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Topical Esmolol Hydrochloride as a Novel Treatment Modality for Diabetic Foot Ulcers

A Phase 3 Randomized Clinical Trial

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Abstract

IMPORTANCE Preclinical and phase 1/2 studies with esmolol hydrochloride suggest its potential role in treatment of diabetic foot ulcers (DFUs).

OBJECTIVE To study the efficacy of topical esmolol for healing of uninfected DFUs.

DESIGN, SETTING, AND PARTICIPANTS A randomized, double-blind, multicenter, phase 3 clinical trial was conducted from December 26, 2018, to August 19, 2020, at 27 referral centers across India. Participants included adults with DFUs.

INTERVENTIONS Participants were randomized after a run-in phase (1 week) to receive esmolol, 14%, gel with standard of care (SoC), SoC only, or vehicle with SoC (3:3:1 proportion) for 12 weeks (treatment phase) and followed up subsequently until week 24.

MAIN OUTCOMES AND MEASURES The primary outcome was the proportion of wound closure within the 12-week treatment phase in the esmolol with SoC and SoC only groups. Analysis was conducted using an intention-to-treat safety evaluable population, full analysis set or efficacy-evaluable population, and per-protocol population comparing the esmolol plus SoC and SoC only treatment groups.

RESULTS In the study, 176 participants (122 men [69.3%]; mean [SD] age, 56.4 [9.0] years; mean [SD] hemoglobin A_{1c} level, 8.6% [1.6%]) with DFUs classified as University of Texas Diabetic Wound Classification system grade IA and IC (mean [SD] ulcer area, 4.7 [2.9] cm^2) were randomized to the 3 groups. A total of 140 participants were analyzed for efficacy. The proportion of participants in the esmolol with SoC group who achieved target ulcer closure within 12 weeks was 41 of 68 (60.3%) compared with 30 of 72 (41.7%) participants in the SoC only group (odds ratio [OR], 2.13; 95% CI, 1.08-4.17; $P = .03$). A total of 120 participants completed the end of study visit which were analyzed. Target ulcer closure by the end of the study (week 24) was achieved in 44 of 57 (77.2%) participants in the esmolol with SoC group and 35 of 63 (55.6%) participants in the SoC only group (OR, 2.71; 95% CI, 1.22-5.99; $P = .01$). The median time for ulcer closure was 85 days for the esmolol with SoC group and was not estimable for SoC only group. Significant benefits of Esmolol with SoC were seen in patients with factors that impede the healing of DFU. Treatment-emergent adverse events were noted in 18.8% of the participants, but most (87.3%) of these events were not attributable to the study drug.

(continued)

Key Points

Question Does esmolol hydrochloride gel improve wound healing in diabetic foot ulcers at greater rates than the standard of care?

Findings In this randomized clinical trial that included 176 patients with diabetic foot ulcers, topical application of esmolol with the standard of care demonstrated a significant proportion of ulcer closure compared with standard of care alone. In addition, benefits were shown in patients with factors that impede the healing of diabetic foot ulcers.

Meaning The findings of this randomized clinical trial indicate that topical esmolol may be an appropriate addition to the standard of care for treating diabetic foot ulcers.

+ Visual Abstract

+ Supplemental content

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