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Original Research Article

Utility of topical timolol in the management of chronic non-healing foot ulcers

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ABSTRACT

Background: Chronic foot ulcers often do not respond to conventional therapy and result in amputations. Treatment is protracted, expensive and affects the quality of life of the patient. The objective of the study is the efficacy of topical timolol in the treatment of chronic non-healing foot ulcers and the feasibility of its use in a rural/semi-urban population.
Methods: An observational, cross-sectional study was conducted at a tertiary hospital situated on the outskirts of Bengaluru from January 2021 to July 2022. Sample size was 95. Topical timolol maleate solution was applied on day 1, 3 and 7 and followed up on days 15 and 30. During each visit the wound was assessed and the area of ulcer was measured. Repeated measures ANOVA was applied to compare the area of ulcer on day 1, 15 and 30 and mean percentage of reduction calculated at different time intervals using post-hoc Bonferroni.
Results: Demographic data: predominantly male (61.1%), mean age 48.74±14.8 years, from lower socioeconomic background. 45.3% were diabetics. Efficacy of timolol: mean ulcer area on day 1, 15 and 30 was 70.95, 51.8 and 39.95 cm^2 respectively (p=0.001). There was a significant reduction in mean percentage of ulcer area on day 15 and day 30 (p=0.001). No adverse effects due to timolol were observed.
Conclusions: Topical timolol is safe, inexpensive and effective. Its use in the treatment of chronic non-healing foot ulcers would be beneficial to a country like India which has a large rural population.

Keywords: Chronic wounds, Non-healing, Foot ulcers, Diabetic foot, Topical timolol

INTRODUCTION

Chronic wounds are commonly encountered in surgical practice. These include diabetic foot ulcers, venous ulcers and pressure ulcers.[1] The prevalence of chronic ulcers is about 1.51 per 1000 population.[2] The condition affects 1% of the adult population and increases to 3.6% in those above 65 years.[3] The disease affects the quality of life and is a burden to the financial resources of the individual and the healthcare system.

Chronic non-healing foot ulcers (CFU) are a variety of recalcitrant lower limb ulcers that have a multi-factorial aetiology. These ulcers are known to be refractory to conventional therapy and may cause severe complications if not treated wisely. There are many modern modalities, types of dressings and topical preparations available in the market. However, they may not be freely available or affordable to the general population. In the search for a preparation that could be used in a country like India where majority of the population resides in the rural areas, we came across various studies that showed topical

solution of timolol to be effective in the treatment of CFU.

Objectives

The main objective of the study was to check the efficacy of topical timolol in accelerating the wound healing process by observing signs of healing and measuring mean reduction in ulcer size at the end of 15 and 30 days. We also studied the feasibility of its use in a rural/semi-urban population.

METHODS

A prospective, observational cross-sectional study was conducted at The Oxford Medical College Hospital and Research Centre (TOMCH & RC), Attibele, Bengaluru from January 2021 to July 2022. 95 patients with chronic non-healing foot ulcers were included in the study.

Inclusion criteria

Age more than 18 years, foot ulcers of more than 4 weeks duration showing no signs of healing.

Exclusion criteria

Age less than 18 years, ulcers with exposed bone, tendon, or joint, patients on beta blockers or history of adverse effect to beta blockers, history of bronchial asthma, COPD, recent myocardial infarction, hypothyroidism or open angle glaucoma.

The following details were recorded in the case sheet:

Demographic data: age, sex, occupation, residential address, education status, socio-economic status.

Medical history: chief complaints, duration of symptoms, past history, co-morbidities, treatment history, personal history.

Ulcer details: site, number and characteristics (shape, margin, edge, floor, base, discharge, surrounding area) were noted. If the ulcers were infected, then a culture swab was taken and sent for culture and sensitivity. Then the appropriate antibiotics were given. Ulcer area measurement was done with calipers and area measured plotted on graph paper. In case of multiple ulcers, the ulcer with the highest grade was chosen. For ulcer with identical grading, the largest ulcer was chosen. Measurements were taken on day 1, day 15 and day 30.

Peripheral pulses: Clinical examination of pedal pulses (anterior tibial artery, posterior tibial artery, dorsalis pedis) was done.

Baseline investigations: Complete blood count, renal function tests, foot X-ray, random blood sugar.

Protocol

Prior to application of timolol all the ulcers that were infected or had slough were debrided mechanically. Dose of timolol was calculated based on the ulcer area (3drops/cm2/day equivalent to 0.25mg /cm2/day) and procedure of application was done on days 1,3 and 7 according to the protocol (Figure 1). A dry dressing was applied. Patients were followed up on day 15 and day 30. During each visit the ulcer was assessed and measured.

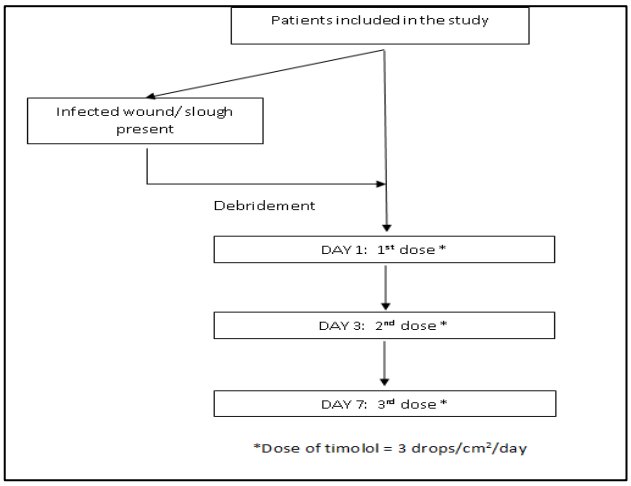

Table 1: Age distribution of patients.

Statistical analysis

SPSS (Statistical Package for Social Sciences) version 20 was used to perform the statistical analysis. Data was entered in Microsoft Excel spread sheet. Descriptive statistics of the explanatory and outcome variables were calculated by frequency and proportion for qualitative variables, mean and standard deviation for quantitative variables. Inferential statistics like percentage of repeated measures ANOVA was applied to compare the changes in wound healing (area in cm^2) from day 1, day 15 and day 30 with comparison of area at different time intervals using post-hoc Bonferroni. Level of significance was set at 5%.

RESULTS

Demography: mean age was 48.74±14.80 years. Youngest subject was 19 years old and oldest was 90 years old. Figure 2 shows the age distribution. 60% of the study population was in the 19-50 years age group. Sex distribution (Figure 3): predominantly male (61.1%). Most of the subjects were of the rural community or worked in agricultural related industries. 91.6% of the study group belonged to class IV or class V of modified Kuppuswamy socio-economic scale.[5]

Ulcer characteristics: all patients had ulcers of more than 4-6 weeks' duration. Majority (25.3%) were of 12-16 weeks' duration (Table 1).

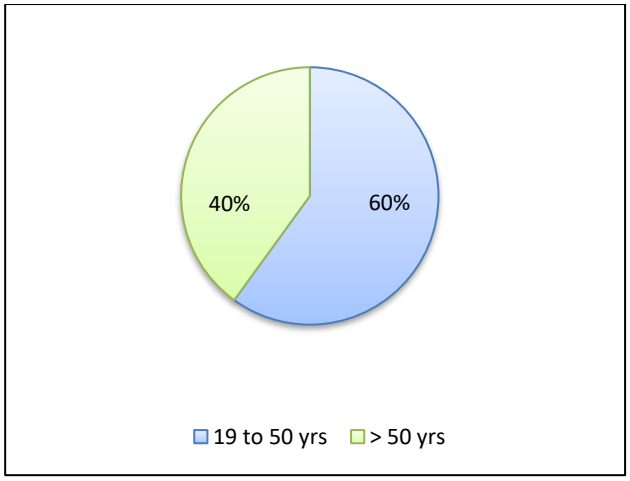

Figure 2: Age distribution.

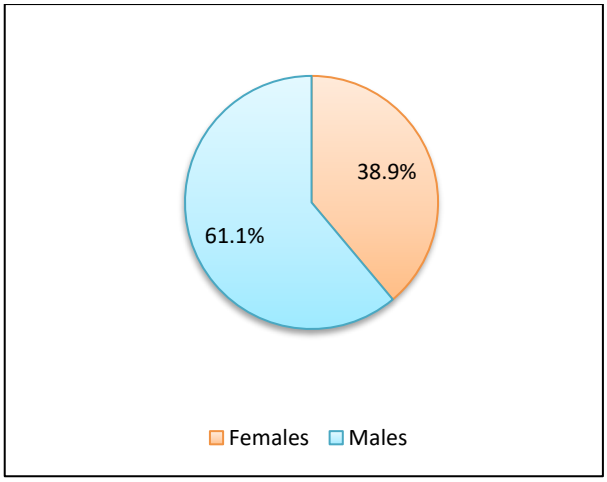

Figure 3: Sex distribution.

Table 1: Distribution of ulcer duration.

Duration (weeks)	Number of patients	Percentage (%)
4-8	20	21.1
8-12	17	17.9
12-16	24	25.3
16-20	12	12.6
20-24	22	23.2
Total	95	100.0

Table 2: Distribution of ulcer site.

Site	Frequency	Percentage (%)
Dorsal surface of left foot	19	20.0
Dorsal surface of right foot	12	12.6
Heel of left foot	23	24.2
Heel of right foot	10	10.5
Plantar surface of left foot	25	26.3
Plantar surface of right foot	6	6.3
Total	95	100.0

Table 3: Comparison of the ulcer area on day 1, 15 and 30 using repeated measures ANOVA.

Days	Number of patients	Minimum area (cm^2)	Maximum area (cm^2)	Mean area (cm^2)	SD	P value
Day 1	95	5.89	357.00	70.95	77.05	
Day 15	95	2.09	327.63	51.88	64.86	0.001*
Day 30	80	1	284	39.95	54.03	

Table 4: Comparison of the area (cm^2) between time intervals using post-hoc Bonferroni.

	Mean diff	P value
Day 1 vs Day 15	20.08	0.001*
Day 1 vs Day 30	39.66	0.001*
Day 15 vs Day 30	19.57	0.001*

Table 5: Mean percentage of reduction at day 15 and day 30.

	No. of Patients	Min	Max	Mean	S.D	Mean diff	P value
% of ulcer area reduction on day 15	95	7.0	68.0	34.78	15.27	-31.65	0.001*
% of ulcer area reduction on day 30	95	20.0	100.0	66.44	22.10		

Table 6: Comparison of the area reduction (cm^2) based on age groups using repeated measures ANOVA.

Age (yrs)	Time interval	No. of patients	Minimum	Maximum	Mean	SD	P value
19-50	Day 1	38	10.64	304.00	80.91	76.32	0.001*
	Day 15	38	5.40	277.20	62.09	66.57	
	Day 30	36	1	224	43.53	53.133	
>50	Day 1	57	5.89	357.00	64.30	77.49	0.001*
	Day 15	57	2.09	327.63	45.08	63.38	
	Day 30	44	1	284	37.02	55.19	

Table 7: Comparison of the area (cm^2) between time intervals using post-hoc Bonferroni.

	19-50 (yrs)		>50 (yrs)	
	Mean diff	**P value**	**Mean diff**	**P value**
Day 1 Vs Day 15	21.422	0.001*	18.446	0.001*
Day 1 Vs Day 30	40.079	0.001*	39.152	0.001*
Day 15 Vs Day 30	18.658	0.001*	20.706	0.001*

Table 2 shows the distribution of ulcer sites in the study group. As expected, most ulcers were on the plantar aspect of the foot in the pressure point areas.

Efficacy of Timolol: the mean ulcer area (cm^2) on day 15 and day 30 was compared with the mean ulcer area on day 1. A significant reduction (p=0.001) in ulcer area was observed (Tables 3 and 4).

There was a significant reduction (p=0.001) in the mean percentage of ulcer area on day 15 and day 30 (Table 5).

Reduction in mean ulcer area on day 15 and day 30 and the percentage decrease in mean ulcer area in the age groups 19-50 years and >50 years was found to be similar (Tables 6 and 7).

DISCUSSION

The aetiology of CFU is multifactorial. Diabetics with CFU have a fifteen-fold risk of lower extremity amputation.[4] In our study most were diabetic foot ulcers which is consistent with other similar studies. The common underlying causes are poor glycaemic control, calluses, foot deformities, improper or ill-fitting footwear, underlying peripheral neuropathy, poor circulation, dry skin etc.[6] In this study most patients were farmers or of rural background. The probable reasons for late presentation were poverty, ignorance, negligence, poor foot hygiene, poor diabetic control, or undiagnosed vascular insufficiency. However, keeping in mind that the purpose of the study was to check the feasibility of using timolol in the management of CFU in a resource-constrained healthcare setup, we did not concentrate on the preventive or diagnostic aspect of management.

Timolol is a potent non-selective beta receptor antagonist. Its use in the treatment of hypertension, congestive heart failure, migraine prophylaxis, open angle glaucoma and intra ocular hypertension is well known.[7] β2 adrenergic receptors (β2-AR) are present on many body tissues including keratinocytes. β2-AR antagonists like timolol promote wound healing by enabling keratinocyte migration into wound to initiate the re-epithelisation.[8,9] The efficacy of topical timolol in the management of chronic wounds is well documented. Rai et al demonstrated its efficacy in treating chronic venous ulcers.[10] Kaur et al showed that timolol was effective in chronic diabetic foot ulcers.[11] The studies of Braun et al and Vestita et al showed the efficacy of timolol in the management of chronic recalcitrant wounds.[12,13] Similarly, there have been many cases reported where chronic wounds were successfully treated with topical timolol.[14-18]

In our study, we used timolol eye drops, commercially available as a 5 ml solution of 0.5% w/v timolol maleate. The cost of the medication was borne by the investigators. It was easily available in the nearby

medical stores and price varied on the brand/ manufacturer. The maximum retail price ranged from ₹55-₹75. The application of the medication did not need any special training and could be done at any level of healthcare. There were no adverse drug reactions or drug interactions seen in our study.

Limitations of the study

The main limitations of the study were the small sample size, non-randomization and selection bias. Multicentric randomized case-control studies would be required to test its true efficacy and utility in the Indian population. In addition, since the aetiology of chronic non-healing foot ulcers are multifactorial it is impossible to truly eliminate the many confounding factors.

CONCLUSION

The management of chronic wounds is complex. Each modality has its own drawbacks and limitations. The data in our study and that of others shows that topical timolol is safe and effective in the treatment of chronic wounds. In addition, in the context of India and those countries with a large rural population, it being affordable, easily available and not requiring any special expertise in its application makes it a good option as a solution that can be used at the primary healthcare level.

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Ethical approval: Approved by the Institutional Ethical Committee of The Oxford Medical College Hospital and Research Centre, Bengaluru

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