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ORIGINAL ARTICLE

Effect of patient and wound characteristics on diabetic foot ulcer healing in phase 3 study of novel topical esmolol hydrochloride

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Abstract

Background Novel topical esmolol is shown to significantly improve wound healing than standard of care. Certain patient-related factors especially anemia and poor glycemic control may impede wound healing.

Objective To study whether novel topical esmolol may circumvent patient-related factors to improve wound healing in diabetic foot ulcer (DFU).

Methods The present study is a double-blind, vehicle (placebo)-controlled, randomized clinical trial in subjects with non-infected DFU of University of Texas grade 1A and 1C. Participants were randomized to receive either topical esmolol gel (Galnobax) with standard of care (SoC), SoC only, and vehicle (Placebo) with SoC in 3:3:1 proportion. The hematologic and biochemistry parameters were evaluated at the screening visit and at every 4 weeks after randomization during treatment phase and at the end of the study (EOS). Outcome was the proportion of complete ulcer closure with reference to baseline hemoglobin, albumin, and HbA1c during the 12-week treatment phase.

Results A total of 176 subjects were included. Ninety-four out of 140 participants (67.1%) had anemia at baseline. Among anemic participants, 57.4% ulcers closed in the Galnobax group whereas 42.6% closed in the SoC only group during the 12-week treatment phase ($p = 0.148$, OR = 1.823, 95% CI = 0.80–4.13). One-third participants reported albumin < 4.0 g/dL. Among participants having albumin < 4.0 g/dL (one-third of participants), the proportion of ulcer closure was 60.9% in the Galnobax group compared to 42.1% in the SoC only group ($p = 0.225$, OR = 2.139, 95% CI = 0.62–7.37). The proportion of ulcer closure in Galnobax with the SoC group was higher (72.5%) compared to the SoC only group (43.5%) ($p = 0.0067$, OR = 3.427, 95% CI = 1.38–8.48) in participants with poor glycemic control (HbA1c > 8%).

Conclusions Novel topical esmolol with SoC treatment exhibited significant DFU healing independent of patient-related factors including anemia, hypoalbuminemia, and poor glycemic control.

Keywords Diabetes · Wound helaing · Esmolol · Novel · Topical · Diabetic foot ulcer · Anemia · Glycemic control

Introduction

Wound healing is known to be impaired in anemia particularly in diabetic foot ulcer (DFU). In patients with diabetes, anemia is more common due to various factors such as poor nutrition, prevalent diabetic nephropathy, or chronic inflammation, increased levels of advanced glycation end products (AGEs), erythropoietin hypo-responsiveness, effects of oxidative stress, and certain anti-diabetic medications including pioglitazone [1, 2]. It has previously been observed that non-healing ulcers are prevalent (53.8%) in people with anemia compared to (29.1%) those without anemia ($p < 0.001$) leading to higher amputation rates [3, 4]. Another study demonstrated that hemoglobin < 11 g/dL is the most important independent factor for major amputation and death in DFU [5]. Further, Xie et al. in univariate analysis found that hemoglobin level was a predictor of mortality after amputation suggesting that lower hemoglobin is associated with poor wound healing [6].

Similarly, normal levels of albumin are required for appropriate wound healing as albumin is necessary for the repair and regeneration of tissues, including the tissues in the foot [7, 8]. Low serum albumin impairs the production

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of collagen and hampers binding to and neutralizing toxins produced by bacteria affecting the ability to fight infection [9]. Also, good glycemic control is likely to hasten wound healing. However, few clinical studies and subsequent meta-analysis showed no significant association between baseline HbA1c and wound healing [10]. A prospective study carried out in DFU [11] showed good correlation of HbA1c (< 7 mmol/L) with proportion of healing as well as time to healing of ulcer.

The association between HbA1c and wound outcomes in patients with DFUs has been investigated by several groups, and no consensus has been arrived. A retrospective analysis of patients with DFU did not show a clinically meaningful relation of ulcer healing with baseline or prospective HbA1c [12]. A recent meta-analysis of glycemic control with healing of DFU showed no association with HbA1c, and there was no compelling evidence to support tight glycemic control for improving DFU healing [13]. Thus, maintaining adequate hemoglobin, albumin, as well as glycemic control is important for the healing of diabetic foot ulcers.

Recently, a novel DFU treatment option in terms of topical gel of esmolol hydrochloride has been found effective for diabetic foot wound healing in phase 1–3 studies [14, 15]. In the phase 3 study, the proportion of DFU closure was significantly more in esmolol hydrochloride when added to standard of care (SoC) compared with the SoC only group. We report additional analysis by investigating the effect of baseline hemoglobin, albumin, and HbA1c levels on healing of DFU during the treatment phase of topical gel of esmolol hydrochloride. Moreover, we further explored any increase in the proportion of ulcer closure upon improvement in hemoglobin and albumin levels during treatment phase from the baseline.

Methods and Materials

The present study is a double-blind, vehicle (placebo)-controlled, randomized clinical trial to investigate the efficacy and safety of topical esmolol hydrochloride gel (Galnobax) treatment in subjects with DFU stratified on the basis of baseline hemoglobin, albumin, and glycemic control. This study was conducted in subjects with non-infected diabetic foot ulcers of grade 1A and 1C in 176 subjects [14]. The study included three groups, viz., topical esmolol gel (Galnobax) with SoC, SoC only, and vehicle (Placebo) with SoC in 3:3:1 proportion and twice daily administration of treatment. Being a double-blind study, the participants, investigator, and nurse performing application of gel were blinded to the randomization. Interactive web response system was utilized for randomization into three groups in the ratio of 3:3:1 as detailed earlier [15].

The study had three phases: screening phase (7 to 10 days from screening), treatment phase (up to 12 weeks starting from baseline visit with weekly visit to site by the subject), and follow-up phase (total of 12 weeks with site visits at week 2, week 4, week 8, and week 12 from the end of treatment). The primary outcome was the proportion of ulcer closure at EOT in Galnobax with SoC against the SoC only group. Target ulcer closure was defined as 100% re-epithelialisation without drainage or dressing requirement, confirmed on two consecutive site visits (2 weeks apart) from the first observation of closure. In this study, efficacy was evaluated in treatment groups of Galnobax with SoC against SoC only having 140 subjects in full analysis set (FAS) population. The SoC included wound cleaning by normal saline, maintenance of moist wound environment, and off-loading of the target ulcer. In addition, during site visits, the removal of necrotic, infected, and/or nonviable tissue by debridement and management of infection was done by the investigator, if required.

The hematologic and biochemistry parameters were evaluated at the screening visit and at every 4 weeks after randomization during the treatment phase and at the end of the study (EOS). The HbA1c was evaluated at screening visit, week 12 or end of treatment (EOT) as well as at week 24 or EOS. Hemoglobin < 13gm/dL (men) < 12 gm/dL (women) was considered anemia, serum albumin < 4 gm/dL as hypoalbuminemia, and HbA1c > 8% as poor glycemic control. For the present study, the proportion of complete ulcer closure was assessed with reference to baseline hemoglobin, albumin levels, and HbA1c as well as change in these levels from baseline during the 12-week treatment phase in two groups, viz Galnobax with SoC and SoC only.

Results

Wound healing outcomes based on anemia

The phase 1/2 study's findings, which showed 60% ulcer closures with esmolol and 14% gel with SoC, compared with 39% with SoC alone, were used to determine the sample size [14].

In this study, 94 out of 140 participants (67.1%) had anemia, whereas 46 participants had no anemia at the baseline. As shown in Table 1, among anemic participants, 57.4% ulcers (i.e., 27 ulcers out of 47) closed in Galnobax with the SoC group whereas only 42.6% (20 out of 47 ulcers) closed in the SoC only group during 12-week treatment phase ($p = 0.148$, OR = 1.823, 95% CI = 0.80–4.13). In non-anemic participants, 66.7% ulcers (i.e., 14 ulcers out of 21) closed in Galnobax with the SoC group whereas only 40.0% (10 out of 25 ulcers) closed in the SoC only group during 12-week treatment phase ($p = 0.071$, OR = 3.000, 95% CI

Table 1 Target ulcer closure within 12 weeks considering various subgroups based on baseline parameters of factors associated with wound healing

Subgroup	Galnobax®+SoC closure *N*/total *N* (%)	SoC only closure *N*/total *N* (%)	*p*-value, OR (95% CI) [1]
Anemic	27/47 (57.4%)	20/47 (42.6%)	0.15, 1.823 (0.80–4.13)
Non-anemic	14/21 (66.7%)	10/25 (40.0%)	0.07, 3.000 (0.89–10.06)
Males Hb < 13.5 g/dL	20/32 (62.5%)	10/31 (32.3%)	0.02, 3.500 (1.24–9.89)
Females Hb < 12.5 g/dL	7/15 (46.7%)	10/16 (62.5%)	0.32, 0.525 (0.13–2.20)
Males Hb ≥ 13.5 g/dL	11/18 (61.1%)	8/18 (44.4%)	0.32, 1.964 (0.52–7.41)
Females Hb ≥ 12.5 g/dL	3/3 (100%)	2/7 (28.6%)	0.43, 15.400 (0.56–425.55)
Albumin < 4 g/dL	14/23 (60.9%)	8/19 (42.1%)	0.23, 2.139 (0.62–7.37)
Albumin ≥ 4 g/dL	27/45 (60.0%)	22/53 (41.5%)	0.07, 2.114 (0.94–4.75)
HbA1c ≤ 8%	12/28 (42.9%)	10/26 (38.5%)	0.74, 1.200 (0.40–3.56)
HbA1c > 8%	29/40 (72.5%)	20/46 (43.5%)	0.007, 3.427 (1.38–8.48)

= 0.89–10.06). Among anemic males, 20 ulcers out of 32 (62.5%) closed within 12-week treatment in Galnobax with the SoC group, whereas only 10 ulcers out of 31 (32.2%) closed in the SoC only group ($p = 0.0163$, OR = 3.50, 95% CI = 1.24–9.89). Overall wound healing is better with topical esmolol irrespective of the presence of anemia. However, the proportion of ulcer closure is higher in male participants with anemia following Galnobax application.

Wound healing outcomes based on albumin

In this study, 42 out of 140 participants (30%) reported albumin below 4.0 g/dL, whereas 98 participants had albumin ≥ 4.0 g/dL at the baseline. As shown in Table 1, among participants having albumin < 4.0 g/dL, the proportion of ulcer closure was 60.9% (14/23 participants) in Galnobax with the SoC group compared to that in the SoC only group (8/19 = 42.1%) during 12-week treatment phase ($p = 0.225$, OR = 2.139, 95% CI = 0.62–7.37). For participants having albumin ≥ 4.0 g/dL, the proportion of ulcer closure in Galnobax with the SoC group was 60% (27 ulcers out of 45) compared to the SoC only group of 41.5% (i.e., 22 ulcers out of 53) during 12-week treatment phase ($p = 0.068$, OR = 2.114, 95% CI = 0.94–4.75).

Wound healing outcomes based on HbA1c

In this study, 54 out of 140 participants (38.6%) reported HbA1c ≤ 8%, whereas 86 participants had HbA1c > 8% at the baseline. As shown in Table 1, the proportion of ulcer closure was similar in Galnobax with the SoC group (11/28 = 42.9%) and SoC only group (10/26 = 38.5%) in subjects with HbA1c ≤ 8%. On the other hand, for subjects with poor glycemic control (HbA1c > 8%), the proportion of ulcer closure in Galnobax with the SoC group was higher (29/40 = 72.5%) compared to the SoC only group (20/46 = 43.5%) and significant ($p = 0.0067$, OR = 3.427, 95% CI = 1.38–8.48).

Change in hemoglobin, albumin, and HbA1c during 12-week treatment phase

We investigated the effect of administered treatment when these parameters improved in the participants during the treatment phase from baseline (i.e., Hb and albumin in treatment ≥ V1 and HbA1c in treatment ≤ V1). Table 2 shows that Galnobax with SoC treatment had significant advantage over SoC only treatment when hemoglobin, albumin, and HbA1c levels are maintained or improved over baseline during the treatment phase of the study. As shown in Table 2, the difference of proportion of ulcer closure in Galnobax with SoC as against SoC only for each parameter was higher than the overall difference in closure (18.6%).

We also investigated the proportion of participants who had their target ulcer closed or not during the 12-week treatment phase when hemoglobin, albumin, and HbA1c levels get worse from baseline when measured at weeks 4, 8, and 12 in the two groups. Table 3 shows that for subjects in Galnobax

Table 2 Proportion of ulcer closure when hemoglobin, albumin, and HbA1c parameters improve from baseline during the treatment phase for Galnobax with SoC and SoC only treatments

Parameter/treatment	Galnobax + SoC (*N* = 68)	SoC only (*N* = 72)	*p*-value (OR, 95% CI)
Hb in treatment ≥ V1 (baseline)	29/48 (60.4%)	19/48 (39.6%)	0.041 (2.33, 1.03–5.28)
Albumin in treatment ≥ V1 (baseline)	29/44 (65.9%)	23/51 (45.1%)	0.042 (2.35, 1.02–5.41)
HbA1c in treatment ≤ V1 (baseline)	27/40 (67.5%)	19/48 (39.6%)	0.009 (3.17, 1.32–7.63)

Table 3 Proportion of participants in the study in the category of closed or open (not closed) ulcers with change in hemoglobin, albumin, and HbA1c for Galnobax with SoC and SoC only treatments

	Galnobax + SoC			SoC only		
Parameter	In closed ulcers (41)	In not closed ulcers (27)	*p*-value	In closed ulcers (30)	In not closed ulcers (42)	*p*-value
Hb in treatment < V1 (baseline)	16/41 (39.0%)	21/27 (77.8%)	0.002	15/30 (50.0%)	25/42 (59.5%)	0.423
Albumin in treatment < V1 (baseline)	18/41 (43.9%)	19/27 (70.4%)	0.032	23/30 (76.7%)	31/42 (73.8%)	0.783
HbA1c in treatment > V1 (baseline)	14/41 (34.1%)	14/27 (51.9%)	0.147	11/30 (36.7%)	13/42 (31.0%)	0.612

with the SoC group, a significant proportion of participants had their ulcers open (77.8% not closed) having Hb level less than baseline during the treatment phase (at any of weeks 4, 8, and 12), whereas correspondingly only 39% subjects had their ulcers closed ($p = 0.002$). Similarly, for subjects whose albumin levels during treatment phase were less than the baseline values, a significant proportion of subjects were from open ulcers (70.4%) whereas only 43.9% subjects from closed ulcers exhibited reduction in albumin for subjects in Galnobax with the SoC group ($p = 0.032$).

For subjects whose HbA1c levels during treatment phase were greater than the baseline values, a high proportion of subjects were from open ulcers (51.9%) whereas only 34.1% subjects from closed ulcers exhibited an increase in HbA1c for subjects in Galnobax with SoC group ($p = 0.147$). Table 3 shows that in the SoC only group, the proportion of subjects having hemoglobin and albumin lower than baseline during treatment phase in open as well as closed ulcers was similar ($p > 0.05$). Similar was observed for the SoC only group when HbA1c was more than baseline during treatment phase in open as well as closed ulcers (36.7% in closed vs 31% in open ulcers, $p = 0.612$). Table 3 shows that worsening of hemoglobin, albumin, and HbA1c levels has significant impact in Galnobax with SoC treatment compared with SoC only treatment. Twenty-one ulcers were not healed in Galnobax + SoC when with Hb in treatment < 1; if appropriate treatment for the increase in Hb is provided, 60.4% of these ulcers, i.e., 13 ulcers are expected visit 1 heal (Table 2), leading to total ulcers that may heal would be (41 + 13 = 54 out 68) 79.4%. Further, 19 ulcers were not healed in Galnobax + SoC when with albumin in treatment < visit 1; if appropriate treatment for the increase in albumin is provided, 65.9% of these ulcers, i.e., 13 ulcers are expected to heal, leading to total ulcers that may heal would be (41 + 13 = 54 out 68) 79.4% (Table 2).

Discussion

This is the first assessment of the effect of presenting hemoglobin, albumin, and glycemic control on healing of DFUs comparing topical esmolol hydrochloride with SoC against SoC only treatment. The study showed that topical esmolol with SoC treatment exhibited significant DFU healing over SoC only treatment for subjects that are anemic or have poor glycemic control (HbA1c > 8%).

Anemia can reduce the amount of oxygen that is delivered to the tissues, delay the repair of damaged tissues, and impair the immune system's ability to fight off infections; all these factors are essential for the healing of diabetic foot ulcers (DFU) [3]. Gezawa ID et al. in a cohort of 336 patients with diabetes hospitalized for DFU found a significant association between anemia and poor wound healing, amputation, and mortality [16]. In diabetic patients having microvascular complications, reduced hemoglobin cannot be compensated by increasing peripheral perfusion or vasoreactivity and elevating erythropoietin [17, 18]. In DFU patients, oxygen delivery to the wound tissue may be achieved by facilitating angiogenesis in granulation tissue through vasodilation by enhancing inducible nitric oxide. As reported recently by Kulkarni et al. [19], topical esmolol hydrochloride gel (Galnobax) induces nitric oxide in wound tissue of diabetic rats thereby enhancing angiogenesis in granulation tissue, which may be the reason for healing of ulcers in a significant proportion of subjects with Galnobax with SoC against SoC only treatment in patients with anemia.

Low levels of albumin can impair the ability to repair wound tissues by reducing the transport of nutrients to the tissues necessary for wound healing. Hypoalbuminemia can also impair the absorption of oral drugs preventing wound healing. Even, albumin infusion has been shown to improve NF-κB signaling and reduce pro-inflammatory cytokines in rats that aids in wound healing [20]. Nagachinta et al. found an association between serum albumin less than 3.9 g/dL and wound infection [21]. According to Foley et al. [22], the postoperative complication rate was higher when albumin was lower than 2.5 g/dL ($p < 0.001$). Similar observation is reported for hemoglobin and albumin during the healing of DFU. We observed a statistically significant healing with topical esmolol gel over SoC only treatment when hemoglobin, albumin, and HbA1c are maintained or improved during the treatment

phase. The present analysis revealed a significant proportion of subjects had open or unhealed ulcers when hemoglobin and albumin during treatment worsened from the baseline as against the subjects having their ulcers closed. Based on this, an estimate for enhanced healing of DFU by topical esmolol gel with SoC treatment due to improvement in hemoglobin and albumin levels has been obtained. This clearly shows that the proportion of ulcer closure is higher in topical esmolol gel with the SoC group vs SoC only group at baseline for subjects with albumin either greater or less than 4.0 g/dL.

Treatment of anemia may include dietary changes, iron supplementation, or blood transfusions, depending on the severity and underlying cause of the anemia. For enhancing serum albumin during treatment, increasing proteins in diet may be useful. By addressing anemia and albumin early in DFU treatment, healthcare providers can improve the chances of successful wound healing and reduce the risk of complications associated with diabetic foot ulcers. The enhancement in ulcer closure may reach up to 79.4% from the current 60.3% if hemoglobin, albumin, and glycemic control are maintained or improved from the baseline levels. The results of the present study suggest maintaining or enhancing hemoglobin and albumin during treatment administration of topical esmolol gel with SoC in regular practice.

Good glycemic control has been considered one of the tenets for wound healing despite limited evidence for the assumption [23]. Poor glycemic control (HbA1c > 8%) is not associated with amputation risk in people presenting with first neuropathic foot ulcer [24]. But that does not undermine the utility of intensive glucose management. We observed that topical esmolol therapy when added to SoC was effective for wound healing even in patients with poor glycemic control at presentation.

If appropriate dietary changes or treatments are provided to subjects on topical esmolol therapy with SoC treatment for enhancing hemoglobin and albumin, about 79.4% ulcers are expected to close which is about 19.1% higher than that observed during phase 3 study [14]. In subjects with controlled HbA1c (< 7mmol/L), 48% ulcers achieved complete healing whereas in subjects with elevated HbA1c (> 10 mmol/L), only 23% ulcers healed within 3 months [11]. Thus, topical esmolol gel with SoC performs better than SoC only treatment for subjects with poor glycemic control.

Conclusion

Despite the presence of factors such as anemia, hypoalbuminemia, and poor glycemic control, which significantly impairing wound healing in patients with DFU, treatment with novel topical esmolol (Galnobax) with SoC exhibited significant DFU healing in subjects with non-infected diabetic foot ulcers of UT grade 1A and 1C at 12 weeks of treatment as compared to SoC. Thus, topical esmolol is a novel approach in the treatment of non-infected DFU.

Author contribution All authors contributed to the study conception and design. Material preparation, data collection, and analysis were performed by Sudhir Kulkarni and Ashu Rastogi. The first draft of the manuscript was written by Sudhir Kulkarni and Ashu Rastogi, and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

Data Availability Data pertaining to the manuscript is available on reasonable request from corresponding author.

Declarations

Ethics approval and consent to participate Involved human participants. A written and informed consent was obtained from all participants.

Conflict of interest Dr. Sudhir Kulkarni has the patent of the topical preparation of Esmolol (Galnobax). The authors declare no conflict of interest.

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