interrelated factors such as fluid and electrolyte loss from the denuded body surface, loss of proteins from ulcer base and depressed immune response against infection, all of which delay wound healing. Apart from this, the underlying causative factor of ulceration needs proper treatment prior to expecting any improvement in the skin defect. Another major factor adding to the miseries of the treating surgeon is the deficiency of donor area for autologous skin graft to cover up the wound, especially in extensive wounds such as caused by burns.

Commentators on this subject have mentioned many drugs and methods which have been thought to be of value in protecting the ulcer from infection and nutrient loss and hasten the healing of ulcer and relieving the patient of the intense pain usually accompanying the ulcer. For these purpose many ingenious types of pastes like vaseline, strips of oil soaked linen over the wound, tinctures and extracts from tea leaves (rich in tannin), tannic acid were used over the wounds. Other methods in vogue like mixture of old swine's seam (lard), resin and bitumen were spread over a cloth and warmed just before application as a bandage, application of rose water cooled by snow or ice water, various emollient preparations with bizarre ingredients, creams like silver sulphadiazine, mafenide, metronidazole, providone iodine, etc.

Since times immemorial man has been interested in finding a method that can prevent the loss of fluid, electrolyte and proteins from the ulcer and aid in fast epithelization.

In recent years several new treatment strategies emerge to stimulate wound healing. These are topical growth factors, extracellular matrix product, bioengineered skin and granulocyte macrophage colony stimulating factors.

New advanced topical dressings are emerging that improve wound care. Such dressings are designed to modulate levels of biological molecules such as growth factors that may promote wound healing. Important examples of such dressings are collagen granules, hyaluronic acid cream, PDGF cream, Feracrylum gel.

Feracrylum is a haemostatic, antimicrobial and hygroscopic agent. Feracrylum having local haemostatic action arrests oozing from the wound site and thus causes haemostasis. Feracrylum has a wide range of antimicrobial activity against both gram positive and gram negative bacteria and pathogenic fungi.

Even after using different modalities of treatment results are not always gratifying. An ideal dressing should be comfortable, pain relieving, harmless to tissue, encourage removable of slough and promote vascularisation and optimal growth of granulation tissue. There is no dressing till date which is ideal but collagen particles is very close to it.

Looking to the beneficial qualities of collagen particles, we planned to use this substance in our study of ulcer to promote healing and compared it with conventional dressing.

II. Material And Method

The study was conducted in the Department of General Surgery, J.L.N. Medical College and Hospital, Ajmer in various surgical units. 100 patients with ulcers of different etiologies and at different sites were enrolled randomly for this study. These patients were divided into two groups of 50 each "study group" and "control group". Informed consent was taken prior to enrolment in the study.

Each selected patient was examined in detail by complete physical examination, complete history regarding age, sex, socio-economic status, rural, urban, duration of ulcer, history of any chronic illness and treatment undertaken for illness and ulcer.

The ulcer was assessed for Location, Shape and size, Edge and margins**,** Base and floor**,** Discharge**,** Depth**,** Surrounding skin**,** Fixity to deeper structures, Any associated disease **(**Diabetes mellitus, Vascular disease**,** Neuropathy)

Appropriate investigation like routine complete blood count, blood sugar, serum cholesterol, serum albumin, wound swabs taken from ulcer discharge for culture and sensitivity.

Management:

Anaemia, nutritional deficiencies and hypoprotenemia treated appropriately. The protocol to be followed in management was as follows:

1. Local management of wound
2. Management of associated condition
3. Antibiotic therapy
4. Rehabilitation, patient education and instruction.

Material used:

1. Collagen granules (particles).
2. Conventional dressing as dressing with antiseptic material.

Method of Application:

Debride and clean the wound and leave the wound moist to facilitate the action of collagen granules (Medifil).

The material used for collagen dressings is Medifil. Medifil is in the form of particles. It is a spherical hydrophilic particle 0.1 to 0.3 mm in diameter. Each gram of collagen about 40 to 60 times its weight in fluid absorption causes suction and capillary action in spaces between particles. It is available in 2.5, 5, 10 and 15 ml packets.

Lightly sprinkle just enough to completely cover the surface of the wound bed and apply moist gauzes as secondary dressing. Secondary dressing must maintain a moist wound environment. Cover with absorbant dressing pads. Change collagen daily until infection is resolved. Once the infection is reduced the change frequency can be extended to once even 2-3 days until wound closure is achieved.

Conventional Dressing: Dressing with antiseptic solution like povidone iodine, saline, eusol, etc.

HYDROGEN PEROXIDE: It is use as debriding agent in sloughly/necrotic wounds when hydrogen peroxide is applied to a wound it combines with catalase produced in the tissue and decomposes into oxygen and water, producing effervescence (Potter and Perry, 1993). This helps to loosen materials that might hinder wound recovery and enables them to be washed off move readily six-percent W/V hydrogen peroxide (known as '20 volume' solution) liberates twenty times its own volume of oxygen upon decomposition (Thomas 1990) and is generally diluted 1 in 3 for the irrigation of wounds. The release of oxygen also kills some anaerobic bacteria that might otherwise infect the wound. This anti-microbial action of hydrogen peroxide can be amplified 100-fold by addition of L-cysteine (Berglin et al., 1982). Hydrogen peroxide also damage the healthy cells (Keratinocytes and fibroblasts) that are needed for wound healing and inhibit their necessary migration into the

damage area (Tantal, Leigh and Gibesion, 1990, O Toole, Goel and Woodley 1996). Now hydrogen peroxide is listed under "Astribens, oxidisers and dyes" and not as a desloughing agent.

POVIDONE - IODINE : Polyvinylpyrrolidone iodine : PVP-I which consist of a water soluble complex of element iodine and a synthetic polymer, have a broad antimicrobial spectrum, and have not been reported to develop bacterial resistance. Four forms of PVP-I were evaluated: PVP-I solution, PVP-I skin cleanser/surgical scrub, PVP-I oint and PVP-I cream. PVP-I solution had no deleterious effect on wound healing. PVP-I skin cleanser/surgical scrubs contain ammonium monoxynol-4-sulphate and lauramide DEA which like all detergents can cause tissue damage and delay healing.

EUSOL: It contains chlorinated lime 1.25 gm, Boric acid 1.25 gm, purified water add 100 ml. It contains approximately 2500 PPM of 'available chlorine' used as a disinfecting solution and as a wet dressing. EUSOL should be freshly prepared within 2 weeks of manufacture.

The ulcers were compared for healing at end of 1st, 2nd, 3rd, 4th and 6th week. The healing process was divided into complete healing, incomplete healing, partial healing and no healing.

III. Results

Our study is a hospital based, randomised case control prospective study done in the 100 patients of chronic ulcers attending surgical out-door or admitted in the Department of General Surgery, J.L.N. Hospital & Associated Group of Hospitals, Ajmer.

Most patients (80%) with ulcers were male.

Majority of patients were in the age group of 41-60 years.

Most common site of ulcer was foot and diabetic etiology was the commonest (30%) followed by infective etiology in 25%, rest 17% were traumatic, 13% postoperative, 10% were venous and 5% were arterial ulcers.

Stage of healing at different time is in following table:

Stage of Healing	**% of patients**									
	1st week		**2nd week**		**3rd week**		**4th week**		**6th week**	
	Study group	**Control group**	**Study group**	**Control group**	**Study group**	**Control group**	**Study group**	**Control group**	**Study group**	**Control group**
Complete healing	20	0	32	4	42	8	50	16	70	28
Near complete healing	30	8	42	20	38	22	32	28	24	36
Partial healing	42	16	18	24	14	30	14	22	4	16
No healing	8	76	8	52	6	40	4	34	2	20

There was significant difference in the result of collagen granules and conventional dressing. Collagen granules had better healing response rate and occasionally dramatic response.

Topical application of collagen granules was found to be free of any significant local, allergic and systemic reactions even after 6 weeks of application.

The treatment with collagen granules is cost effective as compared to conventional dressing in consideration of cost of hospitalization and prevention of morbidity related to amputation in diabetes and peripheral vascular diseases.

IV. Discussion

Ulcers are a troublesome clinical problem. Ulcers are associated with pain and suffering and take months to heal. It leads to loss of working hours, hospitalization and great inconvenience both to the patient and family.

For the treatment of ulcers a variety of clinical measures have been used and despite treating the underlying etiology which may be post operative, post traumatic, arterial disease, venous ulcers and a host of other conditions they do not heal.

To accelerate healing various treatment modalities have been used from time to time. We used collagen granules dressing in our study.

In our study majority of patients 84% were male. This could be due to the fact that males are outdoor workers and more prone to traumatic injuries.

In a similar study by KM Rai et al with collagen particles, male patients were 78% and females were 22%. In the study of Yash Bhargav male patients were 73.33% and female patients were 26.67%. These results are similar to our study.

Maximum patients (29%) in our study were in the age group of 41-50 years and 19 (19%) in age group of 51-60 years. This shows that around 50% patients were in the age group of 4l-60 years in our study. The minimum age of patient was 23 years and maximum age was 70 years.

In the study by VK Shukla et al 62% cases belonged to 40 and above age group while in another study of 50 patients by KM Rai et al with collagen particles age range was 18-74 years. These data show that

maximum patients are in the most productive group of society and these chronic ulcers are a cause of great expense to individual and community.

There were 40 (40%) patients of ulcer foot, 26 (26%) patients of leg ulcer in our study. In contrast in the study by VK Shukla there were predominantly ulcer foot (61%) and leg ulcer (19%). In our study other sites and trunk ulcers constituted 34% of cases whereas only 20% cases constituted the same in study of VK Shukla. Ulcers of different etiologies were selected in our study. Maximum 30(30%) ulcer were diabetic, 25 (25%) were of infectious etiology, 17 (17%) traumatic, 13(13%) postoperative, 10 (10%) venous and 5(5%) were arterial. In contrast in study by VK Shukla et al. maximum cases were leprotic ulcers which showed remarkable healing in study group. In his study 34% cases were leprotic, 19% diabetic, 19% traumatic, 14% venous and 14% ulcer of other etiological were taken. There was no patient of leprosy included in our study. Again in contrast in the study done by K.M. Rai et al. 30% ulcers were venous, 18% arterial, 26% neurogenic, 14% diabetic and 12% ulcers were of other etiology.

In our study we divided our results as:

1. Complete healing stage (showing 100% healing),
2. Near complete healing stage (showing 50% and more healing),
3. Partial healing stage (showing less than 50% healing) and
4. No healing stage (showing no healing response).

After 1st week there was complete healing in 20%, partial healing in 42% cases in study group. Maximum patients were in no healing stage in control group (76%) but in study group only 8% showed no healing response. In a study by Yash Bhargav in year 1992 on diabetic ulcers, there were 17.75% patients in study group showing complete healing, 48% showing partial healing and 10% showing no healing after 1st week. In a study by Dr. Pankaj Kumar Jain in year 2008 on chronic ulcer, there were 20% in study group showing complete healing, 48% showing partial healing, and 8% showing no healing after 1st week.

In our study after 2 weeks treatment with collagen granules 16 (32%) ulcers showed complete healing and 21 (42%) ulcers showed near complete healing. Maximum patients 12 (24%) were in partial healing stage in control group in comparison to collagen granules 9 (18%) group after 2 weeks treatment. There were 52% patients still not showing any kind of healing response in control group. In a similar study done by Yash Bhargav after 2 weeks treatment with collagen granules 30% patients showed complete healing and 42% showed near complete healing. In contrast in study done by VK Shukla 36% patients showed complete healing and 40% showed near complete healing after 2 weeks treatment.

After treatment of 4 weeks in our study 50% patients showed complete healing and only 4% showed no healing in comparison to study done by VK Shukla whose 58% patients showed complete healing and 5% patients showed no healing. The results are almost similar in both the studies.

After 6 weeks follow up in collagen granules group 70% patients showed complete healing response and only 24% near complete healing, 4% partial healing and 2% showed no healing response as compared to only 28% with signs of complete healing, 36% in near complete healing, 16% partial healing and no sign of healing in 20% in control group. Thus, there is vast statistical difference between the two groups.

Pankaj Kumar Jain's study showed complete healing in 60% and near complete healing in 28% with collagen particles after six weeks treatment. Our results were slightly better (70 vs 60%) than his study at six weeks.

Anil Mehtani et al studied the role of collagen dressings in foot ulcer patients and concluded that significant (90%) improvement was found in ulcers in 10 weeks. These results were superior to our study.

A comparative study by KM Rai et al (1986) with collagen granules showed that ulcers took a mean of 39 days to heal. All ulcers treated with collagen healed whereas 8% in control failed to heal after 9 months of treatment. Thus there is similarity with our results where 70% ulcers healed after six weeks treatment.

Ramkumar et al. (1993) showed that treatment of leprosy ulcers with collagen particles demonstrate complete wound healing in 50% patients at 7 to 10 days and in rest 50% at 10 to 14 days. In contrast only 20% of patients showed same results in our study.

In the study of Manu Shankar and Chintamani et al (1998) on different ulcers 44.44% patients showed complete healing and 38.88% showed over 80% healing after 21 day treatment with collagen granules. We studied after 4 weeks (28 days) and found 50% complete healing and 32% near complete healing.

Palmieri B in his study of 72 patients with different type of skin ulcers demonstrated that in all cases wounds healed significantly quicker when treated with collagen granules. His findings are corroborated by our study. Steven A et al showed that average time taken to complete healing was 6.1 weeks which are similar to our studies (6 weeks).

In study of F. Carcano et al. (1991) 70 patients of chronic ulcer treated with collagen granules, healing process in term of scar formation was very good in 70% of patients as compared to 43% of patients in control

group. The period in study was 11 to 33 days. In contrast 50% of our patients showed very good healing in collagen group compared to 12% in control group.

Our results are also comparable to study of Gerderon et al. (2001) on diabetic patients. He found ulcers to heal in 74±31 days with collagen granules and 92±2 5 in control group with significant P values (P=0.008).

Use of collagen granules decreases not only wound healing time but also grafting procedures are decreased. This was proved in a trial in (2001) by Jan R. et al. Similar results were seen in our study where wound healed with collagen granules and grafting was avoided altogether.

Collagen granules have shown good results in our study. Collagen granules are able to create condition essential for good connective tissue organization which requires fibroblast interaction between mucopolysacharides and collagen.

Hyper granulation in 2(4%) patients, burning sensation zero (0%), hyper pigmentation zero (0%) and itching in one (2%) patient was observed with collagen granules application in our series.

In contrast in study done by VK Shukla, 13% patients showed hyper granulation, 2% showed burning sensation, 9% showed hyperpigmentation and 2% showed itching. The incidence of side effects was low in our study.

No doubt till today such kind of dressings are very costly affair in our country, but if we consider the cost of hospitalization and if we can prevent amputation in diabetes and peripheral vascular disease, then these therapies seems to be very logical. Hence such kind of dressing with collagen granules is good option for ulcer. The advantage of early healing and mobilization with early return to work, saving man-hours and finances, definitely outweigh the disadvantage of cost factor. Thus we advocate the routine use of collagen granules in dressing of ulcer.

V. Conclusion

Considering the observations of this study we conclude that collagen granules are a useful topical agent to be applied locally to all types of ulcers except malignant ulcers. Collagen granules enhances the healing process, as evident by early appearance of red granulation tissue and epithelization, smaller lag period in healing and early completion of healing of ulcers.

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