

Original Article

Effects of Ilizarov transverse tibial transport combined with truncated human epidermal growth factor gel on glucose metabolism, inflammation, and pain in patients with diabetic foot

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Abstract: Objective: To investigate the efficacy of Ilizarov transverse tibial bone transport combined with truncated human epidermal growth factor gel in the treatment of Wagner grade 2-3 diabetic foot ulcer, and its effects on glucose metabolism, inflammation, pain, and lower limb circulation. Methods: A retrospective analysis was conducted on 98 patients treated from Oct 2022 to Dec 2024. Patients were divided into a combined therapy group (CG, n=50) and a surgery-only group (MG, n=48). All patients received standard care and tibial bone transport, while patients in the CG additionally received truncated human epidermal growth factor gel treatment. Glycosylated hemoglobin (HbA1c), fasting blood glucose (FBG), 2-hour postprandial blood glucose (2h-PBG), inflammatory markers, coagulation markers, visual analog scale (VAS) pain score, ankle-brachial index (ABI), and limb skin temperature before and after treatment, as well as overall clinical efficacy, were compared between the two groups. Results: Post-treatment HbA1c, FBG, 2h-PBG, inflammatory and coagulation markers were significantly lower in the CG than in the MG (all $P<0.05$). Compared to the MG, the CG showed significantly lower VAS scores and higher ABI values and skin temperature of the affected limb at 14, 28, and 56 days after treatment ($P<0.05$). The total effective rate was 86% in the CG, significantly higher than 68.75% in the MG ($P<0.05$). Conclusions: Combined therapy can improve glucose metabolism, alleviate inflammation and pain, and enhance lower limb perfusion, demonstrating superior clinical efficacy compared to tibial bone transport alone in patients with Wagner grade 2-3 diabetic foot ulcer.

Keywords: DF, Wagner grade 2-3, Ilizarov TTT, human epidermal growth factor (LR truncated) gel, indicators of glucose metabolism

Introduction

Diabetic foot (DF) is a major long-term complication of diabetes mellitus, resulting from persistent hyperglycemia-induced damage to both neural and vascular structures. These pathologic changes lead to sensory loss and circulatory deficits, thereby increasing patients' susceptibility to foot infections, ulcer formation, and gangrene [1-3]. Clinical manifestations of DF include numbness, tingling, or burning sensations in the feet, along with signs of infection such as swelling, exudate, and ulcerative lesions. Since these individuals suffer from diabetes, meticulous foot care is essential; other-

wise, even minor wounds or blisters may progress to severe infections and ultimately necessitate amputation [4, 5]. The Wagner classification system is widely used to assess the severity of DF lesions, relying primarily on ulcer depth and extent of tissue destruction. The Wagner grading system (**Table 1**) generally defines grade 2 lesions as deep ulcers extending to tendons, ligaments, joint capsules, or deep fascia without bone involvement [6]. Grade 3 lesions involve deeper tissues and are typically characterized by osteomyelitis, abscess formation, or joint involvement. For Wagner Grade 2 and 3 lesions, treatment strategies mainly include wound debridement, local dressing changes,

Table 1. Wagner classification criteria

Grading	Description
0	No ulceration; however, there may be foot deformities, sensory abnormalities, or signs of vascular lesions.
1	Superficial ulceration involving the skin and subcutaneous tissue without penetration into deeper structures.
2	Deep ulceration extending to tendons, ligaments, and joint capsules, or deep fascia, without abscess formation, osteomyelitis, or joint involvement.
3	Deep ulceration with abscess formation, osteomyelitis, or joint involvement.
4	Gangrene involving part of the foot.
5	Extensive gangrene involving the entire foot.

foot protection, pain management, and other supportive measures; In addition, glycemic control is required to promote wound healing and prevent further complications [7-13]. Early diagnosis and timely treatment are crucial for preventing progression and reducing the risk of amputation.

Ilizarov transverse tibial transport (TTT) is performed using an Ilizarov external fixation device. This is usually used in the treatment of tibial fractures, delayed fracture healing, bone infections, and limb deformities [14]. During the procedure, an Ilizarov external fixation frame is applied around the affected tibia, followed by gradual adjustment of the screws and fixation components to achieve transverse tibial transport. This technique has demonstrated a high success rate and a shorter recovery period, improving patients' quality of life (QoL) [15]. Truncated human epidermal growth factor gel is a western medicine preparation that can promote epidermal cell proliferation and accelerate wound healing. It has been widely used for the treatment of skin ulcers, wounds, burns, and other skin lesions, contributing to tissue repair and regeneration [16, 17].

A comprehensive treatment strategy is essential for the management of DF, aiming to minimize disease progression and improve patients' QoL. Therefore, this study aimed to investigate the efficacy of Ilizarov TTT combined with truncated human epidermal growth factor gel in the treatment of Wagner grade 2-3 DF and to evaluate changes in serum inflammatory factors. By assessing the effects of surgical intervention combined with adjunctive pharmacologic therapy, this study provides evidence for more effective treatment and clinical guidance to promote DF rehabilitation and prevent disease progression.

Materials and methods

Subjects

Data from the 98 DF patients with Wagner grade 2-3 who were treated at Zhangjiakou First Hospital between October 2022 and December 2024 were collected retrospectively. This study was approved by the Ethics Committee of Zhangjiakou First Hospital.

Inclusion criteria: (1) Age of 40-70 years; (2) Clear consciousness and stable vital signs; (3) Wagner grade 2-3; (4) Good treatment compliance.

Exclusion criteria: (1) Diabetic ketoacidosis or hyperosmolar hyperglycemic state; (2) Severe hepatic or renal dysfunction; (3) Cardiopulmonary insufficiency; (4) Absence of follow-up data during treatment; (5) Incomplete clinical data.

Ethical approval

This study protocol was approved by the Ethics Committee of Zhangjiakou First Hospital. The study was conducted in accordance with the ethical guidelines outlined in the Declaration of Helsinki. Because this study involved a retrospective analysis of medical records without additional clinical interventions, the requirement for informed consent was waived by the ethics committee. All patient data were de-identified to protect privacy.

Grouping and treatment plan

The 98 subjects were divided into the combined therapy group (CG, n=50) and the control group (MG, n=48) according to different treatment regimens. Patients in the MG received Ilizarov TTT in combination with routine founda-

tional therapy, whereas patients in the CG additionally received truncated human epidermal growth factor gel (Guilin Huanuowei Gene Pharmaceutical Co., Ltd., China, 20 g per tube) based on the treatment in the MG. Baseline characteristics, including sex, age, duration of diabetes, body mass index (BMI), and ulcer length, showed no significant differences between the two groups ($P>0.05$), indicating comparability between groups.

All patients received basic treatment. Systemic management included glycemic, blood pressure, and lipid control, anti-inflammatory treatment, nutritional support, and improvement of blood circulation. Local management included wound cleaning, disinfection, dressing changes, pressure offloading to prevent the formation of new ulcers, and surgical intervention if necessary.

Ilizarov TTT: On the day of surgery, patients underwent general anesthesia. After thorough preparation and disinfection of the surgical site, patients were placed in the supine position with venous access established and ECG monitoring performed. A surgical incision was made at the tibia, and the bone was exposed to prepare for transverse bone transport. The tibial bone was then transversely transported using the Ilizarov device, with adjustments performed according to the specific condition of the patient to achieve the planned displacement. After completing the transport procedure, the Ilizarov device was secured to maintain bone stability. During the subsequent treatment period, new bone formation occurred at the transported site.

Truncated human epidermal growth factor gel: After surgery, truncated human epidermal growth factor gel was evenly applied topically to the wound surface three times daily for 3 months.

Collection of clinical indicators

(1) Glucose metabolism indices, including glycosylated hemoglobin (HbA1c), fasting plasma glucose (FPG), and 2-hour postprandial blood glucose (2 h-PBG), serum inflammatory cytokine levels, including C-reactive protein (CRP), interleukin-6 (IL-6), and white blood cell count (WBC), and coagulation function markers, including D-dimer (D-D) and fibrinogen (FIB), were collected before and after treatment.

(2) Pain scores assessed using the visual analog scale (VAS), ankle-brachial index (ABI), and skin temperature of the affected limb were recorded at 14, 28, and 56 days after treatment.

(3) Clinical efficacy was classified into three levels: markedly effective, effective, and ineffective, according to the following quantitative criteria: ① Markedly effective: ulcer area reduction $\geq 70\%$, VAS pain score reduction ≥ 2 points, ABI increase ≥ 0.15 , and at day 56 of treatment, no wound exudate and no recurrent infection; ② Effective: ulcer area reduction of 30%-69%, VAS pain score reduction of 1-2 points, ABI increase of 0.05-0.14, with only occasional minimal exudate and no progressive infection; ③ Ineffective: ulcer area reduction $< 30\%$ or even enlargement, no improvement or worsening of pain symptoms, no increase or a decrease in ABI, and persistent wound exudate or secondary infection.

$$\text{Total effective rate} = \frac{\text{Number of effective cases} + \text{Number of valid cases}}{\text{Total number of cases}}$$

Statistical methods

Statistical analyses were performed using SPSS 19.0. Continuous variables were expressed as mean $\pm$ SD (SD), and compared using an independent-samples t-test. Categorical variables were expressed as numbers and percentages (n, %) and compared between groups using a chi-square test. Repeated-measures analysis of variance (ANOVA) and two-way ANOVA were used for comparisons among groups and time points. A $P<0.05$ was considered significant.

Results

Comparison of baseline characteristics between the two groups

As shown in **Table 2**, no significant differences were observed between the two groups in terms of sex, age, duration of diabetes, body mass index (BMI), ulcer duration, or Wagner grade ($P>0.05$), indicating that the two groups were comparable in baseline characteristics.

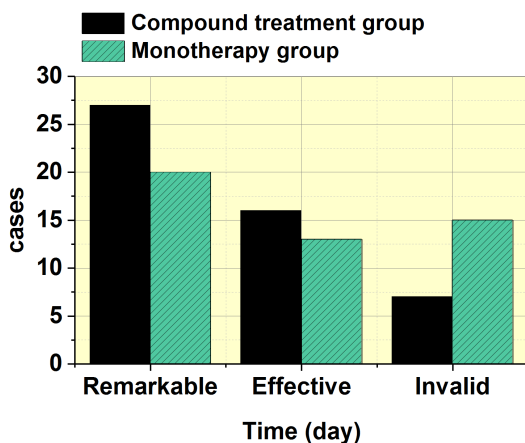
Clinical efficacy

In CG, 43 of the 50 patients achieved markedly effective or effective outcomes, yielding an overall response rate of 86%. In MG, 33 of the

Table 2. Comparison of baseline characteristics between the two groups

Variable	CG (n=50)	MG (n=48)	χ^2/t	P
Sex (n, male/female)	28/22	27/21	0.012	0.913
Age (years, mean $\pm$ SD)	56.3 $\pm$ 7.2	55.8 $\pm$ 7.5	0.341	0.734
Duration of diabetes mellitus (years, mean $\pm$ SD)	10.2 $\pm$ 3.5	9.8 $\pm$ 3.7	0.552	0.582
BMI (kg/m ² , mean $\pm$ SD)	24.1 $\pm$ 2.3	23.8 $\pm$ 2.5	0.633	0.528
Duration of ulcer (months, mean $\pm$ SD)	2.8 $\pm$ 1.1	2.9 $\pm$ 1.2	0.435	0.664
Wagner grade (n)			0.075	0.784
Grade 2	31	29		
Grade 3	19	19		

Notes: CG, combined therapy group (n=50); MG, surgery-only group (n=48); BMI, body mass index.

**Figure 1.** Clinical efficacy in the two groups.

48 patients achieved markedly effective or effective outcomes, with an overall response rate of 68.75%. Compared to the MG, the CG showed a significantly higher overall response rate ($P<0.05$; **Figure 1**).

Glucose metabolism indicators before and after treatment

There were no significant differences in HbA1c, FPG, or 2 h-PBG before and after treatment in the MG ($P>0.05$). After intervention, the levels of these three indicators in the CG were significantly decreased compared to baseline values. Moreover, the CG exhibited substantially lower HbA1c, FPG, and 2 h-PBG levels than the MG after treatment (all $P<0.05$) (**Figure 2**).

Inflammatory factors and coagulation function indicators

There were no significant differences in inflammatory factors, including CRP, IL-6, and WBC,

as well as coagulation function markers, including D-D and FIB, between the two groups before treatment ($P>0.05$). After treatment, the levels of these markers were significantly decreased in the CG compared to baseline values. Furthermore, compared to the MG, the CG exhibited significantly lower levels of inflammatory factors and coagulation markers after treatment (all $P<0.05$) (**Figures 3, 4**).

Pain score, skin temperature of the affected limb, and ankle-brachial index

At 14, 28, and 56 days after treatment, VAS pain scores in both groups were significantly decreased compared with baseline values before treatment. Moreover, the VAS pain scores observed in CG were significantly lower than those in the surgery-only group at each time point (all $P<0.05$) (**Figure 5**).

At 14 days after treatment, no significant differences were detected between the two groups in terms of skin temperature of the affected limb or ABI compared to baseline values ($P>0.05$). However, at 28 and 56 days after treatment, both affected limb skin temperature and ABI were significantly increased compared to baseline, and the combined treatment group had significantly higher values than the surgery-only group (all $P<0.05$) (**Figure 6**).

Discussion

Diabetic foot is a serious complication of diabetes mellitus, characterized primarily by neurological dysfunction, vascular impairment, and foot infections. Regular foot care, routine podiatric assessment, and stringent glycemic control are essential for both preventing and managing DF [18, 19]. Standard clinical man-

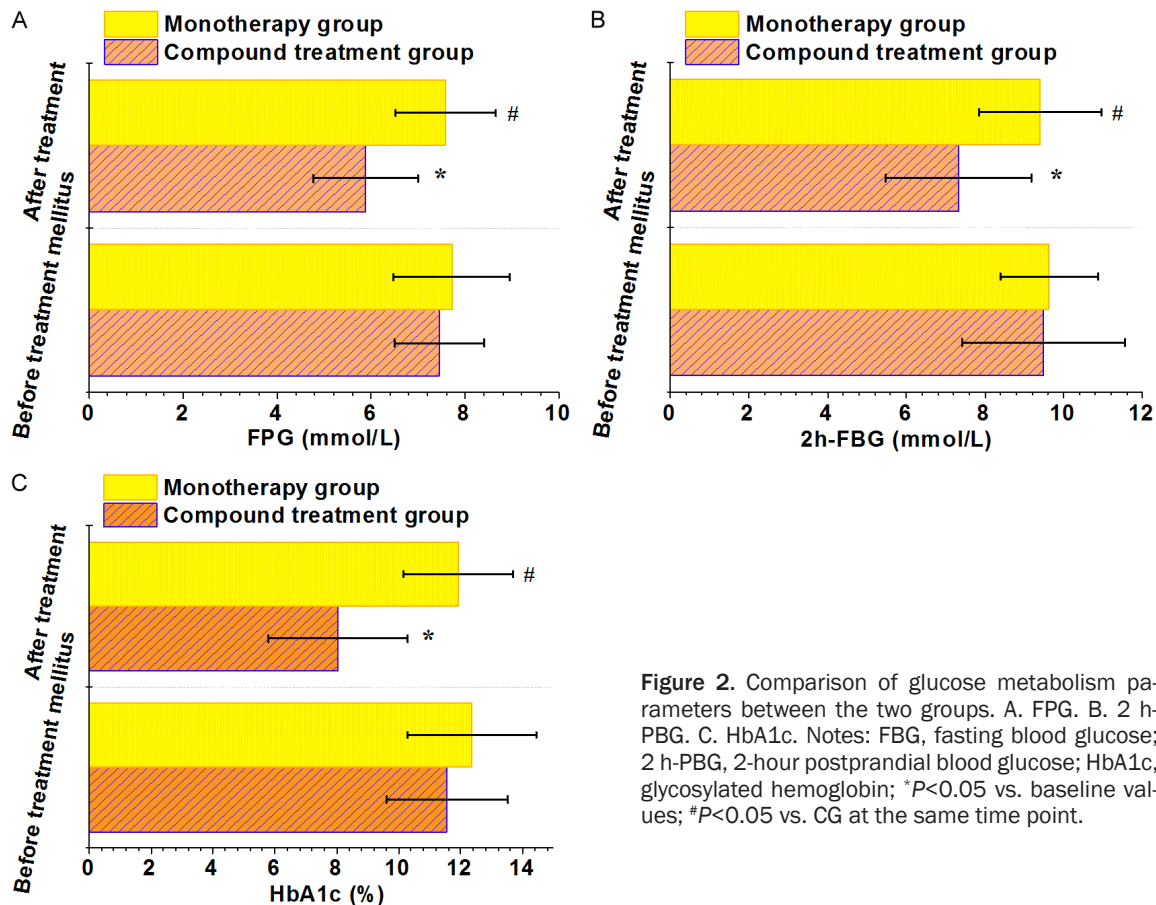


Figure 2. Comparison of glucose metabolism parameters between the two groups. A. FPG. B. 2 h-PBG. C. HbA1c. Notes: FBG, fasting blood glucose; 2 h-PBG, 2-hour postprandial blood glucose; HbA1c, glycosylated hemoglobin; * $P < 0.05$ vs. baseline values; # $P < 0.05$ vs. CG at the same time point.

agement strategies for DF include wound care, infection control, and ulcer treatment; however, considerable variability exists among patients, necessitating personalized therapeutic strategies [20, 21]. This study retrospectively analyzed the clinical data of 98 individuals diagnosed with Wagner grade 2-3 DF who were assigned to either a combined therapy group (50 cases) or a surgery-alone group (48 cases).

Indicators of glucose metabolism reflect the body's capacity to regulate blood glucose levels and are closely associated with wound healing. After treatment, the combined therapy group exhibited significantly lower levels of glycated hemoglobin, fasting plasma glucose, and 2-hour postprandial glucose compared to the surgery-alone group. These findings suggested that the Ilizarov TTT together with truncated human epidermal growth factor gel may contribute to improved glucose metabolism in patients with DF, which was consistent with previous reports [22]. Inflammatory responses also play an important role in the occurrence

and progression of DF ulcers. After treatment, serum levels of CRP, IL-6, and WBC were decreased in both groups compared to baseline values, with a more pronounced reduction observed in the combined therapy group. Zhen et al. [23] employed the Ilizarov technique-based transverse tibial transport to treat patients with severe DF ulcers and reported significant reductions in WBC, erythrocyte sedimentation rate, and CRP levels after treatment. The findings of the present study were consistent with previous reports, suggesting that the combination of truncated human epidermal growth factor gel and Ilizarov TTT may help reduce inflammatory responses and promote wound healing.

Existing basic research has suggested molecular pathways through which tibial transverse transport and epidermal growth factor (EGF) regulate glucose metabolism and inflammation [24]. Tibial transverse transport may improve lower extremity microcirculation, enhance peripheral GLUT4 expression, and alleviate

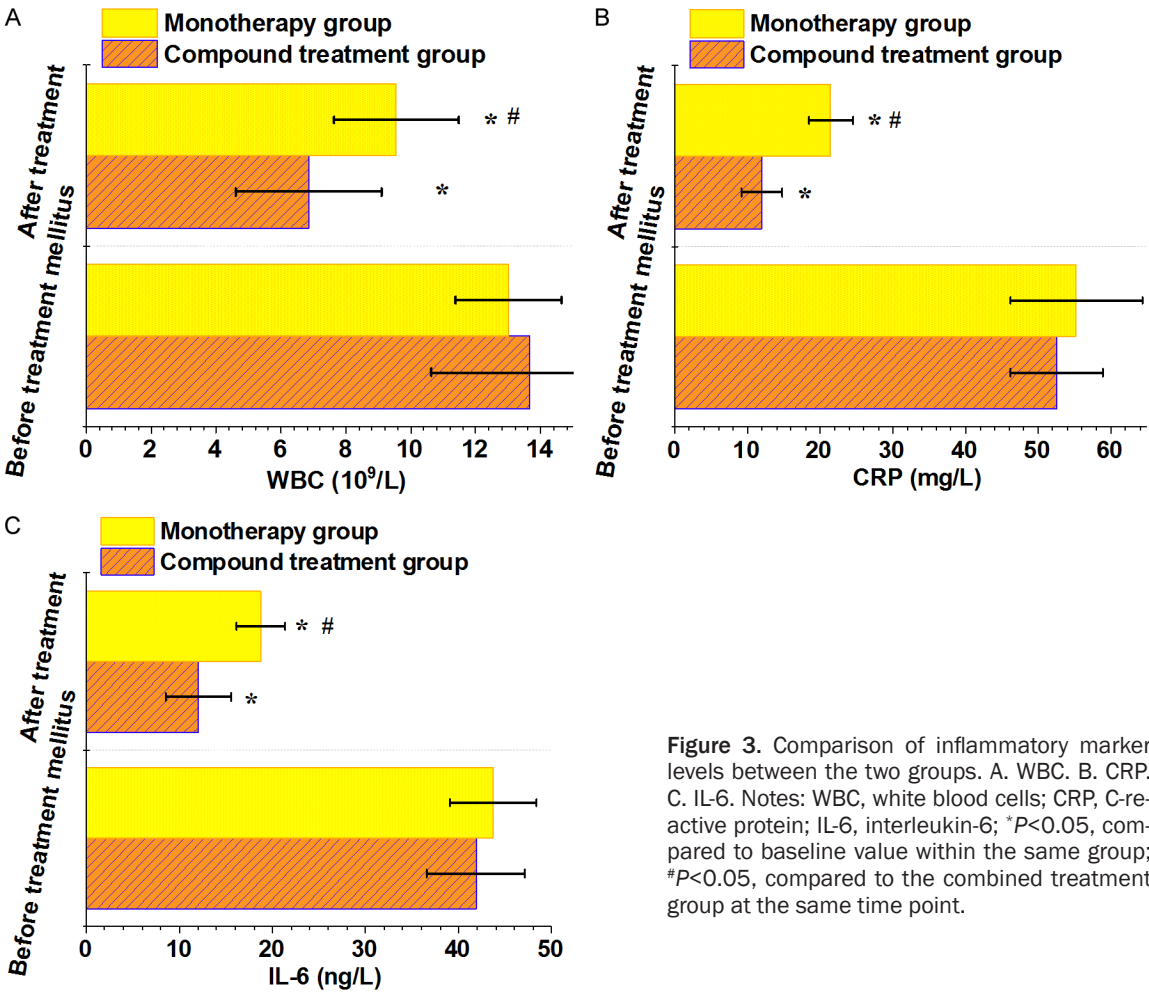


Figure 3. Comparison of inflammatory marker levels between the two groups. A. WBC. B. CRP. C. IL-6. Notes: WBC, white blood cells; CRP, C-reactive protein; IL-6, interleukin-6; * $P<0.05$, compared to baseline value within the same group; # $P<0.05$, compared to the combined treatment group at the same time point.

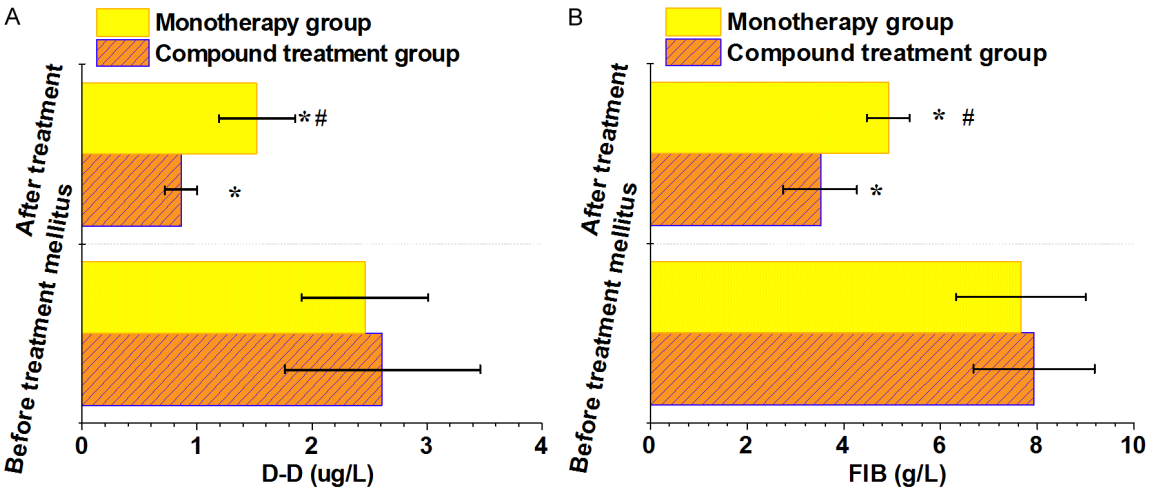


Figure 4. Comparison of coagulation function markers between the two groups. A. D-D. B. FIB. Notes: D-D, D-dimer; FIB, fibrinogen; * $P<0.05$, compared to baseline value; # $P<0.05$ compared to the combined treatment group at the same time point.

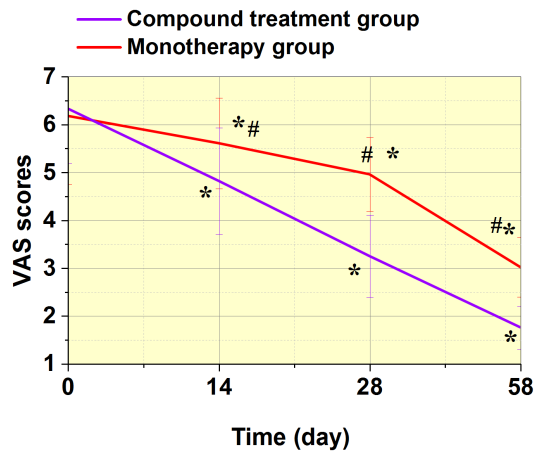


Figure 5. Comparison of VAS pain scores between the two groups. Notes: VAS, visual analog scale; * $P < 0.05$, compared to baseline value; # $P < 0.05$, compared to the combined treatment group at the same time point.

insulin resistance, whereas EGF can inhibit the NF- κ B signaling pathway and reduce the expression of downstream pro-inflammatory cytokines, including TNF- α and IL-1 β [25]. However, due to the retrospective design of this study, molecular assays for these biomarkers were not performed, precluding direct interpretation of underlying mechanisms responsible for improvements in glucose metabolism and inflammatory regulation. Instead, the overall therapeutic effects observed in this study were evaluated based on clinical markers, including blood glucose levels, CRP, IL-6, and WBC.

Previous animal studies have confirmed that tibial transverse transport can reconstruct lower extremity microcirculation and regulate the expression of angiogenesis-related growth factors [26]. However, to date, experimental evidence confirming a synergistic effect between EGF gel and tibial transverse transport in promoting angiogenesis or regulating growth factor expression remains limited. In this study, the combination therapy group achieved superior clinical outcomes and laboratory indicators compared to the surgery-alone group; however, cellular and animal experimental data supporting a synergistic mechanism were unavailable. Therefore, the synergistic mechanism underlying this combined therapeutic approach warrants further investigation in future basic research.

D-dimer and fibrinogen are valuable markers for evaluating coagulation and fibrinolytic system activity, while alterations in affected limb skin temperature and ABI provide valuable information regarding lower limb perfusion and arterial stenosis [27]. In this study, the combined therapy group exhibited lower levels of D-dimer and fibrinogen, as well as higher skin temperature and ABI values of the affected limb, compared to the TTT-alone group after treatment, suggesting that the combined regimen may improve lower extremity circulation and coagulation status. Postoperative pain is an important factor affecting patient recovery. The VAS pain scores of patients in the combined therapy group at 14, 28, and 56 days after treatment were significantly lower than those observed in the surgery-alone group, indicating that the addition of truncated human epidermal growth factor gel to Ilizarov transverse tibial bone transport may contribute to postoperative pain relief [28].

Regarding clinical efficacy, the overall efficacy rate in the combined therapy group reached 86%, which was substantially greater than the 68.75% observed in the surgery-alone group. These findings indicated that the addition of truncated human epidermal growth factor gel as an adjunctive treatment alongside surgery may further improve the overall therapeutic efficacy in patients with Wagner grade 2-3 DF.

Several limitations in this study should be acknowledged. First, this study was based solely on routine clinical and biochemical parameters. Core regulatory molecules involved in glucose metabolism, including insulin, C-peptide, HOMA-IR, and GLUT4, as well as key inflammatory pathway-related proteins, including NF- κ B, TNF- α , and IL-1 β , were not evaluated. Moreover, the underlying molecular mechanisms of the combined therapy could not be directly clarified. In addition, wound tissues were not preserved for histologic or cytologic verification, limiting further verification of tissue-level mechanisms. Second, the relatively small sample size and short follow-up duration may have limited the robustness and generalizability of the findings; Furthermore, as a retrospective study, potential confounding factors could not be completely controlled. Future prospective clinical studies should incorporate standardized molecular assays, collect

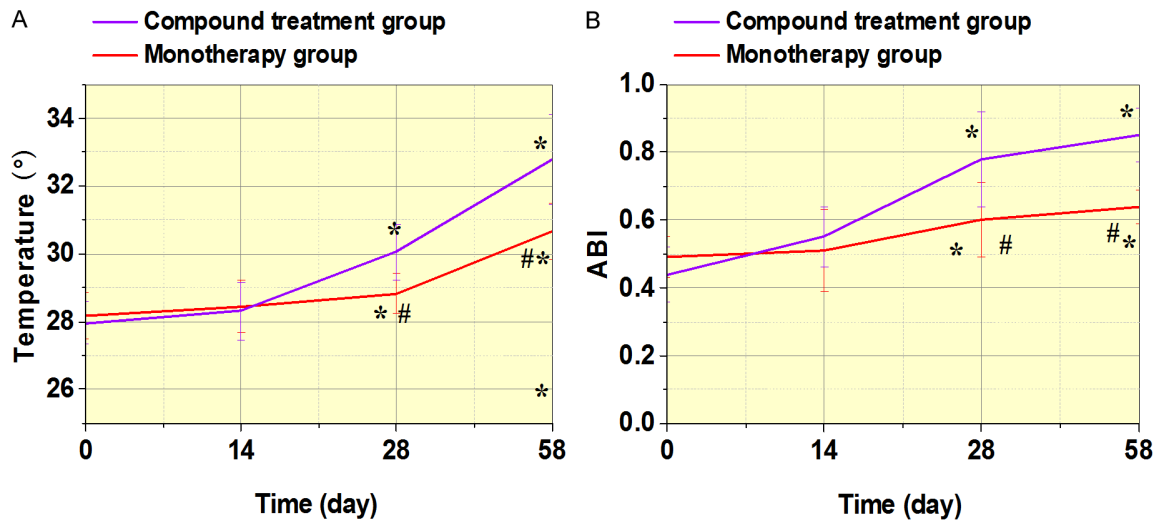


Figure 6. Comparison of affected limb skin temperature and ABI between the two groups. A. Skin temperature. B. Ankle-brachial index. Notes: ABI, ankle-brachial index; * $P < 0.05$, compared to pre-treatment level; ** $P < 0.05$, compared to the combined treatment group at the same time point.

wound granulation tissue for pathologic and cellular analyses, and include larger sample sizes with longer follow-up periods, so as to further explore the mechanisms and long-term efficacy of this combined therapeutic regimen. In addition, animal studies may provide further insight into the mechanism of combined topical EGF gel and surgical intervention in DF treatment.

Conclusion

This retrospective study analyzed the clinical records of 98 individuals diagnosed with Wagner grade 2-3 DF and compared the recovery outcomes among patients receiving different therapeutic regimens. The results indicated that Ilizarov TTT combined with truncated human epidermal growth factor gel was associated with improved glucose metabolism, reduced inflammatory response, alleviated pain, and better overall clinical efficacy compared to Ilizarov TTT alone.

Disclosure of conflict of interest

None.

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