

中药复方治疗慢性难愈性溃疡——非随机对照临床预试验

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[摘要] 目的 过临床预试验确定两味中药组成的简单复方(NF3)对难愈合性溃疡是否有疗效。方法 单一组别、治疗前后对比、开放式临床试验。结果 12名受试病人完成最长6周的NF3治疗。治疗前溃疡面积平均为3.27 cm²。治疗后溃疡面积减少51%至1.81 cm²($P=0.04$)。与治疗前相比,肿瘤坏死因子(TNF- α)在治疗后明显降低($P=0.001$),炎症得到有效控制,溃疡愈合情况有明显改善。结论 本临床预试验结果显示,NF3对难愈合性溃疡安全有效。研究结果提示,值得增加样本量作深入研究。

[关键词] 慢性溃疡;伤口愈合;中药复方

[中图分类号] R632.1 **[文献标识码]** A **[文章编号]** 1000-2715(2013)05-0444-05

Herbal treatment for the patients with chronic ulcers – An open label pilot clinical study

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[Abstract] **Objective** To determine the efficacy of a two-herb recipe (NF3) in the treatment of patients with Chronic Non-healing Ulcers. **Methods** a single arm, pre- and post-treatment comparison clinical trial was conducted. **Results** Twelve subjects were given up to 6 months treatment. The mean ulcer area (cm²) was 3.27 before NF3 treatment; after treatment the ulcer area was reduced 51%, from 3.72 to 1.81 cm² ($P=0.040$). Patients experienced significant improvement in ulcer healing after treatment with the herbal formula. The serum TNF- α was significantly decreased after NF3 treatment when compared with baseline ($P=0.001$). **Conclusion** The data from this pilot study show that NF3 is a safe and effective treatment for chronic ulcers.

[Key words] chronic ulcer ;wound healing; herbal formula

When a chronic ulcer fails to heal, the longer it exists, the more difficulty of the treatment would be expected. Causes of the failure to heal include deformities in the foot, loss of sensation, and bacterial

infections. Known situations of non-healing ulcers of long durations thus occurs among elderly patients suffering from leprosy, diabetes and venous stasis. Such patients usually have received surgery including skin

grafting and plastic repair, yet failed to achieve healing.

We have previously reported the favorable results of chronic ulcer treatment using a herbal formula of Chinese Medicine in patients suffering from type 2 diabetes and persistent foot ulcers^[1-2]. With limited surgical interventions such as limited toe amputations and ulcer debridement, we managed to avoid major amputation in 80% of patients originally scheduled for such intervention unless the ulcer was healed.

Basing on this good experience, we have worked out in the laboratory the biological activities of the herbs on the promotion of tissue healing. The herbs mainly act on the control of inflammation and promotion of granulation formation through stimulation of fibroblast proliferation^[3-4].

We therefore planned to offer treatments to a small group of patients who suffered from chronic ulcers for average three years using the same herbal formula. These patients and their attending physicians lost confidence in surgery or medications and held a pessimistic view that the ulcers would be never healed. They therefore accept the alternative treatment using herbal extracts.

1 Materials and methods

1.1 The patients Totally, twelve patients (male 9, female 3) were recruited for the pilot study. The average age was 66 years old. The patients were referred from the podiatrist, leprosy clinic and community nurses. The duration of chronic ulcer varied from 8 to 520 weeks, average 172 weeks (3.3 years). The causes of chronic ulcer included venous stasis (2 cases), diabetes (9 cases), and diabetes with leprosy (1 case). – All ulcers had failed to heal with standard therapy.

Table 1 Baseline characteristics

Subj. No.	Age(yr)	Sex	Cause of ulcer	Ulcer site
DII-001	80	F	Diabetes	Toes
DII-002	64	M	Venous	Ankle
DII-003	75	F	Venous	Ankle
DII-004	47	M	Diabetes	Toes
DII-005	63	M	Diabetes	Toes
DII-006	67	M	Diabetes	Heel
DII-007	75	F	Diabetes	Plantar
DII-008	55	M	Diabetes	Plantar
DII-009	49	M	Diabetes	Plantar
DII-010	72	M	Diabetes	Plantar
DII-011	86	M	Leprosy	Plantar
DII-013	58	M	Diabetes	Plantar
Mean	66			

Table 2 The changes of individual ulcer sizes, duration of ulcer existence and TNF- α

Subj No	TNF- α		Ulcer duration(wk)	Ulcer area /number change						
	Pre-	Post-		Pre-	V2	V3	V4	V5	V6	V7
DII-001*	1.661		>16	21.00/1						
DII-002	4.562	1.192	156	4.56/5	3.94/5	3.50/7	4.66/7	3.76/5	4.14/7	3.46/6
DII-003*	4.513		147	2.5/2						
DII-004	6.138	2.246	8	0.40/1	0.40/1	0.12/1	0.06/1			
DII-005	4.465		8	0.60/1	1.18/2	0.38/2				
DII-006	4.456	2.134	52	0.35/1	0.09/2	0.12/2	0.05/2			
DII-007	4.883	2.024	95	0.44/1	2.88/1	2.60/1	2.20/1	2.20/1	2.94/1	1.76/1
DII-008	2.151	1.110	91	2.21/1	1.80/1	2.10/1	3.00/1	5.40/1		
DII-009	3.756	2.117	312	6.18/2	1.96/2	3.00/2	1.98/2	2.13/1	4.80/1	3.75/1
DII-010*	4.188		78	0.48/1	6.68/2	4.86/4	0.17/3			
DII-011	3.316	3.144	520	0.66/1	0.66/1	0.50/1	2.04/1	1.98/1	0.80/1	0.66/1
DII-013*	1.795		260	0.60/1	0.55/1					
Mean	3.65	1.99	172	3.72/18	2.55/18	2.68/21	2.20/18	3.15/9	3.75/10	3.27/9

* DII-001 died because of heart problem; * DII-003 defaulted follow-up because of long transportation time. * DII-010 Osteomyelitis; * DII-013 drowsiness and defaulted follow up.

1.2 Methods This pilot study was designed as a non-randomized, single centre, open-label, and single arm cohort study to assess the progress of ulcer

healing among the patients with the failure of all attempted active treatments in the past years. All patients took the herbal treatment being offered as the

test resort for possible healing. They did not agree for placebo assignment in a more sophisticated clinical trial. Proper ethical approval was obtained by the Hospital Ethical Committee. Exclusion criteria included pregnancy, spreading infection or cancerous changes.

The study medication consisted of two herbs, viz. *Radix Rehmanniae* and *Radix Astragali*. The herbs, in the assigned proportions were boiled together in water in the standard way to produce a broth which was hydrolyzed into standard granules (5 gm per sachet) ready to be made into a drink for consumption. Patients were given the herbal medicine with a daily regimen of 2 sachets (5 g/sachet), one in the morning and one in the evening for a total of 6 months.

The study medication was produced by a GMP standard Traditional Chinese Medicine (TCM) manufacturer.

The duration of treatment offered was six months. Follow-up visits were offered every month when the treatment terminated, the healing rate would be revealed, irrespective of whether complete or incomplete healing occurred. This healing rate was taken as the primary outcome.

The medical history showed that the patients' liver and renal functions were stable before entered the pilot study. Ulcer size was measured by placing a ruler on the surface at the widest part of the long axis, and again at the widest part of the short axis. To assess the inflammatory state of the patients with chronic ulcers, the serum expression of TNF- α and C-reactive protein (CRP) were measured before the start of herbal treatment and at the end of the 6 months of treatment, or at the visit when the healing ulcer was discovered. The TNF- α data were taken as secondary outcome. During the treatment period, patients received the standard wound care at out-patient clinics and any regular medications related to diabetes, cardio-vascular control etc.

Standard treatment was given to each patient, according to what they were using before they were recruited. The ulcers were cleaned daily with antiseptic solution (Chlorhexidine 0.05%).

1.3 Statistical analysis Data were presented a means \pm standard deviations (SD). Efficacy data

was performed by using Paired *t*-test or *Mann-Whitney Test* to compare the changes between pre- and post-treatment. Statistical analyses were performed using SPSS for windows, release 16.0 (SPSS. Inc). P-values <0.05 (2-sided test) were considered statistically significant.

2 Results

The pilot study included 12 patients with a total of 18 ulcers. All the patients satisfied the criteria for inclusion; over 18 years of age with a chronic cutaneous ulcer resulting from causes like, venous stasis, leprosy, diabetes or arterial diseases. All showed positive responses after the herbal treatment. The mean ulcer area (cm²) of patients at each visit was shown in Table 1 ~2 and Fig 1.

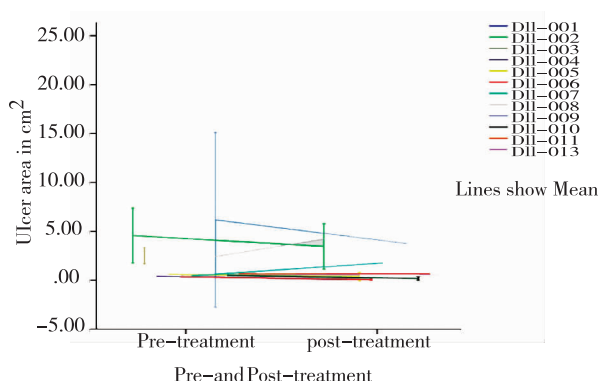


Fig 1 Wound area (cm²) changes after treatment

On completion of the 6 months' treatment, the overall decrease in ulcer area was 51% compared with the baseline ($P=0.04$) (Table 3, Fig 2). The average healing time for the 7 healed ulcers was 89 days (Table 4). Totally there were 15 wounds of the recruited Subjects. 7 wounds were healed The healing rate was 47%. One typical Case DII-011 with diabetics and leprosy the ulcer existed more than 20 years, after 6-month treatment, the ulcer was healed.

Table 3 Changes of ulcer area

Variable	Pre-treatment	Post-treatment	Change	P value
No. of subject	12	10		
No. of ulcer	18	23		
Ulcer area(cm ²)	3.72	1.81	-51.3%	0.040
SD	5.84	2.87		
Minimal(cm ²)	0.35	0.00		
Maximal(cm ²)	21.00	10.20		

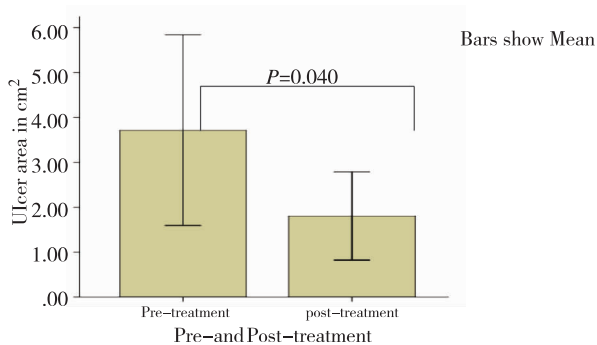


Fig 2 Ulcer area changes pre - and post - treatment comparison

Table 4 Onset ulcer size and healing time of healed ulcer

	Healed ulcer	Minimum	Maximum	Mean	SD
Healing time (day)	7	34.00	207.00	88.57	59.54
Onset ulcer size (cm ²)	7	0.16	12.15	2.75	4.24
Ulcer duration (day)	7	34	2184	510.86	833.25

The TNF- α level was significantly reduced after treatment or healing of ulcer compared with the baseline ($P=0.001$), the CRP levels tended to decrease

Table 6 Healing status of individual healed ulcers

Subj No	Ulcer site	Onset date	Onset size (cm ²)	Healing date	Ulcer duration (day)	Healing time (day)	TNF - α	
							Pre -	Post -
DII - 002	Toes (C)	26/11/2010	1.00	21/6/2011	1092	207	4.562	1.192
DII - 002	Toes (D)	27/1/2011	0.66	11/4/2011	74	74	4.562	1.192
DII - 002	Foot dorsum(B)	18/5/2011	0.16	21/6/2011	34	34	4.562	1.192
DII - 002	Plantar(B)	27/1/2011	1.50	11/4/2011	74	74	4.562	1.192
DII - 009	Foot dorsum	14/12/2010	0.75	11/4/2011	2184	118	3.756	2.117
DII - 010	Foot dorsum	30/12/2010	12.15	18/3/2011	78	78	4.188	1.603
DII - 011	Plantar	11/2/2011	3.06	18/3/2011	35	35	4.188	1.603

During study period no adverse reactions related the study medication were reported.

3 Discussion

Patients suffered from chronic ulcer remains a challenging problem in medicine, society and economy. Many patients with ulcers do not heal and become chronic. The longer the ulcer existed, the greater the possibility that the patients developed serious infection that could lead to hospitalization and possible amputation [5].

Chronic ulcers arising from pathologies of neuropathy and repeated infection fail to heal when the predisposing causes hinder the control of inflamma-

tion, block granulation formation and promote infection. Our herbal formula works as a supplement to control inflammation which has been well expressed in the marked drop in TNF - α level. *Radix Rehmanniae*

Table 5 Changes of TNF- α and CRP

Variable	Pre-treatment (n = 12)	Post - treatment (n = 7)	Change	Pvalue#
TNF- α	3.97 \pm 1.29	1.95 \pm 0.65	-50.9%	0.001
CRP	10.29 \pm 11.58	7.54 \pm 8.20	-26.7%	0.586

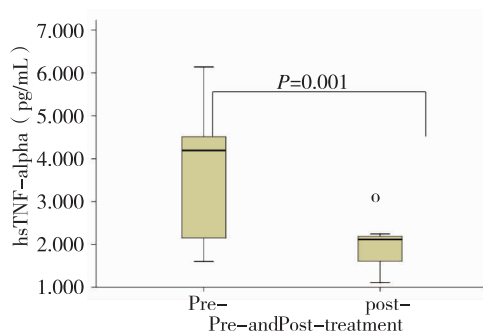


Fig 3 Change of TNF - α pre - and post - treatment ($P=0.001$)

The patient (Subject No. DII-011, male, 86 years old) with diabetes and leprosy suffered from chronic ulcer over 20 years.

tion, block granulation formation and promote infection. Our herbal formula works as a supplement to control inflammation which has been well expressed in the marked drop in TNF - α level. *Radix Rehmanniae* has been shown to greatly facilitate fibroblast proliferation in our laboratory and also in some other studies [3-4,6]. *Astragalus* is well known for its immunomodulating effects.

For those cases recruited under our present cohort study that yet failed to heal completely at the end of the six months of assigned treatment, the herbal drink was discontinued but topical application of the herbal powder (*Radix Rehmanniae*) was used so as to acquire more information about the outcome of topical

use. Results will be discussed in a separate report.

In order to promote tissue healing, attempts have been made on the use of various growth factors. The results had not been totally satisfactory because of the protein nature of the agents making oral and long-term administration unfavorable. For chronic ulcers with long years of existence, one expects a slow progress of healing and patience is required for both clinicians and patients. Our herbal formula works as a supplement that initiates a slow control of the adverse mechanisms affecting the ulcer healing^[7-8].

Although the active ingredients in the herbal formula was unknown and the mechanism of action was not clear, the decline of TNF- α after treatment demonstrated in the chronic ulcer patients indicated that the inflammatory process were under steady control. The fact that the patients taking the herbal supplement experienced a greater decline in TNF- α , which might be a good evidence showing the adjuvant herbal therapy might be working through an anti-inflammatory pathway^[9-10]. Usually the reduction in CRP level may indicate the facilitation of wound healing by inhibiting inflammation^[11]. The present pilot study also showed this trend, however, it did not reach the statistical significance.

The simple combinations of the two herbs have demonstrated good supportive effects on the proliferation of cell cultures. It might be logical, as a next step towards the further development of this ulcer healing agent, to try applying the powder form topically to initiate healing effects. Like all other researches on herbal medicine, we have started the bio-guided chemical analysis of the combined extract to identify a sub-fraction that might be most efficacious when used either topically or systematically.

In conclusion, the studied herbal medicine has been shown in this pilot study to be safe and effective for the treatment of chronic ulcers. However, a further clinical study with proper sample size is needed to verify the efficacy and investigate its action mechanisms.

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[收稿 2013-08-12; 修回 2013-09-12]

(编辑: 谭秀荣)