IOSR Journal of Dental and Medical Sciences (IOSR-JDMS)
e-ISSN: 2279-0853, p-ISSN: 2279-0861.Volume 22, Issue 2 Ser.11 (February. 2023), PP 20-27
www.iosrjournals.org

A Comparative Study of Combination of Collagenase and Metronidazole Versus Povidone Iodine In Non-Diabetic Ulcers OfLower Limb

Bathena Sobha Rani[1], Budamala Sarada[2] , Policherla Maha Lakshmi[3], KorukondaVinod Kumar[4], Menta Yaswanth Kasyap[5], G Dinesh Kumar Yadav[6]
[1](Professor and HOD, Department of General Surgery, S.V.Medical College, Tirupati)[2](Associate Professor, Department of General Surgery, S.V.Medical College, Tirupati)[3](Senior Resident, Department of General Surgery, S.V.Medical College, Tirupati) [4](PostGraduate, Department of General Surgery, S.V.Medical College, Tirupati) [5](PostGraduate, Department of General Surgery, S.V.Medical College, Tirupati) [6](PostGraduate, Department of General Surgery, S.V.Medical College, Tirupati)

Abstract:
Background*: The dressing of wounds is an old art and has undergone a wide variety of changes from ancient herbal dressing to modern dressing materials. The main aim was always to heal the wounds. Wounds and their management are fundamental in the practice of surgery. The prevalence of leg ulceration is approximately 1% to 2%, and is slightly higher in the older adult population. Leg ulcers are an increasing problem worldwide and represent a major health care burden. Patients with leg ulcers are managed by clinicians in multiple specialties, including primary care, vascular surgery, plastic surgery, podiatry, wound care, and dermatology. A leg ulcer is a physical finding that can result from multiple etiology most common due to-Venous disease (estimates range from 40to 80%),Arterial diseases,Neuropathic diabetic foot and Other risk factors include --- trauma, vasculitis, diabetes and neoplasia, rheumatoid arthritis, infective etiology and others. Thus, determination of the causeis essential for selecting appropriate treatment and determining the need for furtherevaluation.All leg ulcers represent a failure of the underlying vessels to effectively transport blood to and from the lower limbs. Most leg ulcers are slow to heal with up to 68% of cases recurring within a two-year period. Chronic leg ulcers are usually associated with significant morbidity, high cost ofhealthcare, loss of productivity, and reduced quality of life. An ideal wound care product in addition to control the infection should also protect the normal tissues andmust not interfere with the normal wound healing. The main aim of the study was to compare the newer dressing materials (Topical collagenase and metronidazole) versus the conventional dressing materials.*
Materials and Methods*: This study was conducted in the Department of General Surgery, SVRRGGH, Tirupati. The materials for the study were collected from patients presenting to surgery outpatient department and emergency with the features of non diabetic ulcers of lower limb during the period of March 2020 to April 2021 were included inthe study.*
Results*: The demographic profile in the Collagenase + Metronidazole group shows mean age in years was 36.62 ±8.76; more prevalence in males and the Povidone Iodine group mean age in years was 39 ± 7.81 ; 52% were male. Based on etiologic, In Collagenase + Metronidazole group, 42% due to Trauma, 28% due to Pressure ulcerand in Povidone Iodine group, 34% of ulcers due to Trauma, 34% due to Pressure, The mean duration in weeks in Collagenase + Metronidazole group was 15.72 ± 4.15. And in Povidone Iodine group, mean duration in weeks was 13.74 ± 3.70. In accordance with Wagener grading, in collagenase + Metronidazole group 42% were Grade 2 and 58% were in Grade 3. In povidone iodine group, Grade 2 in 44% and Grade 3 in 56%. Size of wound in area in mm2 before treatment, the mean in Collagenase + Metronidazole group was 2605.54 ± 733.82 and in Povidone Iodine group was 2699.70 ±680.73. The mean Percentage reduction in area in mm2 after treatment in Collagenase*
+ Metronidazole group was 40.57 ± 9.68 and in Povidone Iodine group was 16.58 ± 12.27. Organisms in Collagenase + Metronidazole group it were Staph Aureus (28%), Proteus (6%), E.Coli (2%), and Klebsiella (4%). In povidone Iodine group, 38% had Culture positive for Staph Aureus, Proteus (8%), E.Coli (10%).Granulation tissue observed in 2nd week in Collagenase + Metronidazole group was 40% and in Povidone iodine group it was 14%.Slough and Discharge in Collagenase + Metronidazole group was 12% and in povidone iodine group was 44%.
Conclusion: *Both i.e the collagenase and metronidazole dressings and povidone iodine dressings are equally effective in the treatment of non- diabetic ulcers of lower limb.The main aim of the study was to prepare the wound to be free of necrotic tissue andremove the dead cells from the bed of the ulcer using collagenase and*

metronidazole which results in wound with a healthy granulation tissue for rapid wound healing.In this study it was observed that the by collagenase and metronidazole there was better reduction in slough, promotes granulation tissue formation and wound healing. This study shows that collagenase and metronidazole combination proved to havebetter wound bed preparation

Date of Submission: 05-02-2023 Date of Acceptance: 17-02-2023

I. Introduction

An ulcer is defined as a breach in the continuity of skin and mucous membrane. [1] Chronic ulceration of the lower limb including the foot is a frequent condition leading to pain, social discomfort and generating significant cost implications; Prevalence number (all ulcers) range from 1 % in the adult population to 3-5 % in the population over 65 years of age.[1,2]

A leg ulcer is a physical finding that can result from multiple etiologies most commonly due to-

- Venous etiology (estimates range from 40 to 80%),
- Arterial etiology,
- Neuropathic diabetic foot and
- Other risk factors like Trauma, diabetes, neoplasia, infective etiology and others; Thus, determination of the cause isessential for selecting appropriate treatment and determining the need for further evaluation.[3]

All leg ulcers represent a failure of the underlying vessels to effectively transport blood to and from the lower limbs; most leg ulcers are slow to heal with up to 68% of cases recurring within a two-year period.[4]

Chronic leg ulcers are usually associated with significant morbidity, high cost of healthcare, loss of productivity, andreduced quality of life. Ideal wound care is control of the infection along with preserving the normal tissue.

The main aim of the study was to combine collagenase and metronidazole dressings versus povidone iodinedressings in non-diabetic ulcers of lower limbs.

II. Material And Methods

This study was conducted in the Department of General Surgery, SVRRGGH, Tirupati. The materials for the study were collected from patients presenting to surgery outpatient department and emergency with the features of non diabetic ulcers of lower limb during the period of March 2020 to April 2021 were included inthe study.

Study Design: Prospective open label observational study

Study Location: This was a tertiary care teaching hospital based study done in Department of General Surgery, atSVRRGG Hospital, Tirupati, Andhrapradesh.

Study Duration: March 2020 to April 2021.

Sample size: 100 patients.

Inclusion criteria:

1. Informed and Written consent
2. Patients between 20-50 years of age.
3. Non-diabetic ulcers of size 2 to 10 cm of lower limb.
4. Wagner's of grade 1 to 4.

Exclusion criteria:

1. Patients with clinical signs of infection and cellulitis.
2. X-RAY of patients showing osteomyelitis.
3. Doppler study showing gross Atherosclerotic arterial changes and venousabnormalities like varicosities.
4. Patients receiving corticosteroids, immunosuppressiveagents, radiation chemotherapy.

The eligible patients divided into test group and control group by alternate selection method.

III. Result

Table no 1 Shows In the present study, in Collagenase + Metronidazole group 32% were in 21-30 yearsage group,26% in 31-40 years age group, 42% in 41-50 years age group. The meanage in years was 36.62 ± 8.76

In Povidone Iodine group 16% were in 21-30 years age group, 18% in 31-40 yearsage group, 48% in 41-50 yearsage group. The mean age in years was 39 ± 7.81..

There was no statistically significant difference observed between the two groupswith relation to age as the p valuecalculated to be >0.05

Table no 1

	Collagenase + Metronidazole Group		Povidone Iodine group	
21 – 30	16	32.0%	8	16.0%
31 – 40	13	26.0%	18	36.0%
41 – 50	21	42.0%	24	48.0%
Total	50	100%	50	100%
Mean ± SD	36.62 ± 8.76		39 ± 7.81	
Chisquare test = 3.67 , p=0.15 , Not statistically significant				

Table no 2 shows In the Collagenase + Metronidazole group, 60% were male and 40% were female. In PovidoneIodine group, 52% were male and 48% were female.
There was no statistically significant difference observed between the two groupswith relation to gender as the p value calculated to be >0.05.

Table no 2

	Collagenase + Metronidazole Group		Povidone Iodine group	
Male	30	60%	26	52%
Female	20	40%	24	48%
Total	50	100%	50	100%
Chisquare test = 0.64, p=0.42 , Not statistically significant				

Table no 3 shows Based on Etiology In Collagenase + Metronidazole group, 42% due to Trauma, 285 due toPressure ulcer, 26% due to Venous ulcers, 4% due to Burns.
In Povidone Iodine group, 34% of ulcers due to Trauma, 345 due to Pressure, 24%due to Venous ulcers, 8% due toBurns.
There was no statistically significant difference observed between the two groupswith relation to Etiology as the pvalue calculated to be >0.05.

Table no 3

	Collagenase + Metronidazole Group		Povidone Iodine group	
Traumatic	21	42%	17	34%
Pressure	14	28%	17	34%
Venous ulcer	13	26%	12	24%
Burns	2	4%	4	8%
Chisquare test = 3.67 , p=0.15 , Not statistically significant				

Table no 4 Shows Based on Site of ulcer, In collagenase metronidazole group Dorsal (22%), Plantar(20%), MedialMalleoli (12%) and Lateral Malleoli (46%)
In Povidone iodine group, Dorsal (20%), Plantar (18%), Medial Malleoli (24%) andLateral Malleoli (38%)
There was no statistically significant difference observed between the two groupswith relation to site of ulcer as the pvalue calculated to be >0.05

Table no 4

	Collagenase + Metronidazole Group		Povidone Iodine group	
Dorsal	11	22%	10	20%
Plantar	10	20%	9	18%
Medial	6	12%	12	24%

Malleoli				

Table no 5 Shows The mean duration in weeks in Collagenase + Metronidazole group was 15.72 ± 4.15. inPovidone Iodine group, mean duration in weeks was 13.74 ± 3.70.
There was no statistically significant difference observed between the two groupswith relation to duration of ulcer inweeks as the p value calculated to be >0.05.

Table no 5

	Collagenase + Metronidazole Group		Povidone Iodine group	
< 10 weeks	7	14%	11	22%
11 – 20 weeks	37	74%	36	72%
> 20 weeks	6	12%	3	6%
Total	50	100%	50	100%
Mean ± SD	15.72 ± 4.15		13.74 ± 3.70	
Chisquare test = 1.90, p=0.38 , Not statistically significant				

Table no 6 shows distribution based on Wagener grade, where in collagenase +Metronidazole group it was Grade 2in 42% and Grade 3 in 58%.
In povidone iodine group, Grade 2 in 44% and Grade 3 in 56%.
There was no statistically significant difference observed between the two groupswith relation to wagener grade asthe p value calculated to be >0.05

Table no 6

Wagener grade	Collagenase + Metronidazole Group		Povidone Iodine group	
Grade 2	21	42%	22	44%
Grade 3	29	58%	28	56%
Total	50	100%	50	100%
Chisquare test = 0.04, p=0.84 , Not statistically significant				

Table no 7 shows distribution based on Slough and Discharge where in Collagenase + Metronidazole group it was12% and in Povidone iodine group it was 44%
There was a statistically significant difference observed between the two groups with relation to slough and Discharge as the p value calculated to be <0.05.

Table no 7

Slough and Discharge	Collagenase + Metronidazole Group		Povidone Iodine group	
Present	6	12%	22	44%
Absent	44	88%	28	56%
Total	50	100%	50	100%
Chisquare test = 12.7, p=<0.0001* ,Statistically significant				

Table no 8 shows distribution based on granulation tissue where in Collagenase +Metronidazole group it was 40%and in Poviodne iodine group it was 14%.
There was a statistically significant difference observed between the two groups withrelation to Granulation tissue asthe p value calculated to be <0.05.

Table no 8

Granulation tissue	Collagenase + Metronidazole Group		Povidone Iodine group	
Present	40	80%	14	28%
Absent	10	20%	36	72%
Total	50	100%	50	100%
Chisquare test = 27.2, p= <0.0001* , Statistically significant				

Table no 9 shows area of wound area in mm2 before and after treatment where a significant difference was observed between the two groups as the p value calculated to be <0.05.

Table no 9

	Collagenase + MetronidazoleGroup	Povidone Iodinegroup	P value
Initial area in mm2	2605.54 ± 733.82	2699.70 ±680.73	0.51
Final area in mm2	1562.91 ±511.95	2282.17 ±704.45	<0.0001*
Initial – final area in mm2	1042.63 ±342.67	417.53 ±235.52	<0.0001*

Table no 10 shows distribution based on Percentage area of reduction in two groups where significant percentage reduction was found in collagenase + metronidazole group compared to Povidone Iodine group as the p value calculated to be <0.05.

Table no 10

	Collagenase + MetronidazoleGroup	Povidone Iodinegroup	P value
Percentage reduction in area inmm2	40.57 ± 9.68	16.58 ± 12.27	<0.0001*

Table no11 shows distribution based on Culture and Sensitivity where in collagenase +Metronidazole group at 1st week 20 were found to be positive and in Povidone iodinegroup 28 were positive.
At 3rd week, 2 were culture positive in Collagenase + Metronidazole Group and 8were positive in Povidone Iodine group.

Table no 11

	Collagenase + Metronidazole Group			Povidone Iodine group		
	1st week	2nd week	3rd week	1st week	2nd week	3rd week
Culture positive	20	7	2	28	11	8
Culture negative	30	43	48	22	39	42

Table no 12 shows distribution based on Organism where in Collagenase + Metronidazole group it was Staph Aureus (28%), Proteus (6%), E.Coli (2%), Klebsiella (4%). In povidone Iodine group, 38% had Culture positive for Staph Aureus, Proteus (8%), and E.Coli (10%).

Table no 12

	Collagenase + Metronidazole Group		Povidone Iodine group	
Staph. Aureus	14	28%	19	38%
Proteus mirabilis	3	6%	4	8%

E. Coli	1	2%	5	10%
Klebsiella	2	4%	0	0%
Chisquare test = 4.35, p=0.22 , Not statistically significant				

IV. Discussion

Antibiotic usage in the recent decade has not reduced the overall incidence of surgical infection. Antibiotics were regarded as safe drugs of wide application from inception but, misused leading to emergence of resistant strains

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.

Objectives of the present study

1. To know the effect of collagenase and metronidazole dressings in non-diabetic ulcers of lower limb.
2. To know the effect of povidone iodine dressings in non-diabetic ulcers oflower limb.
3. To compare outcomes of both modalities in non-diabetic ulcers of lower limb.

To achieve the Objectives an Institutional based Comparative cross sectional study was conducted where patients admitted in S.V.R.R.G.G. hospital with non-diabetic lower limb ulcers were included.
50 patients received Collagenase + Metronidazole dressing and 50 patients received Povidone Iodine dressing.

Demographic profile of Collagenase + Metronidazole group:

Age distribution shows, 32% were in 21-30 years age group, 26% in 31-40 years agegroup, 42% in 41-50 years age group. The mean age in years was 36.62 ± 8.76.

Based on gender, In the Collagenase + Metronidazole group, 60% were male and 40% were female.

Study conducted by Bedi et al[5] shows, majority of the study group were in 41-50 years age group and 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.

Demographic profile of Povidone Iodine group

Age distribution shows In Povidone Iodine group 16% were in 21-30 years age group, 18% in 31-40 years age group, 48% in 41-50 years age group. The mean agein years was 39 ± 7.81. Gender distribution shows, In Povidone Iodine group, 52% were male and 48% were female.

Study by Rahman et al[6] shows, Maximum patients were in the age range of 41-60 years and Male preponderance was seen which is similar to present study.

Etiology

Based on Etiology in Collagenase + Metronidazole group, 42% due to Trauma, 285 due to Pressure ulcer, 26% due to Venous ulcers, 4% due to Burns.

In Povidone Iodine group, 34% of ulcers due to Trauma, 345 due to Pressure, 24% due to Venous ulcers, 8% due to Burns. There was no statistically significant difference observed between the two groups with relation to Etiology asthe p value calculated to be >0.05.

Study by Bedi et al 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.

Size of wound in area in mm2 before treatment

In the present study, the mean Collagenase + Metronidazole group was 2605.54 ± 733.82 and in Povidone Iodinegroup was 2699.70 ±680.73.
Palmieri B et al[7] had included average wound size 56 sq.cm and 60sq.cm respectively and Marazzi M et al[8] had included 48 sq.cm and 42 sq.cm in both methods respectively in their study.
In Bedi et al study, average size of wound was 43 sq. cm. and 42 sq. cm. with p <0.92, suggesting that there was nosignificant difference in size distribution ofwounds in both the groups.

Size of wound after treatment

In the present study, mean Percentage reduction in area in mm2 in Collagenase + Metronidazole group was

40.57 ±
9.68 and in Povidone Iodine group was 16.58 ± 12.27. There was a significant reduction in the wound area as the pvalue calculated to be <0.05.
Palmieri B et al had also observed that application of collagenase ointment over chronic ulcer reduces 10 days tocover the ulcer with granulation tissue compared to placebo ointment.
Marazzi M et al had also observed that application of collagenase ointment over chronic ulcer leads to earlycoverage of complete granulation tissue compared to conventional method of dressing.

Granulation tissue

In the present study, granulation tissue observed in 2nd week in Collagenase + Metronidazole group was 40% and in Povidone iodine group it was 14%.

Bedi et al study 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 18days suggesting a significant difference ($p<0.005$) in covering ulcers with granulationtissue between collagenase and povidone-iodine ointment dressing.

Palmieri B et alhad observed that total hospital stay in application of collagenase ointment over chronic ulcer was 12days 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

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.

Slough and Discharge

In the present study, based on Slough and Discharge where in Collagenase +Metronidazole group it was 12% and inpovidone iodine group it was 44%.

Bedi et al study observed 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.

In the study conducted by Kapur V & Marwaha AK[9] they reported 90% decrease in slough by 18 days (2nd–3rd weeks) with Povidone iodine.

Collagenase ointment dressing is easy to apply and does not stain the clothing; 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

Collagenase ointment is a theoretically selective enzymatic debriding agent derived from the bacterial strain Clostridium histolyticum. It is characterized as selective because it specifically breaks down only one type of protein, collagen, an important component of the extracellular matrix whose selective degradation greatly facilitates healthy wound healing; While excessive matrix metalloproteinase (MMP) activity is a common feature of many chronic wounds, the addition of the bacterial- derived MMP actually provides a benefit to such wounds with debridement, indicating the specificity of collagenase.

According to one systematic review of collagenase for enzymatic debridement, collagenase is an effective, selectivemethod of removing necrotic tissue without harming granulation tissue from pressure ulcers, leg ulcers, and burns. The wound bed preparatory properties of collagenase can be partially attributed to its role in expediting the removal of the necrotic plug. Necrotic tissue isanchored to the wound by strands of denatured collagen; Until these anchoring fibers are severed–thereby allowing the removal of the necrotic plug–debridement cannot take place, granulation is slowed, and no supportive base is available for epithelialization. As described previously, some clinical evidence suggests that collagenase also enhances keratinocyte migration over granulation tissue. In addition Herman and colleagues have shown that matrix pre-treatment with Clostridial collagenase stimulated a two-fold increase in proliferation and post-injury migration of keratinocytes. When the enzyme was added to the growth media, there was approximately five-fold enhancement of keratinocyte proliferation andmigration; the findings fromtheir in vivo swine model have also indicated that Clostridial collagenase promotes epithelial cell proliferation and migration when directly applied to full-thickness wounds. Herman's group attributes thesephenomena to the small collagen split products that act as growth potentiators and signalling ligands.

V. Conclusion

Both i.e the collagenase and metronidazole dressings and povidone iodine dressings are equally effective in the treatment of non- diabetic ulcers of lower limb.

The main aim of the study was to prepare the wound to be free of necrotic tissue andremove the dead cells from the bed of the ulcer using collagenase and metronidazole which results in wound with a healthy granulation tissue for rapid wound healing.

In this study it was observed that the by collagenase and metronidazole there was better reduction in slough, promotes granulation tissue formation and wound healing.

This study shows that collagenase and metronidazole combination proved to havebetter wound bed preparation.

References

[1]. Ryan TG The epidemiology of leg ulcers in diagnosis and treatment (Westerhof W,ed).Amsterdam:Elsevier science publishers BV,1993:19-27.

[2]. Baker SR, Stacey MC,Jopp-McKay AG, et al. Epidemiology of chronic venousulcers. Br J Surg 1991; 78:864-7.

[3]. Casey G. Causes and management of leg and foot ulcers. Nursing Standard2005; 23:601-611.

[4]. Agale SV. Chronic Leg Ulcers: Epidemiology, Aetiopathogenesis, and Management. Ulcers. 2013Apr 22;2013:e413604e

[5]. Bhedi A, Panchal M, Patel H, Sarkar A. A comparative study of collagenase ointment versus povidone-iodine dressing in nonhealing ulcers. Int Surg J 2017;4:1992-6

[6]. Rahaman A, Manjunath A, Bhattacharya AM. Nanosilver versus Povidone iodine dressing-efficacy in the management of chronic diabetic foot ulcers.Journal of Evolution of Medical and Dental Sciences. 2017 Mar 16;6(22):1799- 804

[7]. Palmieri B. A New Formulation of Collagenase Ointment (Iruxol Mono) in the treatment of ulcers of the lower extremities: A randomised, placebocontrolled, double-blind study. Clin Drug Investig. 1998;15(5):381

[8]. Marazzi M. Effect of enzymatic debridement with collagenase on acute and chronic hard-to-heal wounds. J Wound Care. 2006;15(5):222-7.

[9]. Kapur V, Marwaha AK. Evaluation of effect and comparison of superoxidised solution (oxum) v/s povidone iodine (Betadine). Indian J Surg 2011;73(1):48-53.

Bathena Sobha Rani, et. al. "A Comparative Study of Combination of Collagenase and Metronidazole Versus Povidone Iodine In Non-Diabetic Ulcers Of Lower Limb." *IOSR Journal of Dental and Medical Sciences (IOSR-JDMS)*, 22(2), 2023, pp. 20-27.