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Original Research Article

Role of esmolol in non-healing chronic wounds

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ABSTRACT

Background: Diabetic foot ulcers (DFUs) exhibit delayed healing due to persistent inflammation, oxidative stress, microvascular dysfunction, and impaired cellular responses. Topical esmolol hydrochloride has demonstrated wound-healing potential through inhibition of aldose reductase, reduction of advanced glycation end products, and promotion of epithelial and endothelial migration.
Methods: This observational cohort study included 30 patients with chronic, non-infected foot or lower-leg ulcers of more than three weeks' duration, including diabetic (Wagner class 1A/1B) and non-diabetic traumatic wounds. Patients received topical esmolol hydrochloride 14% once daily in addition to standard wound care. Wounds were assessed weekly for nine weeks using the Bates–Jensen wound assessment tool (BWAT). Complete healing was defined as full epithelialization without discharge.
Results: Mean BWAT score improved from 28 at baseline to 3 at week 9, representing an 89.3% reduction. Complete healing within 9 weeks was achieved in 24 patients (80%). Healing was significantly higher in non-anemic patients compared with anemic patients ($p<0.05$). Patients with normal serum albumin showed better outcomes, while glycemic control showed a positive but non-significant association.
Conclusions: Topical esmolol hydrochloride appears to be a safe and effective adjunct to standard wound care for diabetic and traumatic foot ulcers. Correction of systemic factors such as anemia and malnutrition further enhances outcomes. Larger randomized studies are required to confirm efficacy.

Keywords: Diabetic foot ulcer, Esmolol hydrochloride, Wound healing, Topical therapy, Chronic ulcers

INTRODUCTION

Normal wound healing progresses through three sequential phases: inflammation, proliferation, and remodeling.[1] In diabetes, several cellular and molecular processes within these phases are disrupted, contributing to chronic wounds such as diabetic foot ulcers (DFUs). Elevated cytokines including interleukin (IL)-6, IL-1β, and tumor necrosis factor-α sustain inflammation and impair the function of macrophages, fibroblasts, endothelial cells, and keratinocytes, which are essential for tissue repair. During the proliferative phase, reduced growth, extracellular factor production compromises recruitment of fibroblasts, keratinocytes, immune cells, and vascular cells, thereby impairing angiogenesis and extracellular-matrix formation. In the remodeling phase, keratinocyte migration and collagen cross-linking are hindered, further delaying wound closure. In addition, diabetes is associated with impaired nitric-oxide synthesis, which is critical for angiogenesis, epidermal migration, granulation-tissue formation, and collagen deposition.[2] Several pharmacological agents such as topical phenytoin, propranolol, statins, metformin, and valsartan have been evaluated through drug-repurposing

approaches, but with limited or inconsistent efficacy. Despite these findings, there remains no consistently effective pharmacological therapy for DFUs, underscoring the need for novel therapeutic strategies.[2,3]

Esmolol hydrochloride is a short-acting, cardioselective β1-adrenergic receptor antagonist approved for intravenous treatment of supraventricular tachycardia, with an elimination half-life of approximately 9 minutes.[4] In gel formulation, it appears to retrigger intrinsic wound-healing mechanisms. Computational protein–drug docking studies using the GRIP method and crystal structure 1EL3 revealed favorable interactions of esmolol with aldose reductase, an enzyme implicated in diabetic complications. Esmolol prevents the formation of advanced glycation end products (AGEs), thereby lowering macrophage autophagy and oxidative stress, both of which are known to impair healing. With respect to apoptosis, esmolol counters elevated caspase-3 and Bax levels and restores reduced Bcl-2 expression observed in DFU patients. Furthermore, esmolol promotes epithelial-cell migration via ERK1/2 signaling and enhances vascular repair by stimulating neurokinin receptors and substance-P release, thereby improving vasodilatation and tissue perfusion. Based on these findings, esmolol was further investigated for its effects on fibroblasts, endothelial cells, and keratinocytes, the key cellular mediators of wound repair.[5] This preclinical work has culminated in the development of a novel topical formulation of esmolol hydrochloride for DFUs. Early clinical studies suggest potential efficacy, supporting further translational and clinical evaluation of this agent in diabetic wound management. The objective of the study was to evaluate the clinical efficacy of topical esmolol hydrochloride 14% as an adjunct to standard wound care in patients with chronic non-healing diabetic and traumatic foot ulcers.

METHODS

Study design and setting

This was a prospective observational cohort study conducted in the Department of Plastic Surgery, AIIMS Rishikesh, Uttarakhand, India, for the period of 9 months from January 2025 to September 2025.

Selection criteria

Patients aged 18 years and above presenting with chronic, non-infected foot or lower leg ulcers persisting for more than three weeks were included in the study.

Both diabetic ulcers (Wagner class 1A and 1B) and non-diabetic traumatic wounds were eligible irrespective of ulcer size. Exclusion criteria included infected ulcers, ulcers of other etiologies (e.g., venous, arterial, malignant), pregnant women, patients below 18 years of age, and patients unwilling to provide informed consent.

Procedure

After obtaining informed consent, baseline demographic details, comorbidities, hemoglobin levels, serum albumin levels, and glycemic status (HbA1c) were recorded. Initial wound assessment was performed using the Bates–Jensen Wound assessment tool (BWAT). All patients received topical esmolol hydrochloride 14%, applied once daily directly over the ulcer surface. Standard wound care was provided to all patients, including cleansing with normal saline, maintenance of a moist wound environment, and appropriate offloading measures when indicated. Minor debridement was performed where necessary. Wounds were evaluated weekly for up to nine weeks for complete healing. Complete healing was defined as 100% epithelialization without discharge and without the need for further dressing.

Ethical approval

The study was conducted after obtaining approval from the Institutional Ethics Committee.

Statistical analysis

Categorical variables were analyzed using Fisher's exact test due to small subgroup sizes. A p value <0.05 was considered statistically significant.

RESULTS

A total of 30 patients with chronic wounds were treated and followed for nine weeks (Table 1). The mean BWAT score at baseline was 28, indicating moderate wound severity. By week 3, the mean score decreased to 11, representing a 60.7% reduction from baseline. At week 6, the mean score further declined to 7 (75.0% reduction), and by week 9 it reached 3, corresponding to an overall reduction of 89.3%. Categorical analysis demonstrated a significant shift toward lower BWAT categories over time (Figure 1), and Fisher's exact test confirmed a statistically significant association between treatment duration and wound improvement ($p<0.05$).

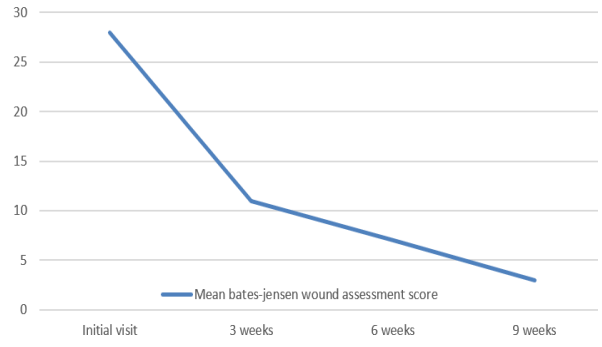

Figure 1: Decrease in mean Bates-Jensen wound assessment score from 28 at initial visit to 3 at 9 weeks.

Time to complete healing

Complete healing occurred within 3 weeks in 12 patients (40%) (figure 7), within 6 weeks in 7 patients (23.3%) (figure 4,5,8), and within 9 weeks in 4 patients (13.3%). Seven patients (23.3%) showed delayed healing beyond 9 weeks or no significant improvement (Figure 3 and 6). Overall, 24 of 30 patients (80%) achieved complete healing within 9 weeks.

Figure 2: Distribution of wound healing time among 30 patients: 12 healed within 3 weeks, 7 within 6 weeks, 4 within 9 weeks, and 7 showed healing after more than 9 weeks or no improvement.

Table 1: Complete wound healing within 9 weeks considering various subgroups based on different parameters.

Subgroups	Frequency (n)	Wound healing	% of wound healing
Anemia	9	5	55.5
Non-anemia	21	19	90
Male Hb >13 g/dl	14	-	-
Female Hb >13 g/dl	7	-	-
Male Hb <13 g/dl	4	-	-
Female Hb <13 g/dl	5	-	-
Albumin >3.5 g/dl	22	19	86
Albumin <3.5 g/dl	8	4	50
HbA1c <6%(non-diabetic)	4	3	75
HbA1c 6-8%	16	14	87.5
HbA1c >8%	10	6	60

Hemoglobin status

Nine patients (30%) were anemic and 21 (70%) were non-anemic. Healing occurred in 19 of 21 non-anemic patients (90%) compared with 5 out of 9 anemic patients (55.5%). This association was statistically significant ($p<0.05$).

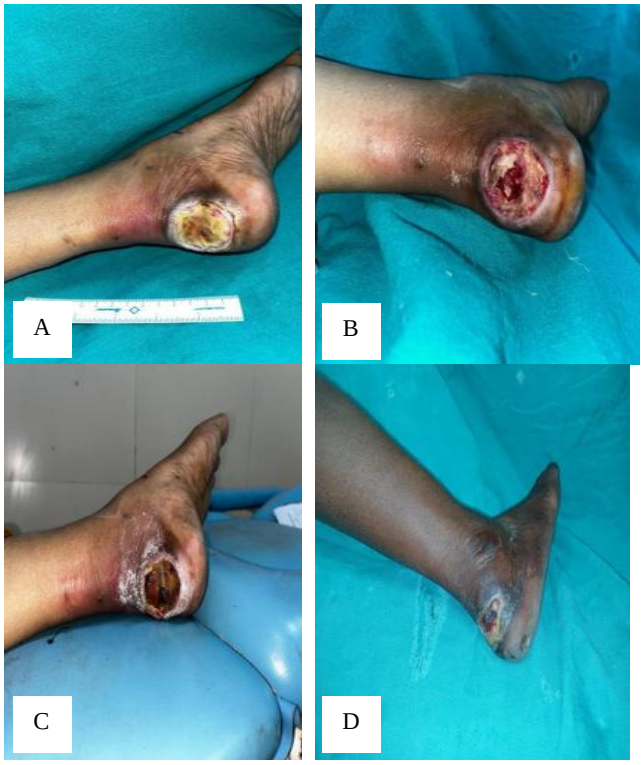

Figure 3: A 56-year male, diabetic with: (A) chronic non-healing 4 cm wound on left heel, (B) post minor debridement, (C) blackish discoloration of wound at 1 week and (D) ~80% reduction of wound size at 8 weeks.

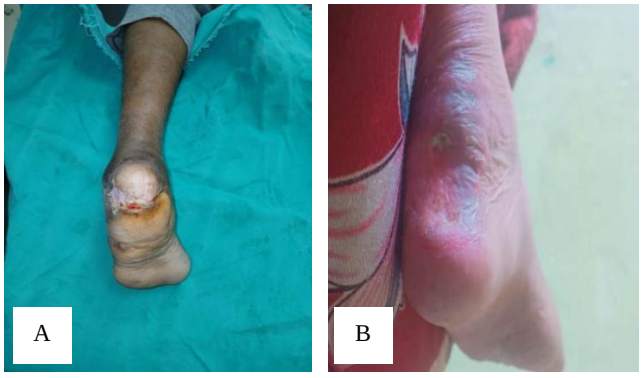

Figure 4: A 45-year diabetic female with: (A) non-healing wound on left heel and (B) showing complete wound healing in 4 weeks.

Serum albumin

Serum albumin exceeded 3.5 g/dl in 22 patients, among whom 19 (86%) achieved healing, whereas only four of

eight patients (50%) with hypoalbuminemia healed. This showed a positive trend toward significance (p≈0.06).

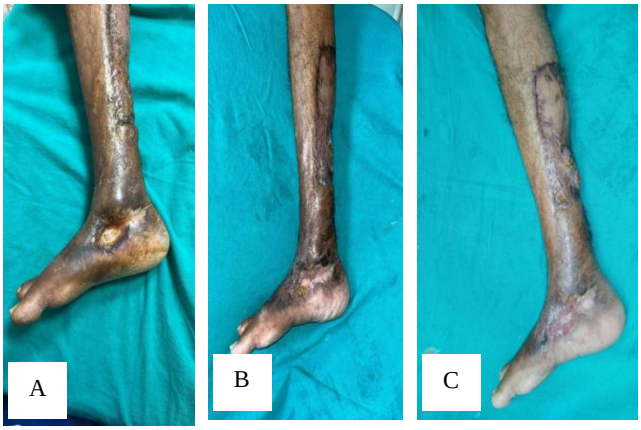

Figure 5: A 48-year-old male with O/C/O: (A) reverse sural artery flap right leg with non-healing wound over medial malleoli, (B) showing 50% wound closure in 3 weeks and (C) complete wound closure at 5 weeks.

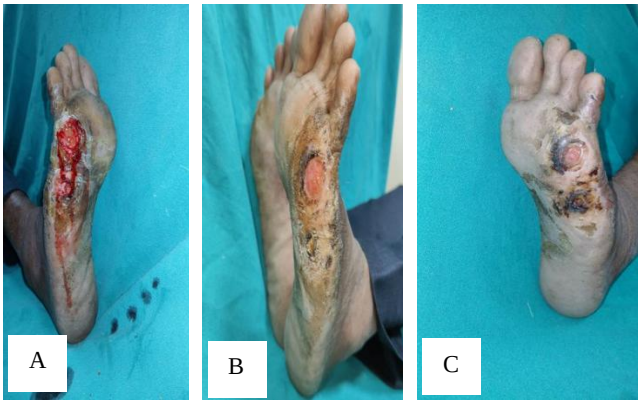

Figure 6: A 47-year diabetic male with (A) chronic wound over left ball of little toe after minor debridement, (B) showing >50% reduction at 5 weeks and (C) patient has complete wound closure at 12 weeks.

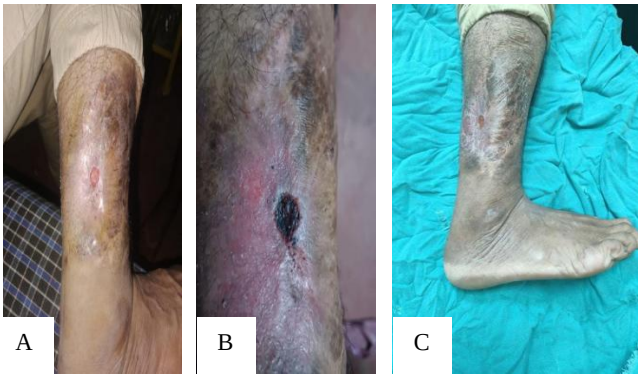

Figure 7: A 35-year-old male with (A) traumatic non-healing wound over right lateral aspect of lower leg, (B) showing healing with blackish discoloration at 1 week and (C) complete wound healing at 3 weeks.

Glycemic control

Patients were categorized into 3 groups: HbA1c <6% (n=4), HbA1c 6-8% (n=16), and HbA1c >8% (n=10). Complete healing was observed in 3 of 4 patients (75%) in the non-diabetic group (Figure 5 and 7), 14 of 16 patients (87.5%) with HbA1c 6-8%, and 6 of 10 patients (60%) (Figure 4 and 6) with HbA1c >8% (Figure 3 and 8). For analysis, patients were grouped into HbA1c ≤8% (n=20) (Figure 3 and 4) and >8% (n=10) (Figure 5,6 and 8). Healing occurred in 17 of 20 patients (85%) with HbA1c ≤8% and in six of 10 patients (60%) with HbA1c >8%. This association was not statistically significant (p> 0.05).

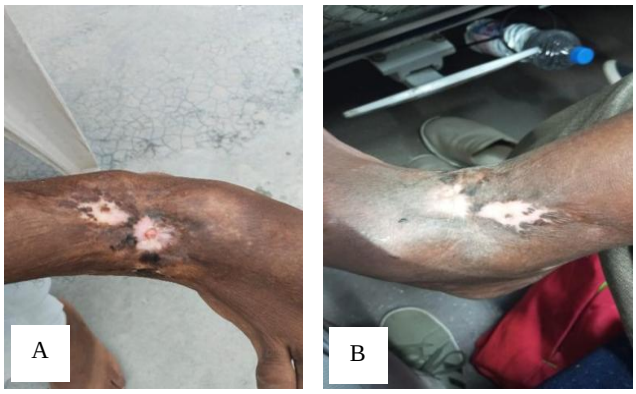

Figure 8: A 38-year-old non diabetic male with: (A) non-healing wound of more than 6 weeks over right deformed foot and (B) showing 100% wound healing at 6 weeks.

DISCUSSION

The present prospective observational study demonstrated significant improvement in chronic non-healing wounds treated with topical esmolol hydrochloride, reflected by marked reduction in wound size and improvement in BWAT scores over the treatment period. These findings suggest a favorable therapeutic role of topical esmolol as an adjunct in wound management.

Very limited clinical studies have evaluated topical esmolol in chronic wound healing. Kulkarni et al reported that esmolol enhances diabetic wound repair through inhibition of aldose reductase, reduction in advanced glycation end-product formation, and promotion of fibroblast migration.[5] In a randomized double-blind phase 1/2 study, Rastogi et al observed an 86.6% reduction in ulcer area and a 99.4% reduction in ulcer volume with 14% topical esmolol gel.[6] Subsequently, a phase 3 randomized clinical trial demonstrated ulcer closure in 57.4% of patients in the esmolol group compared to 42.6% in the standard-of-care group during a 12-week treatment phase, although the difference did not reach statistical significance.[7] A further analysis highlighted the influence of patient and wound characteristics on healing outcomes.[8] The results of our study are broadly consistent

with these findings. Unlike previous trials that focused primarily on diabetic foot ulcers, our study also included traumatic non-healing wounds, thereby expanding the clinical spectrum of esmolol application. Additionally, serial photographic documentation provided objective visual assessment of wound progression in a real-world clinical setting. Wound healing is influenced by multiple systemic factors, including glycemic control, nutritional status, anemia, and infection.[9-13] Optimization of these parameters likely contributed to the favorable outcomes observed in our cohort. Importantly, no major adverse effects were noted, supporting the safety profile of topical esmolol.

The present study has certain limitations, including its single-center observational design, relatively small sample size, and limited follow-up duration. Larger multicentric trials are required to further validate these findings and establish standardized treatment protocols.

CONCLUSION

In this prospective observational study, topical esmolol hydrochloride demonstrated promising efficacy in the management of chronic non-healing wounds, including both diabetic foot ulcers and traumatic wounds, with significant improvement in wound size and BWAT scores and no major adverse effects. Although these results are encouraging, the observational design and relatively small sample size warrant cautious interpretation, and larger trials are needed to further establish its definitive role in chronic wound management.

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Conflict of interest: None declared
Ethical approval: The study was approved by the Institutional Ethics Committee

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