Autologous platelet-rich gel in the treatment of diabetic foot ulcers
A retrospective study
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Abstract
This study retrospectively investigated the effectiveness and safety of autologous platelet-rich gel (APRG) for the treatment of diabetic foot ulcers (DFU). In this retrospective study, we reviewed the electronic medical records (EMR) of 72 patients with DFU. The patients were allocated to a treatment group (n = 36) or a control group (n = 36). The patients in both groups received standard care (SC) and dressing change. In addition, patients in the treatment group also received APRG. Patients in both groups were treated for 12 weeks. The outcomes were DFU healing time (days), length of hospital stay (days), healing rate of DFU, DFU surface area reduction (cm²), and adverse events. We assessed and analyzed the outcomes before and after the 12-week treatment period. After treatment, there were significant differences in DFU healing time (P = .04), length of hospital stay (P = .04), DFU healing rate, and DFU surface area reduction (P < .01). Regarding safety, no EMR reported adverse events in this study. The results of this study showed that the APRG may benefit patients with DFU. However, high-quality prospective randomized controlled trials are required to verify these findings.

Abbreviations: APRG = autologous platelet-rich gel, DFU = diabetic foot ulcers, DM = diabetes mellitus, EMR = electronic medical records, SC = standard care.

Keywords: autologous platelet-rich gel, diabetic foot ulcers, effectiveness, standard care

1. Introduction
Diabetic foot ulcer (DFU) is one of the most common complications of diabetes mellitus (DM), which often result in disability and is associated with an increase risk of mortality.[1–3] It is also a leading cause of lower extremity amputation in patients with diabetes.[4] It has been reported that about 15% to 25% of patients with DM experience DFU in their lifetime.[5–7] Previous studies also reported that its annual incidence varied from 9.1 million to 26.1 million around the world.[7,8] Other studies have reported that the incidence of DFU is approximately 8% in hospitalized patients with DM in China.[9,10] Studies have found that DFU pathogenesis generally involves peripheral nerve lesions and peripheral artery diseases.[11,12]

DFU can occur at any age; however, it mostly affects patients with DM at or over 45 years old. Its etiology commonly includes glycemic control, calluses, foot deformities, and improper footwear. Its management modalities include standard care (SC) (debridement, offloading, moist-retain dressings, and infection management), cellular or/tissue-based products, ozone therapy, local warming therapy, and Chinese herbal medicine.[11–16] In addition, an increasing number of studies have focused on autologous platelet-rich gel (APRG) for the treatment of DFU.[17–24] However, there is limited evidence to support the effectiveness and safety of APRG for the treatment of DFU. Therefore, this retrospective study investigated the effectiveness and safety of the APRG in the management of patients with DFU.

2. Methods
2.1. Ethical statement
The need for ethical approval for this study was waived because all data were retrospectively collected and analyzed from the completed patient records. Written informed consent was obtained from all included patients.

2.2. Study population
This study retrospectively collected electronic medical records (EMR) of adults patients (≥18 years old) with DFU who were admitted to Yanan University Affiliated Hospital from November 2019 to December 2021. DFU was diagnosed on the basis of the World Health Organization diagnostic criteria for diabetes in 1999.[25,26]

The exclusion criteria were as follows: patients with severe diseases, such as cancers; patients who received organ...
transplantation; patients who were unable to communicate or had mental disorders; and incomplete information on EMR.

2.3. Treatment modality
This retrospective study analyzed 72 eligible patient EMR with DFU. They were divided into a treatment group (n = 36) or a control group (n = 36). The patients in both groups received SC and dressing change. Additionally, patients in the treatment group underwent APRG.

2.3.1. SC in both groups. Patients in both groups received SC. SC included intensive insulin therapy for strictly controlling blood glucose, serum lipid and blood pressure, as well as administering anti-platelets, improving microcirculation, repairing nerve and anti-infection therapy. In addition, techniques such as vasodilator therapy or vascular bypass were used to improve the local blood supply. Furthermore, patients were asked to rest in bed or use a wheelchair or to raise the affected limb properly in order to promote local blood reflux and edema resolution. Finally, the diabetic skin ulcers were treated with standard management (debridement, drainage, decompensation, dressing change, and moisturizing).

2.3.2. Self-made APRG. The self-made APRG was produced based on the previous study.[27] Before preparation, venous blood was collected from the patients with 3.2% vacutainer sodium citrate. The amount of blood was determined according to the size of the ulcer surface (10 mL/1 cm²). The collected blood was centrifuged at a low speed of 2000 r/min for 5 minutes, then the supernatant was collected, and the mixture of the supernatant and the supernatant was put into another centrifuge tube at a low speed of 2000 r/min and 3 mm below the boundary of the stratification. After 3 minutes of resting, the supernatant was centrifuged at 1200 r/min for 10 minutes, and 3/4 of the supernatant was discarded, get platelet-rich plasma. In addition, thrombin powder 5000 was added to 5 mL of 10% calcium chloride to prepare thrombin-calcium agent mixture, which was mixed with blood-rich small, platelet-rich plasma in a 1:10 ratio to obtain platelet-rich gel, store in 4°C refrigerator for later use.

2.3.3. Treatment group. Patients in the treatment group were treated with self-made APRG, which was injected into the sinus or covered evenly on the surface of the ulcer after thorough debridement of the ulcer.[28] After the APRG coagulated and stabilized, the DFU was sealed with Suyule dressings and bandaged with secondary dressings. The APRG was changed every 2 weeks until the wound healed or at the end of the 12th week. The dressing was changed every 3 days until the wound healed or at the end of the 12th week.

2.3.4. Control group. Patients in the control group were directly administered a Suyule dressing to seal the wound and then bandaged with a secondary dressing. The dressing was changed every 3 days until the wound healed or at the end of the 12th week.

2.4. Outcome measurements
Outcomes included DFU healing time (days), length of hospital stay (days), DFU healing rate, and DFU surface area reduction (cm²), and adverse events.

DFU healing time was defined as the time of complete DFU healing. Length of hospital stay was defined from the hospital admission day until discharge. DFU healing rate (including cure rate and total effective rate) was defined as follows: DFU cure: the ulcer wound healed completely at the end of the treatment course and the walking function was restored; DFU improvement: the ulcer healing area or volume was 80% more than the original wound area or volume at the end of the treatment course; Ineffectiveness: the area or volume of ulcer healing was less than 30% of the original wound area or volume, the ulcer did not heal or the wound did not change or enlarge at the end of the treatment course.[29] DFU cure rate was defined as the number of patient cured/36 patients, and total effective rate was defined as the number of patient cured and improved/36 patients. DFU surface area reduction was expressed as surface area change in cm² since baseline. Outcome data were collected and analyzed before and after 12-week treatment.

2.5. Statistical analysis
SPSS software (SPSS 17.0, IBM Corp., Armonk, NY) was used for data analysis. For continuous data, Student’s t test (such as length of hospital stay) or Mann–Whitney U test (such as DFU healing time, DFU surface area reduction) was applied based on data with normal or non-normal distribution. For discontinuous data, Fisher’s exact test (such as DFU healing rate) was utilized. We set a value of P < .05 (2-side) as having statistically significant.

3. Results
The EMR of the DFU are presented in Figure 1. A total of 178 EMR from DFU patients were initially screened. One hundred and six EMR were excluded because of incomplete medical records (n = 56), age < 18 years (n = 25), severe disease (n = 19), and organ transplantation (n = 6). After elimination, 72 eligible EMR were included in the final data analysis.

General EMR information is summarized in Table 1. There were no significant differences in age, sex, body mass index, DM duration, DFU duration, DFU surface area, platelet count, albumin/globulin level, creatinine level, glycosylated hemoglobin A1, and hemoglobin.

There were significant statistical differences on DFU healing time (days) (treatment group, 32.7 ± 20.3 vs control group, 43.2 ± 22.1) (P = .04), length of hospital stay (days) (treatment group, 50.4 ± 23.2 vs control group, 62.1 ± 25.6) (P = .04), DFU cure rate (number (%) (treatment group, 35 (97.2%) vs control group, 19 (52.8%)) (P < .01), and total effective rate (number (%%)) (treatment group, 36 (100.0%) vs control group, 27 (75.0%)) (P < .05) between the 2 groups.

The DFU surface area (cm²) are listed in Table 2. There were no significant difference in DFU surface area (treatment group, 3.3 ± 2.1 vs control group, 3.1 ± 2.4; P = .71). However, significant difference in the DFU surface area reduction was identified between the 2 groups (P < .01; Table 2).

In terms of safety, no EMR recorded any APRG-related adverse events in this study.

4. Discussion
DFU is caused by neuropathy, insufficient blood supply, excessive local tissue degradation, increased senescent cells, and decreased responsiveness to cell signals, resulting in a poor response to general therapy.[30] Chronic refractory ulcers often develop when wounds are invaded by exogenous factors such as trauma and infection.[31] Studies have found that platelets not only have a hemostatic effect but also release many growth factors and cytokines after their activation, which play a key role in tissue regeneration and wound healing.

APRG, as a secondary platelet-derived agent, is easy to obtain and prepare, and it has become an effective and adjunctive modality for chronic or acute wounds. It mainly includes platelets, leukocytes, fibrin, growth factors and cytokines, and it has a function of anti-infection[32] and immunomodulatory.[33] On the other hand, leukocytes also affect the release of growth factors such as transforming growth factor and the production
of vascular endothelial growth factor, which plays an important role in promoting angiogenesis.\(^{34}\) Fibrin in APRG, owing to its adhesive properties and the role of fibronectin, has the potential to promote healing. When APRG is evenly applied to wounds or skin ulcers due to platelet rupture, the wound or ulcer surface is covered with a layer of high concentrations of growth factors to promote wound healing, and platelets themselves and platelet activation releases antimicrobial active peptides to fight microbes to prevent wound infection.\(^{35,36}\)

In this retrospective study, we analyzed the EMR of patients with DFU. A total of 72 eligible EMR were allocated to the treatment and control groups, with 36 patients in each group. Patients in both groups received SC. In addition, patients in the treatment group also received APRG. The results showed that patients in the treatment group achieved better outcomes in DFU healing time (days), length of hospital stay (days), healing rate of DFU, and DFU surface area (cm\(^2\)) than those in the control group. These findings suggest that the APRG may be effective in...

### Table 1
Comparison of general characteristics between 2 groups.

| Characteristics        | Treatment group (n = 36) | Control group (n = 36) | P    |
|------------------------|--------------------------|------------------------|------|
| Age (yrs)              | 62.5 (10.1)              | 64.2 (9.8)             | .47  |
| Gender                 |                          |                        |      |
| Male                   | 22 (61.1)                | 20 (55.6)              | .63  |
| Female                 | 14 (38.9)                | 16 (44.4)              | .      |
| BMI (kg/m\(^2\))       | 25.7 (3.1)               | 25.0 (3.3)             | .35  |
| DM duration (yrs)      | 10.4 (5.7)               | 11.1 (5.3)             | .59  |
| DFU duration (d)       | 28.2 (17.8)              | 26.9 (18.3)            | .76  |
| PLT (10\(^9\)/L)       | 243.7 (82.4)             | 229.3 (89.1)           | .48  |
| A/G                    | 1.11 (0.29)              | 1.09 (0.31)            | .78  |
| Cr (μmol/L)            | 89.8 (44.5)              | 92.4 (50.8)            | .82  |
| HbA1c (%)              | 9.45 (2.8)               | 9.50 (3.0)             | .87  |
| Hb (g/L)               | 110.0 (21.7)             | 114.8 (24.4)           | .38  |

Data are present as mean ± standard deviation or number (%). A = albumin, BMI = body mass index, Cr = creatinine, DM = diabetes mellitus, G = globulin, Hb = hemoglobin, HbA1c = glycosylated hemoglobin A1C, PLT = platelet.

### Table 2
Comparison of DFU surface area reduction between the 2 groups.

| DFU surface area (cm\(^2\)) | Treatment group (n = 36) | Control group (n = 36) | P    |
|-----------------------------|--------------------------|------------------------|------|
| Before treatment            | 3.3 (2.1)                | 3.1 (2.4)              | .71  |
| Area reduction after treatment | −3.1 (−5.9, −2.3)      | −2.3 (−3.0, −1.5)      | <.01 |

Data are present as mean ± standard deviation (range). DFU = diabetic foot ulcers.
the treatment of patients with DFU. Regarding safety, no EMR documented any adverse events in this study. There are several limitations in this study. First, the results and findings of this study may have been influenced by confounding factors, such as patient comorbidities; wound duration, and severity of DFU. Second, this study may have had sufficient outcomes because of the limited data of the existing EMR. Third, no data of adverse events was recorded in the original patient records, which may affect safety profile of APRG in patients with DFU. Fourth, all data were collected from Yanan University Affiliated Hospital, which may restrict its generalization to other hospitals.

5. Conclusion
This study showed that the APRG exerted promising efficacy in the treatment of patients with DFU. Further clinical trials are required to warrant the present findings.

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