Original Article

Effect of Yinqi Ointment on Wound Morphology and Growth Factor in Treating Diabetic Foot Ulcer

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Abstract

Objective: To investigate the effect of Yinqi ointment on wound morphology and growth factor in treating diabetic foot ulcer (DFU). **Methods:** From December 2016 to December 2017, 92 cases of DFU with deficiency of both Qi and Yin syndrome were randomly divided into treatment group and control group (44 cases in each group). The treatment group was treated with Yinqi ointment, while the control group was treated with mupirocin ointment. After 4 weeks of treatment, the ulcer healing effect, ulcer area, granulation tissue, epithelial tissue coverage, pain score, and dynamic analysis of vascular endothelial growth factor (VEGF), epidermis growth factor (EGF), and basic fibroblast growth factor (bFGF) in local granulation tissue were statistically analyzed before and after treatment in both groups. **Results:** The total effective rate was 88.37% in the treatment group and 74.42% in the control group. The wound reduction rate, epithelial tissue coverage rate, granulation tissue growth rate, and local pain relief rate in the treatment group were significantly superior to those in the control group ($P < 0.05$). Through the local granulation detection, the treatment group and the control group have increased VEGF, EGF, and bFGF, but the treatment group increased the role of growth factor than the control group. **Conclusion:** Yinqi ointment can promote the healing of DFU, and its mechanism may be related to the increase of the content of growth factor in granulation tissue.

Keywords: Diabetic foot ulcer, growth factor, wound healing, Yinqi ointment

Introduction

Diabetic foot ulcer (DFU) is characterized by high incidence,[1] high disability,[2] and high cost.[3] According to the latest survey of diabetes epidemiology, the prevalence rate of diabetes in the adult population in China is close to 12%. There are about 140 million diabetes patients in the whole country, accounting for 1/4 of all diabetes patients in the world. At the same time, the study also showed that in patients with amputation, patients with diabetes are far greater than the risk of nondiabetic patients.[4] Evidence-based medicine also shows that the integrated internal and external treatment of DFU is far more effective than a single treatment, can effectively prevent the occurrence of foot ulcer, and can avoid amputation.[5] Prof. Pang He (1952), Director of Oriental Hospital of Beijing University of traditional Chinese Medicine, Ph. D., Supervisor, the Fifth Group of Chinese Medicine Experts in the whole country, inherited the academic experience of the old Chinese medicine experts, The experience of "Yinqi ointment" in the treatment of DFUs has achieved some results. The following is the report: (1) "Yinqi ointment" is an effective method for the treatment of DFUs.

Access this article online

Quick Response Code:

Website: www.wjtcm.net

DOI: 10.4103/wjtcm.wjtcm_6_19

Data and Methods

General information

From December 2016 to December 2017, 92 patients with DFU were selected from the Department of Peripheral Vascular and Endocrinology of Dongzhimen Hospital. A randomized, open, single-center, positive drug-controlled study was conducted. The patients were divided into two groups: treatment group ($n = 46$) and control group ($n = 46$). There were two cases of exfoliation in the treatment group and two cases in the control group. Eighty-eight cases were completed and included in the statistics.

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Received: 12-09-2018, **Accepted:** 29-01-2019

How to cite this article: Liu YL, Li YS, Du YQ, Dai S. Effect of Yinqi ointment on wound morphology and growth factor in treating diabetic foot ulcer. World J Tradit Chin Med 2019;5:29-35.

Table 1: Clinical efficacy evaluation

	Ulcer area	Ulcer depth	Granulation
Principal syndrome			
0 score	Healing	Healing	Healing, no pus, no redness around sores
2 score	≤3 cm^2	Deep in epidermis	Red activity, purulent seroid secretion, redness and swelling around sores <0.5 cm from the edge of the wound
4 score	4-6 cm^2	Deep in dermis	Light red, thick pus, redness around sores 0.5 cm-1 cm away from the edge of the wound
6 score	>6 cm^2	Deep under the skin	Edema, large volume of pus, filth, redness around sores from wound margin >1 cm
Secondary syndrome			
0 score	No pain		No thirsty, no dry stool, no yellow urine
1 score	Slight pain, not affecting work or daily life		Thirst, dry stools, yellow urine
2 score	Moderate pain, affecting work and daily life		
3 score	The pain is obvious, affects the work and the daily life, and needs the bed rest		

Table 2: Comparison of age distribution

Subset	*n*	40-49	50-59	60-70 (%)	70-80 (%)	$\bar{X}+S$
Treatment group	44	9 (20.45)	9 (20.45)	15 (34.09)	11 (25)	64.32±10.62
Control group	44	8 (18.18)	10 (22.72)	14 (31.82)	12 (27.27)	65.38±10.18

Table 3: Comparison of gender composition (%)

Subset	*n*	Male (%)	Female (%)
Treatment group (Chinese medicine group)	44	27 (61.36)	17 (38.63)
Control group (Western medicine group)	44	25 (56.82)	19 (43.18)

Diagnostic Criteria

- Diagnostic criteria of Western Medicine: Diabetic foot was diagnosed according to the Chinese Diagnostic guidelines for Diabetic foot (2017 Edition)
- Standard of differentiation of symptoms and signs of traditional Chinese medicine (TCM) refers to the teaching material for planning of Chinese medical colleges and universities in the new century, "TCM surgery" for removing both Qi and Yin of anthrax: The course of disease is long; the sore surface does not heal long after the necrotic tissue falls off, the granulation is dark red or pale but not fresh; the lassitude is weak. The complexion is little, the physique is emaciated, and the five is upset hot; the tongue is light and pointed red, few moss; the pulse is thin and weak.

Inclusion criteria

(1) In accordance with the diagnostic and dialectical criteria of diabetic foot, (2) diabetic foot II–III grade ulcer, (3) ages in 18, 80 years, (4) wound area ≤30 cm^2, and (5) voluntary to participate in this study, signed informed consent, good compliance.

Exclusion criteria

(1) Cancerous, tuberculous and other specific ulcers, hypersensitivity, (2) severe internal diseases such as heart, brain, liver, kidney, hematopoiesis, and endocrine system, (3) acute lower limb ischemia, (4) lactation and pregnancy, (5) history of mental illness, (6) severe malnutrition, and (7) those who could not be corrected were enrolled in other trials during the first 2 months of the study.

Methods of intervention

In this study, a randomized, open, single-center, positive drug-controlled clinical study was conducted. Baseline therapy: (1) Active stabilization of underlying diseases, control of blood lipids, blood pressure, blood sugar within the normal range, (2) necessary anti-infection, nutritional nerve, and improvement of microcirculation therapy. Wound management: (1) Wound bed preparation: According to the specific situation of the wound, the necessary debridement was carried out. Make the wound base no bleeding, no bone exposure, granulation red activity, (2) wound dressing: Treatment group with Yinqi ointment (prepared by the preparation room of Dongzhimen Hospital) evenly smeared on sterile gauze, covered in wound bandage, three times a week. The patients in the control group were treated with mupirocin ointment (more than 100 Bang, Chinese Medicine Standard Character H10930064, batch number: 16100279) evenly applied to the wound and bandaged three times a week for 4 weeks.

Observed indicators

The wound area of the two groups was taken at 0d, 7d, 14d, 21d, and 28d, respectively, and the area was measured by Photoshop CS image processing software (Adobe Systems Incorporated, San Jose, State of California, USA). The same clinician who did not know the classification of the patients was required to perform.

The venous blood of the patients was taken at 0d, 7d, 14d, 21d, and 28d to detect the content of vascular endothelial

Table 4: Comparison of diabetes duration (year)

Subset	*n*	0-1 year	1-5 years	5-10 years	10-20 years	>20 years	$\bar{X}+S$
Treatment group	44	5	6	6	14	13	10.92±6.48
Control group	44	6	5	6	13	14	11.21±5.39

Table 5: Comparison of diabetic foot ulcer duration (month)

Subset	*n*	0-1 month	1-2 months	2-6 months	6-12 months	>12 months	$\bar{X}+S$
Treatment group	44	3	9	17	12	5	7.01±6.02
Control group	44	2	10	17	11	4	6.78±5.82

Table 6: Comparison of therapeutic effects

Subset	*n*	Recovery (case)	Remarkable effect (case)	Effective (case)	Invalid (case)	Cure rate + apparent efficiency (%)	Total effective rate (%)
Treatment group	44	6	18	14	5	55.81	88.37
Control group	44	4	12	16	11	37.21	74.42

Table 7: Comparison of ulcer area before and after treatment (S)

Subset	*n*	Ulcer area before treatment (cm^2)	Ulcer area after treatment (cm^2)	*Z*	*P*	Wound reduction rate (%)
Treatment group	44	7.13±6.01	3.45±1.73	−4.214	0.000	42.61±18.42
Control group	44	7.54±7.98	5.28±3.21	−4.312	0.000	40.21±22.18
Z		−0.392	−0.376			−2.266
P		0.547	0.318			0.042

Table 8: Comparison of granulation tissue changes before and after treatment with ($\bar{X}\pm S$)

Subset	Treatment group	Control group	t/Z	*P*
n	44	44		
Granulation tissue area before treatment (cm^2)	0.89±0.78	0.78±1.21	−0.112 (*Z*)	0.567
Granulation tissue area after treatment (cm^2)	1.87±1.54	1.38±1.78	−0.492 (*Z*)	0.478
t/Z	−2.785 (t)	−1.574 (*Z*)		
P	0.001	0.100		
Granulation tissue coverage before treatment (%)	12.78±12.45	17.30±13.42	−0.814 (*Z*)	0.523
Granulation tissue coverage after treatment (%)	56.34±23.22	40.21±21.80	−4.456 (*Z*)	0.004
t	−9.823	−3.982		
P	0.000	0.000		
Granulation tissue growth rate (%)	61.18±22.24	40.67±22.70	2.636 (t)	0.006

Table 9: Comparison of epithelial tissue coverage after treatment ($\bar{X}+S$)

Subset	*n*	Epithelial tissue coverage (cm^2)	Epithelial tissue coverage (%)
Treatment group	44	5.73±4.18	59.72±24.22
Control group	44	4.67±4.34	45.56±23.42
t/Z		−1.345 (*Z*)	−2.732 (*t*)
P		0.228	0.009

growth factor (VEGF), epidermal growth factor (EGF), and basic fibroblast growth factor (bFGF). The curative effect was evaluated. The granulation tissue (about 0.3 cm × 0.3 cm) at the wound center of the patients with good compliance was taken at day 0, 14, and 28, respectively, and soaked in paraformaldehyde solution. The granulation tissue was desiccated, embedded, sliced, and detected in the later stage. The pathological sections were observed under 100- and 400-fold microscope, and the cells of VEGF, EGF, and bFGF in blood were counted by Image-Pro Plus 6 image processing software (MEDIA CYBERNETICS, Bethesda, USA), and the curative effect was counted by numerical density.

Safety indexes: monitoring basic vital signs, Blood routine, Urine routine, Stool routine, liver and kidney function, electrocardiogram, Chest x-ray and so on.

Clinical curative effect evaluation combined with clinical practice to draw up curative effect standard and according

Table 10: Comparison of pain scores before and after treatment ($\bar{X}$+S)

Subset	*n*	Pain score before treatment	Pain score after treatment	*Z*	*P*	Pain score reduction rate (%)
Treatment group	44	2.13±0.18	1.09±0.67	−3.267	0.000	52.28±26.87
Control group	44	2.21±0.67	1.32±0.68	−3.186	0.000	48.21±25.37
Z		−0.098	−0.097			−0.324
P		0.324	0.267			0.623

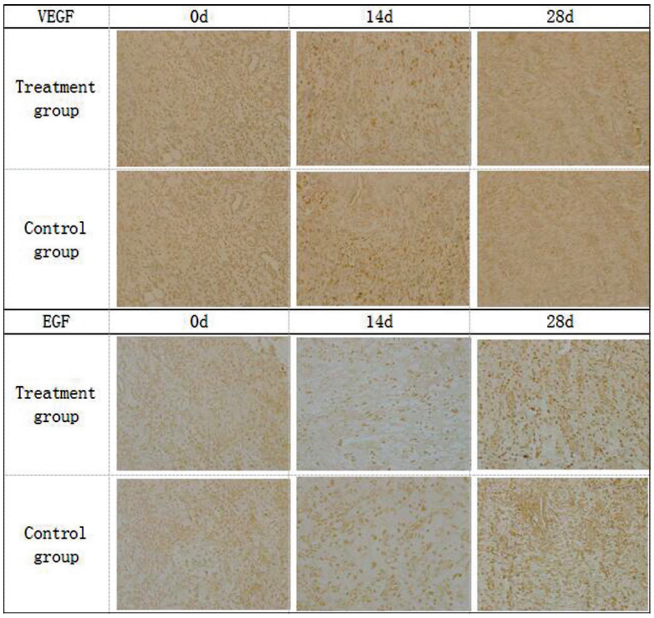

Figure 1: Morphological changes of vascular endothelial growth factor and epidermis growth factor in granulation tissue (×200)

to the "TCM disease and syndrome diagnosis curative effect standard." The standard was showed in Table 1.

Nimodipine method was used to evaluate the curative effect: recovery: Syndrome score decreased ≥90%, clinical symptoms and signs disappeared or basically disappeared; marked effect: 70% ≥ syndrome score decreased <90%, clinical symptoms, and signs improved obviously; effective: <70%, clinical symptoms, and signs were improved; ineffective: syndrome scores <30% and clinical symptoms and signs were not significantly improved or even aggravated.

Study of associated adverse events

No serious adverse events and adverse reactions occurred during the study.

Ethical approval

This clinical study has been approved by the ethics committee of our hospital, and the patients have signed the informed consent form before joining the group.

Statistical methods

The data were processed by SPSS20.0 software (International Business Machines Corporation, AMONG, NEW YORK, USA), the metrological data were described by $\bar{x}$±s, and the counting data were expressed by constituent ratio.

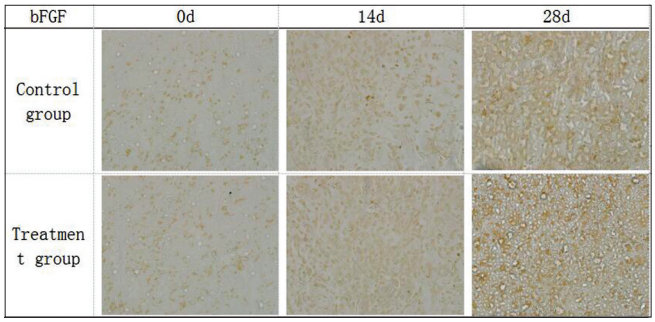

Figure 2: Morphological changes of basic fibroblast growth factor in granulation tissue (×400)

Does not conform to the normal distribution, the variance is not homogeneous, uses the rank sum test. The difference was statistically significant ($P < 0.05$). The results were in accordance with normal distribution and uniform variance. *t*-test was used for comparison between the two groups.

Results and Analysis

Comparison of baseline data

At the end of the trial, 88 cases were included in the study, including 44 cases in the treatment group and 44 cases in the control group. The result was showed in Table 2. The general situation before treatment in the two groups was as follows:

Comparison of age distribution

By rank sum test, $P = 0.763 > 0.05$, there was no significant difference in age distribution between the two groups.

Comparison of gender composition

The result was showed in Table 3. By Chi-square test, $P = 0.463 > 0.05$, there was no significant difference in the distribution of sex composition between the two groups.

Comparison of diabetes duration

The result was showed in Table 4. By rank sum test, $P = 0.792 > 0.05$, there was no significant difference in the course of diabetes between the two groups.

Comparison of the progression of diabetic foot ulcer

The result was showed in Table 5. By rank sum test, $P = 0.735 > 0.05$, there was no significant difference between the two groups.

Comparison of curative effect indicators

Comparison of therapeutic effects

The result was showed in Table 6. By rank sum test, $Z = -6.105$, $P = 0.000 < 0.05$. There was significant difference

between the two groups. The total effective rate was 88.37% in the treatment group and 74.42% in the control group. The curative effect of the treatment group was better than that of the control group.

Comparison of ulcer area before and after treatment

The result was showed in Table 7. There was no significant difference in ulcer area ($P = 0.547 > 0.05$) between the treatment group and the control group before treatment. There was no significant difference in ulcer area ($P = 0.318 > 0.05$) between the two groups after treatment. After treatment, the wound reduction rates of the two groups were compared, $P = 0.042 < 0.05$; the difference was statistically significant. The ulcer area of the two groups after treatment was significantly smaller than that before treatment ($P < 0.05$). The wound reduction rate of the treatment group was better than that of the control group ($P < 0.05$).

Comparison of granulation tissue changes before and after treatment

The result was showed in Table 8. There was no significant difference between the two groups in granulation tissue area, $P = 0.536 > 0.05$ and $P = 0.571 > 0.05$ in the two groups before treatment; however, there was no significant difference in the granulation tissue coverage before treatment between the two groups ($P = 0.561 > 0.05$, $P = 0.536 > 0.05$, $P = 0.561 > 0.05$, $P = 0.536 > 0.05$). After treatment, the granulation tissue area of the two groups were compared, $P = 0.478 > 0.05$; there was no significant difference between the two groups. After treatment, the granulation tissue coverage of the two groups were compared, $P = 0.004 < 0.05$; the difference between the two groups was statistically significant. The comparison of granulation tissue growth rate between the two groups after treatment, $P = 0.006 < 0.05$; the difference between the two groups was statistically significant. Comparison of granulation tissue coverage before and after treatment: the two groups were $P = 0.000 < 0.05$, the difference was statistically significant. The comparison of granulation tissue area before and after treatment: $P = 0.001 < 0.05$ in treatment group and $P = 0.100 > 0.05$ in control group, there was no significant difference.

Results

The granulation tissue area and granulation tissue coverage rate in the treatment group were significantly higher than those before treatment ($P < 0.05$), and the granulation tissue coverage and growth rate in the treatment group were superior to those in the control group ($P < 0.05$).

Comparison of epithelial tissue coverage after treatment

The result was showed in Table 9. There was no significant difference in the coverage of epithelial tissue before treatment between the treatment group and the control group ($P = 0.228 > 0.05$). On comparing the epithelial tissue coverage after treatment, $P = 0.009 < 0.05$, the difference was statistically significant.

Results

After treatment, the coverage of epithelial tissue in the treatment group was better than that in the control group, and the difference was statistically significant ($P < 0.05$).

Comparison of pain scores before and after treatment

The result was showed in Table 10. There was no significant difference between the two groups in pain score, $P = 0.324 > 0.05$. There was no significant difference between the two groups in the reduction rate of scores after treatment, $P = 0.623 > 0.05$. The pain scores of the two groups before and after treatment were $P = 0.000l < 0.05$. The difference was statistically significant.

Results

There was no significant difference in the reduction rate of pain score between the two groups after treatment, but the pain score of the two groups after treatment was lower than that before treatment, and the difference was statistically significant.

Dynamic changes of serum growth factors vascular endothelial growth factor, epidermis growth factor, and basic fibroblast growth factor

There was no significant difference in serum VEGF, EGF, and bFGF between the treatment group and the control group before treatment. The results are showen in Tables 11-13. Compared with the control group, the VEGF, EGF, and bFGF in the treatment group were significantly higher than that in the control group, and the VEGF, EGF, and bFGF in the treatment group were significantly higher than that in the control group ($P < 0.05$).The results showed that both the treatment group and the control group had the effect of increasing VEGF, EGF, and bFGF, and the effect of increasing the growth factor was significant in the treatment group. The results are shown in Tables 11-13.

Morphological changes of vascular endothelial growth factor and epidermis growth factor in granulation tissue was showed in Figure 1, while morphological changes of basic fibroblast growth factor in granulation tissue was showed in Figure 2.

Discussion

DFU is a serious complication of diabetes mellitus. Because of infection, lower limb blood vessel ischemia, and related neuropathy, the disease course is long and difficult to heal, and it is easy to cause lower limb amputation. The TCM surgery uses the medicine external application method to treat this sickness. On the basis of local differentiation of symptoms and signs of ulceration, the TCM with the right symptoms was selected, and good curative effect was obtained in clinic.

The basic pathogenesis of diabetes is deficiency of spleen and kidney, yin deficiency, and internal heat. Water dampness stagnates, turns into dampness and heat, then flows in the bloodstream. Dampness and heat accumulate heat to produce poison, place a wager on the foot, or because of scratching, scratching trauma, etc., then give birth to sores. The local

Table 11: Dynamic changes of VEGF ($\bar{x}\pm s$, ng · L-1)

Subset	*n*	0 day	7 days	14 days	21 days	28 days
Treatment group	44	87.62±0.34	99.98±0.34*	118.01±0.19*	125.73±0.28*	133.39±0.42*
Control group	44	87.54±0.28	91.71±0.45	99.45±0.14	108.05±0.32	117.54±0.82
t		0.082	8.27	18.55	17.68	15.85
P		0.34	0.042	0.002	0.000	0.000

Compared with control group, *$P < 0.05$

Table 12: Dynamic changes of EGF ($\bar{x}\pm s$, ng · L-1)

Subset	*n*	0 day	7 days	14 days	21 days	28 days
Treatment group	44	445.32±0.42	565.11±0.33*	698.52±0.11*	856.31±0.33*	992.14±0.13*
Control group	44	448.72±0.48	523.38±0.39	611.54±0.37	739.14±0.57	857.79±0.38
t		−3.4	41.73	86.98	117.17	134.35
P		0.28	0.028	0.016	0.013	0.006

Compared with control group, *$P < 0.05$

Table 13: Dynamic changes of bFGF ($\bar{x}\pm s$, ug · L-1)

Subset	*n*	0 day	7 days	14 days	21 days	28 days
Treatment group	44	33.18±2.13	57.31±4.24*	75.23±3.54*	90.13±4.66*	108.05±5.18*
Control group	44	32.81±2.35	38.16±3.82	52.36±4.65	72.17±3.46	88.28±3.27
t		0.37	22.19	17.09	18.04	20.17
P		0.07	0.017	0.018	0.012	0.006

Compared with control group, *$P < 0.05$

external therapy for DFU is clearing dampness and heat, activating blood, and removing blood stasis.

Yinqi ointment is the fifth batch of famous and old Chinese Medicine Prof. Pang He experience formula; for many years applied to external treatment of DFU, the curative effect is significant, This prescription consists of Astragalus membranaceus, honeysuckle, and Notoginseng (the proportion is 4:5:1), crushed into fine powder, blending; then 1:1 dissolve in Vaseline ointment, natural dry after the patent medicine. In the formula, honeysuckle is used to clear heat and detoxify; health Astragalus is used to replenish Qi and Nourish Yin; Panax notoginseng is used to promote blood circulation and dissipate blood stasis. Modern pharmacological studies have shown that honeysuckle has anti-inflammatory, antibacterial, anti-virus, and other effects;[6] Radix Astragali has the effect of invigorating Qi and invigorating the spleen, raising Yang and raising depression, reducing swelling of water, and nourishing toxin and generating muscle;[7] Panax notoginseng has the effects of anti-inflammation, hemostasis, and promoting blood circulation.[8] All drugs combined with clearing dampness heat, promoting blood circulation to remove blood stasis, nourishing toxin to generate muscle as a method play a new role to remove rot, ulcer wound healing as soon as possible. Pharmacological studies have confirmed that Panax notoginseng has many pharmacological effects, such as hemostasis, anti-platelet aggregation, changing erythrocyte deformability, protecting brain tissue, lowering blood pressure, immune regulation and so on.[9] Astragalus membranaceus can increase the influx and release of calciumion, inhibit phosphodiesterase, thus enhance the contractility of blood vessels, and thus play the role of hemostasis and blood circulation.[10] The pharmacological effects of Flos lonicerae are mainly anti-inflammation and pain, hemostasis, anti-virus, and anti-oxidation.[11]

The wound-healing speed of DFU is lower than that of common wound because of the lower microvessel density and less granulation tissue formation, which is also an important factor of DFU healing.[12,13] In the early stage of wound healing, macrophages were activated to release VGEF, bFGF, EGF, and other growth factors. It accelerates the growth of granulation tissue by promoting the proliferation of fibroblasts and vascular endothelial cells, thus promoting wound healing. Recent studies have shown that VEGF can enhance vascular permeability, provide nutrition for the growth of new blood vessels, promote endothelial cell mitosis and proliferation, and thus promote angiogenesis, and fusion promotes the formation of small vessels into large vessels.[14,15] bFGF belongs to exogenous growth factor; its function is to promote the repair and regeneration of cells and accelerate the healing of multiple injuries in the body.[16] bFGF can stimulate neovascularization, granulation tissue proliferation, collagen synthesis, and epithelial hyperplasia, which is the key factor to promote wound healing.[17] EGF is mainly secreted by macrophages and monocytes, promotes cell mitosis, stimulates the transcription of RNA and DNA in epidermal cells, induces proliferation of keratinocytes and thickening of stratum corneum, and stimulates peripheral nerve regeneration.[18] EGF improved the microenvironment

of the wound, promoted granulation of wound tissue, and increased the number of local fibroblasts, thus promoting wound healing.[19,20] This study showed that Yinqi ointment increased the content and activity of VEGF, bFGF, and EGF in serum and tissue, promoted cell proliferation and granulation tissue growth, promoted angiogenesis and scar formation, and finally promoted wound healing.

The results showed that the wound reduction rate, epithelial tissue coverage rate, granulation tissue growth rate, and local pain relief rate in the treatment group were significantly better than those in the control group ($P < 0.05$). Through the local granulation detection, the treatment group and the control group have increased VEGF, EGF, and bFGF and the treatment group increased the role of growth factor than the control group.

Conclusion

Yinqi ointment is better than mupirocin ointment in promoting the healing of DFU, and its mechanism may be related to increasing the content of growth factors in granulation tissue.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

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