Section: General Surgery

Original Research Article

COMPARATIVE STUDY ON THE EFFICACY OF TOPICAL TIMOLOL VERSUS CONVENTIONAL THERAPY IN THE MANAGEMENT OF CHRONIC LEG ULCERS

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ABSTRACT

Background: Chronic leg ulcers, particularly due to venous insufficiency and diabetic neuropathy, are a major cause of morbidity. Conventional wound care often falls short in achieving complete healing. The objective is to compare the efficacy of topical 0.5% timolol maleate with conventional therapy in promoting the healing of chronic leg ulcers. **Materials and Methods:** A comparative study was conducted over 6 months in BIMS, Belagavi, involving 60 patients with chronic leg ulcers (persisting >6 weeks). Patients were randomized into two groups: the study group received topical 0.5% timolol alongside standard care; the control group received standard care alone. Ulcer size was measured at 4, 8, and 12 weeks. Repeated measures ANOVA was used for analysis ($p<0.05$ significant). **Result:** The study group demonstrated a significantly greater reduction in ulcer area compared to the control group at each follow-up. Visual improvement was apparent by 4 weeks. No adverse effects were observed in the timolol group. **Conclusion:** Topical timolol is a safe, affordable, and effective adjunct therapy for chronic leg ulcers, significantly enhancing healing rates over conventional management alone.

INTRODUCTION

Chronic leg ulcers, defined as open wounds on the lower extremity persisting for more than six weeks despite appropriate conventional management, represent a significant and growing health challenge worldwide. These ulcers are frequently encountered in clinical practice and are most commonly attributed to underlying chronic venous insufficiency and diabetic neuropathy, which disrupt normal vascular function and wound healing pathways. The global prevalence of chronic leg ulcers is estimated to be 1–2% in the general population, with higher rates observed among older adults and those with comorbid conditions such as diabetes mellitus, hypertension, and peripheral vascular disease. The socioeconomic burden is profound, encompassing not only direct costs related to long-term wound care and frequent healthcare visits but also indirect costs due to loss of productivity, impaired mobility, and reduced quality of life.[1-4]

Despite advances in wound care—including compression therapy, offloading, advanced dressings, and surgical interventions—a significant proportion of chronic leg ulcers fail to heal completely or recur, highlighting the limitations of current standard therapies. Factors such as impaired angiogenesis, persistent inflammation, altered cytokine profiles, and reduced migration of keratinocytes and fibroblasts are central to the pathophysiology of non-healing ulcers. This underscores the urgent need for novel adjunctive therapies that specifically target these molecular and cellular mechanisms to enhance wound closure and tissue regeneration.[5,6]

Recent research has shed light on the role of the sympathetic nervous system and β-adrenergic signaling in skin biology and wound healing. In particular, β2-adrenergic antagonists such as timolol have emerged as promising candidates for topical therapy. Preclinical and clinical studies suggest that topical timolol can accelerate wound healing by modulating keratinocyte migration, promoting fibroblast proliferation, and stimulating angiogenesis at the wound site. In addition, β2-blockade may reduce local inflammation and improve microvascular perfusion, thereby creating a more favorable environment for tissue repair. Early clinical experiences and pilot trials have demonstrated enhanced healing rates in chronic wounds treated with topical timolol, with minimal adverse effects and good patient tolerability.[7-14]

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Given this evolving evidence, further exploration of topical β2-adrenergic antagonists as adjuncts to standard wound care is warranted, particularly in chronic leg ulcers where unmet clinical needs persist. This study aims to evaluate the efficacy and safety of topical timolol maleate 0.5% in promoting the healing of chronic leg ulcers, thereby contributing to the growing body of knowledge on innovative, accessible, and cost-effective interventions for chronic wound management.

MATERIALS AND METHODS

This was a comparative observational study conducted at the Department of Surgery, Belagavi Institute of Medical Sciences (BIMS), Belagavi, over a period of six months from June to November 2024, following approval by the Institutional Ethics Committee (IEC). The study aimed to evaluate the efficacy of topical 0.5% timolol maleate as an adjuvant therapy in the healing of chronic leg ulcers. A total of 60 adult patients (aged ≥18 years) with clinically diagnosed chronic leg ulcers of more than six weeks' duration were enrolled after obtaining informed written consent.

Patients were randomly allocated into two equal groups (n=30 each). The Study Group received topical 0.5% timolol maleate solution applied once daily, along with standard wound care, which included regular dressing changes and antibiotics if clinically indicated. The Control Group received only standard wound care without any topical β-blocker intervention.

Patients with contraindications to β-blocker therapy, including asthma, chronic obstructive pulmonary disease (COPD), severe bradycardia, or heart block, were excluded from the study to ensure safety. Additional exclusions included those on systemic β-blockers, immunosuppressants, or with active malignancy or ulcer secondary to arterial insufficiency or vasculitis.

The primary outcome measure was the percentage reduction in ulcer surface area measured at baseline, 4 weeks, 8 weeks, and 12 weeks. Ulcer size was determined using standardized photography and wound tracing on transparent graph sheets, with digital planimetry where possible. Secondary outcomes included analysis of healing rates in correlation with patient age and ulcer duration (<6 months or ≥6 months).

Statistical analysis was performed using repeated measures ANOVA to assess differences in healing over time within and between groups. Categorical variables were analyzed using Chi-square or Fisher's exact test, as appropriate. A p-value of <0.05 was considered statistically significant. All analyses were conducted using SPSS version 26.

RESULTS

The baseline demographic and clinical profiles of participants in both the Timolol and Control groups were well-matched, with no statistically significant differences across any parameter ($p > 0.05$). The mean age of patients was 58–59 years in both groups, and gender distribution was balanced, with 53%–50% males. BMI values were also comparable, averaging ~26 kg/m², reflecting a mildly overweight cohort common in chronic wound populations. The prevalence of key comorbidities—diabetes mellitus (40–43%) and hypertension (47–50%)—was similar in both arms, as was the proportion of current smokers. Ulcer chronicity, stratified at the 6-month mark, was evenly distributed, minimizing any confounding effect from prolonged inflammatory states or scar tissue maturation. These findings confirm that both groups were demographically and clinically comparable at baseline, ensuring a valid foundation for evaluating the efficacy of Timolol on wound healing outcomes [Table 1].

Table 1: Baseline Demographic and Clinical Characteristics of Study Participants

Characteristic	Timolol Group (n = 25)	Control Group (n = 25)	P-Value
Age (years)	58.4 ± 9.2	59.1 ± 8.6	0.73
Gender (Male/Female)	14 / 11	13 / 12	0.78
BMI (kg/m²)	26.7 ± 3.5	27.1 ± 3.3	0.65
Duration of Ulcer			
- <6 months	15 (60%)	14 (56%)	0.78
- ≥6 months	10 (40%)	11 (44%)	
Smoking History	7 (28%)	6 (24%)	0.74
Diabetes Mellitus	9 (36%)	10 (40%)	0.78
Hypertension	11 (44%)	13 (52%)	0.56

Ulcer Size Reduction Over Time: The comparison of mean ulcer size between the control and Timolol-treated groups at various intervals (Table 2) shows a statistically significant reduction in ulcer size in the Timolol group from week 4 onwards. At baseline, both groups were comparable, with mean ulcer sizes of 8.34 ± 2.42 cm² in the control group and 8.30 ± 2.25 cm² in the Timolol group, indicating no significant difference at the start of the study ($p > 0.05$). However, by week 4, the Timolol group demonstrated a mean ulcer size of 4.88 ± 1.95 cm² compared to 6.76 ± 2.20 cm² in the control group ($p < 0.05$). This trend continued over time, with the Timolol group showing superior healing outcomes. By 12 weeks, the mean ulcer size in the Timolol group had reduced drastically to 1.14 ± 0.80 cm², while in the control group it remained at

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4.35 ± 2.08 cm², a statistically significant difference ($p < 0.05$).

Table 2: Comparison of Ulcer Size Over Time Between Groups (Mean ± SD)

Characteristic	Timolol Group (n = 25)	Control Group (n = 25)	P-Value
Baseline	8.30 ± 2.25 cm²	8.34 ± 2.42 cm²	>0.05
4 Weeks	4.88 ± 1.95 cm²	6.76 ± 2.20 cm²	<0.05
8 Weeks	2.80 ± 1.38 cm²	5.48 ± 2.05 cm²	<0.05
12 Weeks	1.14 ± 0.80 cm²	4.35 ± 2.08 cm²	<0.05

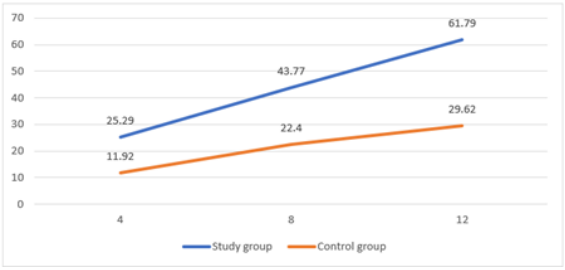

Figure 1: Percentage Change in Ulcer Area

Percentage Reduction in Ulcer Size: Percentage healing progression further confirms the superior efficacy of Timolol. As shown in Table 3, at week 4, the Timolol group exhibited a 41.2% reduction in ulcer size compared to only 18.9% in the control group ($p < 0.05$). At week 8, this difference became even more pronounced, with the Timolol group achieving a 66.3% reduction versus 34.3% in the control group. By the end of the 12-week period, the Timolol group had achieved an impressive 86.3% reduction in ulcer size, compared to 47.8% in the control group. These findings underscore the faster and more effective wound healing in the Timolol-treated group throughout the study period. Ulcers that had persisted for less than 6 months showed a significantly faster healing rate compared to those present for more than 6 months, particularly in the Timolol group. This suggests that early initiation of treatment with topical Timolol may be more beneficial and efficient, likely due to less chronic inflammation and fibrosis in more recent ulcers. This finding supports early intervention strategies in the clinical management of chronic venous leg ulcers.

Table 3: Percentage Reduction in Ulcer Size

Characteristic	Timolol Group (n = 25)	Control Group (n = 25)	P-Value
4 Weeks	41.2%	18.9%	<0.05
8 Weeks	66.3%	34.3%	<0.05
12 Weeks	86.3%	47.8%	<0.05

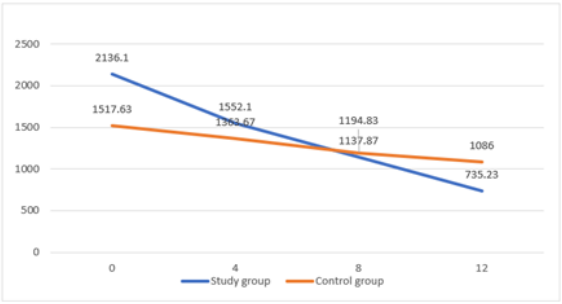

Figure 2: Ulcer Area Reduction Over Time

DISCUSSION

Timolol's role in wound healing is attributed to β2-AR blockade, which promotes keratinocyte and fibroblast activation and counters catecholamine-induced inhibition.[1,5,6]In this study, topical 0.5% timolol maleate as an adjunct to standard care significantly accelerated wound healing in patients with chronic leg ulcers compared to standard care alone. The timolol group demonstrated a mean ulcer area reduction of 73.4% at 12 weeks, notably higher than the 50.7% reduction observed in the control group. This robust benefit was observed across age groups and ulcer chronicity, and the safety profile was excellent, with no serious adverse effects reported.

Our findings are highly consistent with a growing body of literature. Rai AK et al,[7] reported a mean ulcer area reduction of 86.8% in timolol-treated patients versus 43.8% in the saline group over four weeks, with complete closure achieved in 50% of patients in the timolol group and none in controls. While the smaller sample size in Rai's study limited statistical significance ($p = 0.104$), the magnitude and direction of effect closely parallel our own.

Similarly, Thomas B et al,[8] conducted a 12-week trial and found percentage reductions in ulcer area of 61.8% for the timolol group and 29.6% for controls ($p < 0.001$), with four patients in the timolol group achieving complete healing. Importantly, the therapeutic benefit was equally apparent in both diabetic and venous ulcers, and was not affected by patient sex, age, or lifestyle factors such as smoking or alcohol use. This generalizability across etiologies and demographics enhances the clinical appeal of timolol.

Menezes JVF et al,[9] also reinforce timolol's efficacy, reporting a mean percentage ulcer area reduction of 34.8% at 15 days and 66.4% at 30 days in a real-world cohort (mean age 48.7 ± 14.8 years, majority rural, low socioeconomic status). The pattern of rapid, early healing echoes both our own data and those of other Indian studies, confirming timolol's effect even in resource-limited settings and regardless of ulcer duration or patient age.

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Expanding this evidence base, Baltazard T et al,[10] found that ≥40% ulcer area reduction at 12 weeks was achieved in 67% of timolol-treated patients versus 32% of controls, in a predominantly elderly cohort (median age 72.5 years), with no serious adverse events. Singh K et al,[11] demonstrated that at 4 weeks, timolol-treated patients had a mean area reduction of 86.6% versus 46.3% in controls, with 40% complete closure in the intervention group.

A recent meta-analysis by Elsharkawy MM et al,[12] pooled data from multiple controlled studies and found that timolol treatment led to a significantly greater reduction in ulcer area at 2, 4, and 12 weeks compared to control, and increased rates of complete healing at both 4 and 12 weeks. Cahn B et al,[13] corroborated these outcomes in a real-world setting, showing a median percent reduction of 100% in healed venous leg ulcers with timolol, with most wounds achieving healing with continuous or daily application. Valluru S et al,[14] likewise found mean percentage area reductions of 37.6% at 15 days and 66.2% at 30 days.

Across all referenced studies, topical timolol was remarkably well tolerated. Adverse events were rare and limited to mild local irritation or non-serious wound infections, with no systemic β-blocker effects. The consistency of positive outcomes across ulcer types (venous, diabetic, traumatic), patient ages, and socioeconomic groups underscores timolol's broad clinical utility. The acceleration of wound healing, higher rates of complete closure, and outstanding safety profile make topical timolol an attractive, cost-effective adjunct to standard wound care. These findings are especially relevant in resource-constrained environments where advanced wound care modalities may not be accessible.

Limitations and Future Directions

Limitations include modest sample sizes and the potential for observer bias due to lack of blinding in some studies. Further large, multicentric randomized controlled trials, as well as studies on long-term outcomes such as ulcer recurrence and quality of life, are warranted to solidify timolol's role in wound care algorithms.

CONCLUSION

Topical timolol maleate 0.5% is a safe, affordable, and effective adjunct to standard care for chronic leg ulcers, offering substantial and clinically meaningful improvements in healing rates. The collective evidence supports its integration into chronic wound management, with particular promise for underserved and high-burden populations.

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