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A randomized controlled study of autogenous platelet-rich gel and standard therapy in the treatment of diabetic refractory skin ulcer

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Abstract

Objective To evaluate the efficacy and safety of autogenous platelet-rich gel (APG) in the treatment of diabetic refractory skin ulcers. Methods from April 2017 to February 2018, 56 patients with diabetic skin ulcers hospitalized in our department were randomly divided into APG treatment (23 cases) and standard treatment group (33 cases). Both groups of patients used insulin to control blood sugar, strictly control the orbit and blood lipids, and were given anti-blood plates, improved microcirculation, anti-infection and other general treatments and standard treatment of local ulcer wounds. Patients in the APG treatment group used self-made APG and applied wound dressing according to the wound volume / area; the standard treatment group applied wound dressing directly. The course of treatment is until the wound is healed, a flap transplant is performed, or it is over 12 weeks. Results All patients except the standard treatment group were lost to follow-up. The ulcer healing rate in the APG group was 22/23 (95.7%) and the total effective rate was 100%; the ulcer healing rate in the standard treatment group was 23/33 (69.6%) and the total effective rate was 72.1% The difference between the two groups was statistically significant (P values were o.002 and O.009, respectively); analysis of the healing curve and sinus closure curve during Meier ulcer in Kaplan Meier analysis P <O. 05, showing that APG treatment was significantly better than standard treatment; no side effects related to APG treatment were found during treatment. Conclusion APG is better than standard treatment for diabetic refractory skin ulcers, and it has more advantages in treating ulcers with sinus tract; APG is safe, effective and feasible for diabetic refractory skin ulcers.

Keywords*: autogenous platelet-rich gel; randomized controlled trial; diabetic foot; refractory skin ulcer.*

Introduction

The probability of diabetic foot (DF) in diabetic patients is as high as 12% to 25% [1], and the skin ulcers of diabetic hands, back, neck and other parts also tend to increase. Traditional debridement, callus dressing and the efficacy of a single growth factor dressing is not satisfactory. The application of autogenous platelet-rich gel (APG) in the treatment of DF ulcers has opened up a new way. To date, the only two randomized controlled studies [2,3] results show that the effect of APG treatment is significantly better than the standard treatment group; The pre-test study found that in 13 patients with diabetic refractory skin ulcers, after 12 weeks of APG treatment, the ulcer healing rate was 69.2%, the sinus tract healing rate was 83.3%, and there was no adverse reaction during treatment occur. However, these studies still have defects such as small sample size and high loss of follow-up rate. Therefore, based on the previous study, we again designed a

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randomized controlled trial for 12 weeks of treatment and observation to further verify that APG is difficult to treat diabetes. The effectiveness and safety of curative skin ulcers.

Research Object

For the inclusion and exclusion of research subjects and the criteria for determining efficacy, see the literature [4]. From April 2017 to February 2018, 142 patients with diabetic skin ulcers hospitalized in our department were screened. According to the inclusion and exclusion criteria, a total of 46 patients (26 males and 20 females) were included, of which 44 were type 2 diabetes, 2 cases of type 1 diabetes, with an average age of 61.2 ± 9.3 years old. Before the start of the trial, a random number table was generated by the computer, and the patients were randomly divided into the experimental group (APG treatment group) and the control group (standard treatment group) in the order of enrollment time. There were 19 cases of DF ulcer in the APG treatment group (10 cases of DF grade II and 9 cases of grade III), 1 case of gluteal pressure ulcer grade IV, 1 case of neck ulcer, 1 case of diabetic hand, and 1 case of rouge abscess; standard treatment group DF ulcer 22 cases (13 cases of DF grade II, 9 cases of grade III), 1 case of gluteal pressure sore (grade IV).

Research methods

1. Treatment methods: (1) Both groups of patients are controlled by insulin to control blood sugar, strict control of blood lipids, blood pressure, while giving anti-platelet, improve microcirculation, nutritional nerve, anti-infection treatment; if necessary, vasodilator therapy, percutaneous intraluminal balloon Dilatation, stent implantation, or vascular bypass improve blood supply; brake (bed rest or wheelchair); properly raise the affected limb to promote blood reflux and edema resolution. (2) Apply standard treatment for diabetic skin ulcers on local wounds (debridement, drainage, decompression, dressing replacement, moisturizing, etc.). The patients in the standard treatment group were selected to complete the debridement of the ulcer wounds, directly use wound dressing to pack and apply the dressing, and use a second-level dressing for external dressing. Patients in the APG treatment group, after the patient's ulcers were completely debrided, the self-made APG was quickly injected into the sinus tract and sprayed evenly on the wound surface. After the APG coagulated and stabilized, the wound surface was closed with wound dressing and externally covered with secondary dressing. For the preparation of APG, see [5]. (3) All patients used digital photography to retain ulcer picture data for ulcer area assessment before entering the group [6], and recorded the presence or absence of ulcer sinus tract. Replace in 2 ~ 3 days wound dressing once, until the patient's wound healed, transferred to orthopedics for flap transplantation or amputation. The ulcer did not heal and the discharged patient continued to change the dressing. The total observation period is 12 weeks (84 days). According to the wound outcome during the treatment, the secretions are cultured if necessary. After discharge, all patients were followed by outpatient or telephone visits every 3 months.
2. Observation indicators: ulcer healing rate, total effective rate, time for ulcer to reach the end point (ulcer healing / suitable skin grafting / expiration of observation period), sinus tract closure time, hospitalization time Strictly monitor and record systemic clinical symptoms, changes in local ulcer wounds and changes in laboratory examination indicators, and determine the relationship with the test method.

Statistical processing

Use SPSSl3. o Software analysis. The measurement data of normal distribution is described by i ± s, and the independent sample 𝔈 test is used; the measurement data of non-normal data distribution is described by the median (25th to 75th)%, and Wilcoxon rank sum test is used; Y2 test; Kaplan Meier survival analysis was used to test the rate of ulcer healing and sinus tract closure in the two groups. Inspection level is 1.05.

1. Comparison of the general conditions of the two groups of patients

A total of 46 patients were included, 23 in each of the APG group and the standard treatment group. Except for one case lost in the standard treatment group, the remaining patients completed the trial. The age, sex, duration of diabetes, duration of ulcer, and HbA of the two groups of patients. c. There is no statistical difference between the ankle-brachial index (AIX), the distribution of sinus tracts and the initial ulcer area and volume (P> 0.05, Table 1); FPG, 2hPG, BP, blood routine, There was no statistically significant difference in liver and kidney function, blood lipids and other indicators (P> 0.05); during the treatment, 22 pathogens were detected in the standard treatment group, 21 pathogens were detected in the APG treatment

group, and the two groups of patients There was no statistically significant difference in the infection rate of pathogens in ulcers ($\chi^2 = 0.357$, $P > 0.05$).

Table l: I clinical data comparison between the two groups (i ± s, median energy)

Group	n(M/F)	Age(yr)	DM Duration (months)	DF Duration (d)	Sinus (y/n)	HbA_{1c} (%)	Initial wound area (cm^2)	Initial wound volume (cm3)	ABI
Standard	23(13/10)	66±10	121±90	25(16~76)	13/10	8.95±2.54	2.49(1.37~3.44)	1.00(0.37~1.44)	1.00±0.28
APG	23(13/10)	61±14	113±77	23(13~55)	16/7	10.9±3.52	3.12(1.47~10.20)	1.72(0.42~3.78)	1.00±0.16
P	1.00	0.144	0.724	0.542	0.538	0.203	0.309	0.122	0.396

2. Comparison of treatment effect between two groups of patients

The ulcer healing rate of patients in the APG treatment group was 22/23 (95.7%), and the total effective rate was 100%. The ulcer healing rate in the standard treatment group was 13/23 (56.5%), and the total effective rate was 73.9%. The difference between the two groups was statistically significant (P values were 0.002 and 0.009, respectively); Kaplan-Meier ulcer time healing curve analysis and sinus tract closure curve analysis showed that with the prolongation of treatment time, the treatment observation period ended At the time, the estimated healing rate of the target ulcer in the APG treatment group was 95.7%, while the estimated healing rate in the standard treatment group was 56.5% (P=0.006); the estimated closure rate of the target sinus tract in the APG treatment group was loo . o%, and the estimated healing rate of the standard treatment group is 31.5% (P=O.000), showing that whether it is ulcer or sinus, APG treatment is significantly better than standard treatment (see Figures 1, 2); but two The time for the patients to reach the end point of treatment in the group (33.04 ± 24.15 days, 44.87 ± 26.05 days), the healing time of the cured patients (32.44 ± 23.20 days, still 35.93 ± 20.74 days)) And hospitalization time (51.78 ± 28.15 days, Handan 58.52 ± 28.73 days), the difference was not statistically significant (all P> 0.05).

3. Follow-up observation

After the end of the observation period of 12 weeks, 2 patients in the standard treatment group were judged to be significantly effective in the treatment of skin ulcers (1 of which was automatically discharged and lost to follow-up), and 2 patients were judged to be effective (1 of whom died 20 days after the automatic discharge Heart failure), 3 patients were judged to be ineffective; 5 patients who continued treatment in the hospital were all transferred to APG treatment, and the sinus tract was closed after 3 to 6 days, and 4 patients were on the 9th, 15th, and 15th days after APG treatment. The ulcer healed in 97 days. One patient was discharged on the 18th day after treatment, and the ulcer healed in February. One patient in the APG treatment group was effective, and was transferred to the orthopedics department for flap transplantation on the 36th day after treatment due to joint capsule defect, and healed on the 58th day after the end of the observation period. After treatment, there were 18 patients with adverse events (12 in the APG treatment group and 6 in the standard treatment group P> 0.05). During treatment, ant ulcers and tingling sensations appeared on the ulcer wounds, and the granulation tissue and epithelium of the wounds during the same period the tissue grows well, and the above discomforts are not treated with special treatment, and all relieve themselves. During the course of treatment, 2 patients in the control group were discharged from hospital with acute renal insufficiency, but their ulcers were better than before. In the APG treatment group, one patient failed the first APG treatment, and the secretion culture was the same as before treatment, which was Pseudomonas aeruginosa; the other patient had infection in the sinus after two APG treatments, and the secretion culture Proteus mirabilis and Candida albicans, consistent with the microbial culture results before APG treatment; suggesting that the failure of APG treatment has nothing to do with APG itself, but because of insufficient wound treatment before treatment, there are still bacterial and fungal infections, non-APG preparation Pollution in the process; the two patients were cured after sufficient treatment of the wound and then APG treatment. No adverse events related to APG treatment occurred during the entire treatment.

Discussion

Diabetic skin ulcers due to neuropathy, insufficient blood supply, excessive local tissue degradation, increased senescent cells, and decreased reactivity to cell signals, resulting in low responsiveness to general treatment [8]. Under the influence of exogenous factors (such as trauma, infection), the wound is often difficult to heal and form

Chronic incurable ulcer [7]. A large number of studies have found that platelets not only have hemostatic effect, but also release a large amount of growth factors and cytokines after their activation, which plays a key role in tissue regeneration and wound healing.

As a second-generation platelet-derived preparation, APG is easy to obtain and easy to manufacture. A certain percentage of thrombin and calcium is added to platelet-rich plasma (PRP) to form a plastic gel, which has become an auxiliary treatment method for chronic or acute wounds One. The results of this study show that the ulcer healing rate in the APG treatment group reached 95.7% during the 12-week observation period, while the standard treatment group only

56.5%, the total effective rate of the two groups is 100. O% and 73.9%, the difference was statistically significant; survival analysis of ulcer healing time indicated that the non-healing rate of ulcers in the standard treatment group was significantly higher than that in the APG treatment group. In addition, APG showed a more obvious advantage in the treatment of refractory skin ulcer sinus tract closure. Survival analysis of sinus tract closure time of skin ulcers indicated that the rate of sinus tract closure by APG treatment was significantly better than that of standard treatment. The results of our previous studies suggest that APG is effective, safe and feasible for the treatment of refractory diabetic skin ulcers.

APG is rich in a large number of growth factors and cytokines [5]. The literature reports that growth factors have the advantage of reducing local wound edema and analgesia, thereby shortening the time for ulcer healing and hospital stay [9]. This study reached the end event (healing / suitable for skin grafting / expiry of observation period)

12 weeks) and hospitalization time, the results found that APG treatment of ulcer healing time was shortened by nearly 12 days, and hospitalization time was shortened by at least 1 week, but none of them reached statistical significance. These results are inconsistent with literature reports, which may be due to this study Due to the small sample size, the study needs to be continued to increase the sample size.

A total of 46 patients were included in this study. Except for one patient who was lost to follow-up in the standard treatment group (the lost-to-interview rate was 4.34%), all other patients completed the observation of the trial. During the entire treatment and follow-up process, no side effects related to APG treatment were observed, which was consistent with the previous observations [3 to 5].

How does APG promote the healing of diabetic refractory skin ulcers? Research shows that after adding thrombin and calcium to PRP to form APG, platelets are quickly activated, and activated platelets are considered to be the initiating factors for the regeneration and repair of all tissues. The most critical regulatory factor. In the granulation tissue of the wound after APG treatment, a variety of growth factors and cytokines have been significantly increased, including platelet-derived growth factor (PDGF), transforming growth factor (TGF) a, p, and epidermal growth factor (EGF), Insulin-like growth factor (IGF-1), vascular skin growth factor (VEGF), connective tissue growth factor (CTGF), platelet activating factor (PAF), p-thrombin-sensitive protein, antibacterial peptides, platelet factor 4 (PF4) , And a variety of proteins such as fibrinogen, fibronectin, soluble complement, vitrioling, etc. [10 to 12], among which PDGF and TGF are the most important growth factors for tissue regeneration and wound healing, while CTGF is tissue repair The central activating factor can promote chondrocytes, endothelial cells, fibroblasts chemotaxis, migration, adhesion, proliferation and differentiation; after the release of activated platelet a particles, they bind to cell membrane receptors and act on neutrophils and macrophages 、 Fibroblasts, induce the aggregation of inflammatory cells, and further release growth factors, cytokines and various proteases PG fibrin scaffold,

which is combined with the cell membrane of undifferentiated cells, regulates the signal transmission between them and initiates cell differentiation; promotes the proliferation, migration and neovascularization of fibroblasts, endothelial cells and keratinocytes, and then Collagen deposition, tissue reconstruction. Ulcers with severe bacterial infections are often accompanied by increased inflammation and tissue inactivation, which induces abnormally increased levels of matrix metalloproteinases (MMPs) and imbalances of MMPs / matrix metalloproteinase inhibitors, while degrading inactivated tissues and destroying a large number of Growth factors and cytokines. Our research found that in vitro experiments, APG has a significant inhibitory activity against Staphylococcus aureus with a parabolic change trend with the course of disease, It has a certain bacteriostatic effect on Escherichia coli and Pseudomonas aeruginosa; at the same time, it was found that APG treatment can reduce the content of matrix metalloproteinases in granulation tissue of refractory skin ulcers of diabetes to a certain extent, and increase matrix metalloproteinases. The content of inhibitors can regulate the imbalance of proteolytic enzymes in diabetic chronic ulcers (data to be published); and because APG not only contains a high concentration of activated platelets, but also contains a large amount of fibrin, it can also play a better role in ulcers Sinus occlusion and wound defect filling, these mechanisms may partially explain the reason why the sinus tract closure rate in the APG treatment group was significantly greater than the standard treatment group in this study. In conclusion, the results of this study show that APG is better than standard treatment for diabetic refractory skin ulcers and has more prominent advantages in the treatment of sinus ulcers; APG is safe, effective and feasible for the treatment of diabetic refractory skin ulcer It is worthy of clinical application.

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