



A prospective comparative trial of collagenase and metronidazole in the topical management of diabetic foot ulcer

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Abstract

Objective: To assess the efficacy of metronidazole and collagenase combination in the treatment of diabetic foot ulcers with regard to the reduction of slough formation, enhancement of granulation tissue and re-epithelization.

Study design: Prospective, comparative study.

Place and duration of study: Surgery department of a tertiary care teaching centre of rural Haryana, from January 2011 to February 2013.



Methodology: The patients who were admitted for diabetic foot ulcers at Surgery Department of a tertiary care teaching centre during the study period were screened. 42 patients in the test group were treated with topical dressings of collagenase and metronidazole. The control group of 40 patients was treated with conventional topical dressings and bed side debridement. Ulcer's status was noted using visual score.

Results: The number of patients with no necrotic tissue was significantly higher in test group at 3rd, 4th, 5th, 6th and 7th weeks than control group. Granulation tissue was significantly higher in test group at 3rd, 4th, 5th and 6th week. The test group patients had a faster wound bed preparation resulting in faster wound cover using secondary suturing, S.S.G., flap cover at the third week itself.

Conclusion: Combination of collagenase and metronidazole topical application enhanced wound healing of diabetic foot ulcer as compared to conventional treatment modalities.

Key words

Diabetic foot, Collagenase, Metronidazole.

Introduction

Over the past few decades there has been an alarming rise in prevalence of Diabetes [1, 2]. The world health organization (WHO) report says diabetes in India will rise from 135 million in 1995 to 300 million by 2025 and India will become Diabetic capital of World [3]. The risk of ulcers or amputations is increased in people who have had diabetes ≥ 10 years, are male, have poor glucose control, or have cardiovascular, retinal, or renal complications [4].

Foot problems such as ulceration, infection, gangrene are quiet common in Diabetic subjects. These accounts for the frequent and prolonged mortality and a rough estimate yields that 25% of all hospital admission of Diabetes are due to foot problems and nearly 5-10% needs foot or leg amputations, 50% are related to Diabetes [5, 6].

However with proper foot care these problems would be prevented or minimised to a certain extent. Collagenase and metronidazole are being used as one of the topical modalities of

treatment of diabetic foot ulcer [7]. In this context no study has been conducted in our set up. Hence present study was planned to ascertain the efficacy of metronidazole and collagenase combination in the treatment of diabetic foot ulcers with regard to the reduction of slough formation, enhancement of granulation tissue and re-epithelization.

Material and methods

The present prospective, comparative trial was conducted in the patients who were admitted with diabetic foot ulcer in Surgery Department of a tertiary care teaching centre. All the patients admitted for diabetic foot ulcer between Jan 2011 to February 2013 were screened for a period of 2 weeks and those who fulfilled the inclusion criteria were included in study. Finally sample size was 82 out of which 42 were in test group and 40 were in control group.

Inclusion criteria

- Patients aged more than 20 years with diabetic foot ulcer.
- Ulcers of Wagener's Grade II – IV.

Exclusion criteria

- Clinical signs of infection, cellulitis.
- Ulcers of Wagener's Grade V and VI.
- X-ray showing osteomyelitis.
- Doppler showing gross atherosclerotic arterial changes and venous abnormalities like varicosities.
- Malnutrition, uncontrolled diabetes.
- Other clinically significant medical conditions that would impair wound healing including renal, hepatic, hematological, neurological, and immunological diseases.
- Patients receiving corticosteroids, immunosuppressive agents, radiation, or chemotherapy within one month prior to entry into the study were also excluded.

After the initial screening period the eligible patients who required bed side debridement were divided randomly in to test group and control groups. Test group received collagenase ointment with bed side surgical debridement when ever required for wounds / ulcers which had slough in the floor and till granulation tissue appeared. Metronidazole ointment was applied along with it to promote the growth of healthy granulation tissue. Control group received bed side surgical debridement with conventional local antiseptics. Both the test and control groups were matched regarding their age, diabetic status, nutritional status, and grade of ulcer. Wounds were treated once daily until complete debridement or up to seven weeks. The amount of nonviable tissue, degree of wound granulation, and overall wound response was evaluated weekly using a visual score [8]. The final parameters and wound characteristics of the two randomized groups were analysed and compared.

Results

Data of 82 subjects were analysed. Most of the patients fell in the age group between 40 to 70 years. The Mean \pm SD for test group was (57.33 \pm 14.67) and control was (55.35 \pm 14.40). Male and female ratio of the test group was 61.9: 39.1 and the control group was 67.5: 32.5. It was observed in our study most of the patients presented with diabetes mellitus of duration with Mean \pm SD of test group 10.1 \pm 6.72 and control 10.2 \pm 5.62, most of the patients had Grade III and IV ulcers in both test and control groups. The grade of ulcer was statistically similar between the two groups.

Number of patients with no necrotic tissue were significantly higher in test group at 3rd week follow up (P = 0.001), at 4th week (P < 0.001), at 5th Week (P < 0.001), at 6th week (P < 0.001) and at the 7th week (P = 0.002) when compared to control group as per the Chi-Square /Fisher Exact test.

The number of patients with no necrotic tissue was significantly higher in test group at 3rd, 4th, 5th, 6th and 7th weeks with significant p value < 0.002, than control group. Granulation tissue was significantly higher in test group at 3rd, 4th, 5th and 6th week with p value < 0.001. The test group patients had a faster wound bed preparation resulting in faster wound cover using secondary suturing, **S.S.G**, flap cover at the third week itself as per **Table – 1**.

The number of patients with 75-100% wound filled by granulation tissue was significantly higher in test group at 3rd week follow up (P = 0.001), at 4th week (P < 0.001), at 5th Week (P < 0.001), at 6th week (P < 0.001) and at the 7th week (P = 0.024) when compared to control group as per **Table – 2**.

The duration of hospital stay was less in test group compared to control group.

Discussion

Our study presented use of metronidazole and collagenase combination in the treatment of diabetic foot ulcers with regard to the reduction of slough formation, enhancement of granulation tissue and re-epithelization. The patients treated with collagenase and metronidazole gel had faster reduction of slough/ necrotic tissue and increased granulation tissue, compared to study by Alvarez OM, Fernandez-Obregon A, Rogers RS, et al. The study showed that the papain urea debridement ointment was more effective than the collagenase in the 3rd and 4th week recording the reduction of slough, increasing the growth of granulation tissue. In our study patients showed similar improvement in 3rd and 4th week [8].

Another study observed that the collagenase is a well known and established enzyme preparation for wound debridement and helps in healing of the ulcers [9]. Similar results were obtained in our study.

Collagenase ointment is a sterile enzymatic debriding ointment containing collagenase in petrolatum. Its labelled Indications include debriding dermal ulcers and severely burned areas. Dermal ulcers include pressure ulcers, arterial ulcers, venous ulcers and Diabetic ulcers. There are no recent clinical trials that compare collagenase ointment with placebo in burns or decubitus ulcers. Published studies are poorly controlled and unblinded. Although not well done these studies suggest that collagenase ointment is an effective enzymatic debriding agent [10].

Conclusion

Our study concluded that collagenase with metronidazole is an effective topical applicant in faster reduction of slough, regeneration of granulation tissue and re-epithelization in diabetic foot ulcer. This helps in faster wound bed preparation for healing, suturing, skin graft and flap.

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Table - 1: Distribution of subjects according to presence of necrotic tissue or slough.

Study Period	Test group (n = 42), Number (%)						Control group (n = 40), Number (%)					
	Visual score of slough covering the ulcer						Visual score of slough Study covering the ulcer					
	1	2	3	4	5	6	1	2	3	4	5	6
Baseline	23 (54.8)	12 (28.6)	6 (14.3)	1 (2.4)	-	-	23 (57.5)	10 (25.0)	7 (17.5)	-	-	-
1st Week	10 (23.8)	11 (26.2)	8 (19.0)	7 (16.7)	5 (11.9)	1 (2.4)	20 (50.0)	9 (22.5)	5 (12.5)	3 (7.5)	3 (7.5)	-
2nd Week	1 (2.4)	9 (21.4)	8 (19.0)	4 (9.5)	11 (26.2)	9 (21.4)	6 (15.0)	17 (42.5)	6 (15.0)	4 (10.0)	2 (5.0)	5 (12.5)
3rd Week	-	2 (4.8)	5 (11.9)	10 (23.8)	1 (2.4)	24 (57.1)	2 (5.0)	12 (30.0)	9 (22.5)	4 (10.0)	5 (12.5)	8 (20.0)
4th Week	-	-	2 (4.8)	4 (9.5)	4 (9.5)	32 (76.2)	-	1 (2.5)	14 (35.0)	8 (20.0)	4 (10.0)	13 (32.5)
5th Week	-	-	-	2 (4.8)	3 (11.9)	37 (88.1)	-	-	4 (10.0)	11 (27.5)	9 (22.5)	16 (40.0)
6th Week	-	-	-	-	1 (2.4)	41 (97.6)	-	-	-	6 (15.0)	11 (27.5)	23 (57.5)
7th Week	-	-	-	-	-	42 (100.0)	-	-	-	-	8 (20.0)	32 (80.0%)

Table - 2: Distribution of subjects according to presence of granulation tissue.

Study period	Test group (n = 42), Number (%)				Control group (n = 40), Number (%)			
	Visual score of presence of granulation tissue				Visual score of presence of granulation tissue			
	1	2	3	4	1	2	3	4
Baseline	23 (54.8)	15 (35.7)	4 (9.5)		23 (57.5)	13 (32.5)	4 (10.0)	-
1st Week	11 (26.2)	12 (28.6)	18 (42.9)	1 (2.4)	23 (57.5)	9 (22.5)	8 (20.0)	-
2 nd Week	1 (2.4)	12 (28.6)	19 (45.2)	10 (23.8)	9 (22.5)	17 (42.5)	9 (22.5)	5 (12.5)
3 rd Week	-	3 (7.1)	17 (40.5)	22 (52.4)	1 (2.5)	22 (55.0)	9 (22.5)	8 (20.0)
4 th Week	-	1 (2.4)	10 (23.8)	31 (73.8)	-	12 (30.0)	16 (40.0)	12 (30.0)
5 th Week	-	-	4 (9.5)	38 (90.5)	-	-	24 (60.0)	16 (40.0)
6 th Week	-	-	2 (4.8)	40 (95.2)	-	-	21 (52.5)	19 (47.5)
7 th Week	-	-	-	42 (100.0)	-	-	5 (12.5)	35 (87.5)