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Original Research Article

A comparative study of collagenase ointment versus povidone-iodine dressing in non-healing ulcers

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ABSTRACT

Background: The aim of the study was to evaluate effect of collagenase ointment and povidone-iodine on non-healing ulcer in the form of duration of ulcer covered with red granulation tissue and total hospital stay.
Methods: The Study was conducted on 80 patients admitted in Surgery Department, SSG Hospital and Medical College Baroda, Gujarat, India during November 2006 to October 2008. All ulcers due to trauma, chronic ulcer or infected ulcer following debridement and incision and drainage were included in this study. In group A were wounds dressed in collagenase ointment and in group B were wounds dressed in povidone-iodine ointment till second surgery or complete healing. All data from both groups were collected and analyzed by chi-square test.
Results: In this study, there was no difference in age distribution ($p=0.62$, $p>0.05$) with similar male to female ratio in both groups and also no significant difference in distribution of wounds size in both groups ($p=0.92$, $p>0.05$). Average size of wound in group A was 43 sq. cm and group B was 44 sq. cm. The significant difference was seen on floor of ulcer by healthy granulation which came on an average of within 11days in group A and within 18 days in group B ($p=0.005$, $p<0.05$). There was also a significant difference in average hospital stay, which was 25 days in group A and 35 days in group B ($p=0.01$, $p<0.05$).
Conclusions: Collagenase ointment is clinically more efficient as a topical dressing and lowers the morbidity by reducing the hospital stay and the duration of dressing by promoting healing in non-healing wounds than povidine-iodine ointment.

Keywords: Collagenase, Non-healing ulcer, Povidine-iodine, Wound dressing

INTRODUCTION

The earliest accounts of wound healing dates back to about 2000 B.C., when the Sumerians employed two modes of treatment: a spiritual method consisting of incantations and a physical method of applying poultice-like materials to the wound.[1] The Egyptians were the first to differentiate between infected and diseased wounds compared to non-infected wounds. Wounds are classified as either acute or chronic. Acute wounds heal in a predictable manner and time frame.[2] The process occurs with few, if any, complications, and the end result is a well-healed wound. Surgical wounds can heal in several ways. An incised wound that is clean and closed by sutures is said to heal by primary intention. Often, because of bacterial contamination or tissue loss, a wound will be left open to heal by granulation tissue formation and contraction; this constitutes healing by secondary intention.[3]

All the surgeons in their practice of surgery have to face the problem of infected ulcers. The nature of infection

may differ, as does the type of surgery but sepsis still threatens many patients. After the first world war in 1919, Sir Alexander Fleming in his lecture on antiseptics said, "It seems a pity that surgeon should wish to share his glory with chemical antiseptic of more than doubtful value.".[4,5]

Wide use of antibiotic therapy in last decade has not decreased the overall incidence of surgical infection. From their inception, antibiotics have been regarded as safe drugs of wide application but, consequently they have been misused. As a result, the value of these agents has been undermined, for they are not without side-effect like allergy. An infection by opportunistic organism leads to emergence of resistant strains.

The surgical practice primarily depends upon the healing of wounds without serious complication and infection occurring in post-operative or accidental wounds and wounds of violence can have significant effect on the patient's mortality and morbidity, as well as on the wound infection. Many surgeons have anticipated a marked decrease in incidence of post-operative wound infection after the introduction and general use of antibiotics and local antibacterial agent.

In the treatment of infected wounds, the use of a topical antiseptic is adjunctive to the meticulous application of the principles of good surgical technique.[4,5] The ideal antiseptic is one that is rapidly lethal to all the forms of the bacteria and their spores, capable of bactericidal activity for prolonged periods, has no injurious effect on the wound tissues or skin, delineates the operative site and can be easily applied and removed. Collagenase ointment is topical agent which is used locally and thought to promote healing of ulcer with less pain. It also has most of the properties of an ideal topically applied dressing material.

These dressing materials applied over ulcer need to be painless, nontoxic, soothing and should require less frequent dressing, simultaneously promoting healing process to be best for the patient's health and emerge the need of developing a dressing material which fulfills these criteria.[4,5]

METHODS

This was a prospective interventional randomized comparative study conducted on 80 patients coming to Department of Surgery, SSG Hospital and Medical College Baroda, Gujarat, India during November 2006 to October 2008. By simple randomization, all patients were divided into two groups. In group A, 40 patients with ulcer underwent dressing with collagenase ointment and in group B, 40 patients with ulcer underwent dressing with povidone-iodine ointment till the second surgery or complete healing.

On presentation, a thorough history was taken regarding the complaints and their duration, progress and contributing factors to the non-healing of ulcer. The patients having various diseases were matched considering the clinical nature of non-healing ulcer.

No distinct criteria were led on for patient matching except for good, thorough and detailed clinical examination. Routine investigation like haemogram and urine analysis was done in all the patients. Special investigations were done as per requirements. Wound culture sensitivity test was done in all ulcers and according to that antibiotics were started. In traumatic and contaminated wounds, the wound was cleaned thoroughly and debridement was done. When slough was present, it was removed.

The method of dressing was same for all the patients. The surrounding area of the wound was cleaned with saline commencing from the edge of the wound to distal area. The wound was cleaned with saline solution. All the discharge or the pus was wiped out. If there was any loose slough, it was removed. Then the wound was covered either collagenase ointment or povidone-iodine ointment.

The amount of collagenase ointment and povidine-iodine ointment used in each wound was decided from the size of wound, the depth of the wound and the amount of discharge. It differed in each patient and at times in the same patient. During the daily examination of the wound, following points were noted: reduction of discharge, reduction in pain, reduction in edema, nature of granulation tissue, reduction in amount of slough and condition of wound healing. Data was analyzed by chi-square test.

Once the wound was clinically no more infective and in healing stage, it was either dressed till it healed completely by epithelization or grafted with split thickness skin. The total duration for the wound healed was decided on clinical examination and further study of the wound was terminated. However, on follow up the healing of the wound was noted and the part on which the wound presented on body was examined for any loss of function.

RESULTS

The present study of 80 patients prospectively randomized into group A (collagenase ointment group) and group B (povidone-iodine group) of 40 patients each, was conducted with inclusion of same graded wounds in both groups. Table 1 shows age distribution in both groups. More patients between 20-60 years were included in this study. There was no significant difference in distribution of age in both groups ($p=0.62$, $p>0.05$) (Table 1).

Table 1: Age distribution.

Age (years)	No. of patients in study (%)		P value
	Group A	Group B	
0-19	6 (15%)	6 (15%)	0.62
20-39	13 (32.5%)	8 (20%)	
40-59	14(35%)	18 (45%)	
60-79	7 (17.5%)	8 (20%)	

In this study, there was equal distribution of male and female patients in each group with 31 males (77.5%) and 9 females (22.5%) out of 80 with M: F ratio of 3.4:1. Table 2 shows patients presented with infected ulcers were 87.5% and 82.5% in both groups A and B, trophic ulcers were 10% and 7.5%, gangrenous toes/foot were 0% and 5% and varicose ulcers were 2.5% and 5% respectively. In causes of ulcer, spontaneous onset was 57.5% and 55% in group A and group B, insect bite/animal bite were 7.5% in each group, traumatic were 35% and 32.55% and amputated were 0% and 5% respectively (Table 2).

Table 2: Distribution of patients according to presenting lesion and causes of ulcer.

Presenting lesion	Group A	Group B
Infected ulcer	35 (87.5%)	33 (82.5%)
Trophic ulcer	4 (10%)	3 (7.5%)
Gangrene of toes/foot	0	2 (5%)
Varicose ulcer	1 (2.5%)	2 (5%)
Causes		
Spontaneous	23 (57.5%)	22 (55%)
Insect/animal bite	3 (7.5%)	3 (7.5%)
Trauma	14 (35%)	13 (32.5%)
Post gangrene (amputation)	0	2 (5%)

Table 3 shows the distribution of patients having different size of wounds. No significant difference in size distribution of the wounds was noted in both groups (p=0.92, p>0.05) (Table 3).

Table 3: Distribution of patients according to size of ulcer.

Size (sq. cm.)	No. of patients in present study		p-value
	(Group A)	(Group B)	
Up to 10	5 (12.5%)	6 (15%)	0.92
11-25	18 (45%)	20 (50%)	
26-50	10 (25%)	8 (20%)	
51-75	5 (12.5%)	3 (7.5%)	
76-100	2 (5%)	3 (7.5%)	
Average size of the wound	43 Sq. cm	44 Sq. cm	

Table 4 shows the time taken for the total coverage of floor of ulcer by healthy granulation tissue. The average days were 11 days in group A and 18 days was in group B. The level of significance in both group of the study is p=0.005 (p<0.05) which suggests there is a significant difference of appearance of granulation tissue in both groups (Table 4).

Table 4: Distribution of patients according to duration taken for coverage of ulcer floor by healthy granulation tissue.

Days	No. of patients in present study		P value
	(Group A)	(Group B)	
6-10	12 (30%)	10 (25%)	0.005
11-15	15 (37.5%)	12 (30%)	
16-20	10 (25%)	6 (15%)	
21-25	3 (7.5%)	6 (15%)	
26-30	0	4 (10%)	
31-35	0	2 (5%)	
Average days	11 Days	18 Days	

Table 5 shows number of patients who required any intervention for healing after floor of ulcer covered with healthy granulation tissue either by continued dressing or skin grafting/ suturing.

Table 5: Distribution of patients according to surgical intervention for healing.

Surgery	No. of patients		P value
	Group A	Group B	
Conservative (dressing)	25	21	0.37
Skin grafting/ Secondary suturing	15	19	

Table 6: Total hospital stay.

Days	No. of patients in present study		P value
	(Group A)	(Group B)	
1-10	11(27.5%)	7 (17.5%)	0.01
11-20	21 (52.5%)	14 (35%)	
21-30	5 (12.5%)	14 (35 %)	
31-40	2 (5%)	2 (5%)	
41-50	1 (2.5%)	3 (7.5%)	
51-60	0	1 (2.5%)	
61-70	0	5 (12.5%)	
Average days	25 days	35 days	

Conservative and skin grafting/suturing management were required in 25 and 15 patients in group A and 21 and 19 patients in group B respectively. There were no significant differences, but more number of patients were managed conservatively and less by skin grafting/suturing in group A than group B (Table 5). Table 6 shows average hospital stay of patients in this study which was 25 days in Group A and 35 days in

group B. The level of significance between two groups was p <0.01, suggestive that collagenase ointment is highly significant in reducing total hospital stay in the patients (Table 6).

During this study, it was observed that collagenase ointment was very effective for reducing pain at wound site and patients with non-healing ulcers with malnutrition, anaemia, hypoproteinemia had given better results when compared to povidone-iodine ointment. Rashes or itching, blisters or allergic manifestations or super-added fungal infection had not developed in any patients treated with collagenase or povidone-iodine ointment.

DISCUSSION

This study was conducted on 80 patients coming to Department of Surgery, S.S.G Hospital, Baroda, Gujarat, India during November 2007 to October 2008 for the efficacy of collagenase ointment dressing in treatment of non-healing wounds as compared to dressing with povidone-iodine ointment dressing. In present study, comparing age distribution in two groups, P value is 0.62 which means there is no significant difference in age distribution in the study with ratio of male: female being 3.4:1 in both the groups. Present study was compared with other studies done by Marazzi M et al in 2006 and Palmieri B et al in 1998.[6,7] Palmieri B et al had similarly compared effect of collagenase ointment and placebo ointment, and Marazzi M et al had compared collagenase ointment with conventional method over chronic wound.

Palmieri B et al had included average wound size 56 sq.cm and 60sq.cm respectively and Marazzi M et al had included 48 sq.cm and 42 sq.cm in both methods respectively in their study (Table 7). In present study, average size of wound was 43 sq. cm. and 42 sq. cm. with p <0.92, suggesting that there was no significant difference in size distribution of wounds in both the groups.

Palmieri B et al had also observed that application of collagenase ointment over chronic ulcer reduces 10 days to cover the ulcer with granulation tissue compared to placebo ointment (Table 7). Marazzi M et al had also observed that application of collagenase ointment over chronic ulcer leads to early coverage of complete granulation tissue compared to conventional method of dressing (Table 7).

Table 7: Comparison of present study with others study.

	Present study		Palmieri B et al[6]		Marazzi M et al[7]	
	Group A	**Group B**	**Collagenase ointment**	**Placebo**	**Collagenase ointment**	**Conventional**
Average size of the wound	43Sq.cm	44Sq.cm	56Sq.cm	60Sq.cm	48Sq.cm	42Sq.cm
Coverage of granulation tissue over floor	11 days	18 days	15 days	25 days	23 days	36days
Total hospital stay	25 days	35 days	28 days			

In present study, it was observed that the ulcer is completely covered by granulation tissue within 11 days in group A which was earlier than in group B which was 18 days suggesting a significant difference (p<0.005) in covering ulcers with granulation tissue between collagenase and povidone-iodine ointment dressing.

Palmieri B et al had observed that total hospital stay in application of collagenase ointment over chronic ulcer was 12 days less than in placebo ointment group. The level of significance was p<0.001 suggesting that collagenase ointment application significantly reduces the total hospital stay in patients with chronic ulcer (Table 7).

Marazzi M et al had also observed that total hospital stay in collagenase ointment group was 46 days compared to 63 days in conventional dressing group. The level of significance was p <0.001 suggesting that collagenase ointment is very effective in reducing the total hospital stay compared to conventional dressing (Table 7). In present study, it was observed that total hospital stay in group A was 25 days including surgical treatment while in group B it was 35 days. The level of significance between two groups is p<0.01 suggestive that collagenase ointment is highly significant in reducing total hospital stay in the patients.

On comparing it seems that there is significant difference in reducing amount of slough and total hospital stay with collagenase ointment compared to conventional treatment in chronic non-healing ulcers. Collagenase helps in removing slough from the tissue as well as helps in formation of new granulation tissue fast. It also helps in contraction of the wound and prevents from forming hypertrophied scar after healing.

Collagenase ointment dressing is easy to apply and does not stain the clothing. Resistant strains do not develop

following the use of collagenase ointment. It acts synergistically with antibiotics. It promotes healing faster than povidone-iodine ointment and saline dressing without causing interference to granulation tissue. From both routine daily clinical examination and statistically, it was proved that collagenase ointment was more efficient as topical dressing material compared to povidone-iodine and saline dressing. Hence, we concluded from this study that collagenase ointment satisfies most of the criteria of an ideal dressing material, and in coming years it has the potential to become a gold standard for dressing of non-healing ulcers.

CONCLUSION

Collagenase ointment was clinically more efficient as a topical dressing material in non-healing wounds. It lowers the morbidity by reducing the dressing duration and hospital stay by promoting healing in non-healing wounds. Collagenase ointment was an ideal topical dressing material without adverse effects, during its topical use as a dressing material over patients with non-healing wounds, so it was more effective in local wound management as compared to povidone-iodine dressing used topically.

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