ORIGINAL ARTICLE

Limb salvage in extensive diabetic foot ulceration: an extended study using a herbal supplement

PC Leung 梁秉中
Margaret WN Wong 王韻娜
WC Wong 王榮祥

Objective To further study the clinical value of a herbal supplement in the treatment of chronic foot ulcers in diabetic patients.

Design Double-blind randomised, placebo-control trial.

Setting Two general hospitals in Hong Kong.

Patients Eighty patients were recruited according to strict selection criteria.

Interventions Clinical measures included standard antidiabetic treatment, daily wound care including antiseptic bath, debridement, toe removal for gangrene when necessary, and the daily consumption of a herbal drink or placebo.

Main outcome measures The primary outcome was limb salvage. Secondary outcomes included: granulation maturation, local temperature and circulatory changes, tumour necrosis factor–alpha levels, and adverse events.

Results Limb salvage was achieved in 85% of the patients. Among the early failures, three each came from the treatment and placebo groups. After shifting to herbal treatment (without unblinding of the original treatment), all were rescued in those initially assigned to herbal concoction (6 out of 6) while only 50% (6 out of 12) were rescued from among those initially assigned to placebo. The speed of granulation maturation, and decline in tumour necrosis factor–alpha levels indicating control of inflammation, were also more favourable with the herbal group. No serious adverse events were observed.

Conclusion The herbal adjuvant therapy was effective in helping the healing of chronic diabetic ulcers.

Introduction

In December 2001, we published a paper entitled 'Limb salvage in extensive diabetic foot ulceration—a preliminary clinical study using simple debridement and herbal drinks'.[1] Instead of amputations, attempts at limb rescue with the addition of an adjuvant herbal drink achieved an 85% success rate for limb salvage.[2] These encouraging results prompted the organisation of this more definitive double-blind randomised trial to assess the efficacy of the herbal supplement.

Orthopaedic surgeons seldom have favourable results; limited local amputations of the foot commonly result in non-healing stumps. Below-knee amputation was therefore the remedy usually resorted to. If objective evidence on the efficacy of the herbal formulation could be obtained, it would be logical to offer it as an adjunctive treatment.

Subjects and methods

Type II diabetic patients being treated for chronic foot ulcers and in receipt of regular antidiabetic treatment were recruited from the orthopaedic units of two general hospitals (Prince of Wales Hospital and Kwong Wah Hospital) in Hong Kong. The patients were known to have had diabetes for 7 to 12 years and had had the ulcers for 7 to 25 weeks, without signs of healing. Among them, 47% had gangrenous toes associated with the ulcers. These patients were therefore scheduled for amputation of the affected leg in their respective orthopaedic units. Patients suffering from serious cardiac and renal deficiencies were excluded from the study. Inclusion and exclusion criteria were the same as in the preliminary study. Details of the selected patients are given in Table 1.

Key words
Diabetes mellitus; Drugs, Chinese herbal; Wound healing

Hong Kong Med J 2008;14:29-33

Institute of Chinese Medicine, The Chinese University of Hong Kong, Shatin, Hong Kong
PC Leung, DSc, FRACS
Department of Orthopaedics and Traumatology, The Chinese University of Hong Kong, Prince of Wales Hospital, Shatin, Hong Kong
MWN Wong, FRCS, FHKAM (Orthopaedic Surgery)
Department of Orthopaedics and Traumatology, Kwong Wah Hospital, Hong Kong
WC Wong, FRCS, FHKAM (Orthopaedic Surgery)

Correspondence to: Prof PC Leung
Email: pingcleung@cuhk.edu.hk

糖尿病足嚴重潰瘍的保肢治療：草藥補充劑的擴展研究

目的 進一步研究一種草藥補充劑在治療糖尿病慢性足潰瘍的臨床價值。

設計 雙盲隨機安慰劑對照研究。

安排 香港兩間普通科醫院。

患者 按嚴格的挑選準則，選出80位患者參與研究。

療法 治療措施包括例行的抗糖尿病治療，日常的傷口護理如抗菌浴、清創、需要時切除壞疽性腳趾，以及每天飲用草藥茶或安慰劑。

主要結果測量 主要療效指標是保肢，次要療效指標則包括肉芽的成熟速度、局部溫度和循環的改變、腫瘤壞死因子α的水平，以及各種不良事件。

結果 85%病人能成功保肢。在早期保肢失敗的病例中，治療組和安慰劑對照組各有三宗。療效不理想的患者轉而接受草藥補充劑治療後，在破盲的情況下，草藥組6位病人全部可保肢，但安慰劑對照組則只有五成（12位病人中有6位）。肉芽的成熟速度和腫瘤壞死因子α下降，都顯示草藥組的炎症控制較為理想。研究期間沒有觀察到嚴重不良事件。

結論 草藥佐劑療法對治療慢性糖尿病足相當見效。

The herbal formulation or a placebo was given as an adjuvant therapy for the treatment of the unhealing ulcers in these diabetic patients, according to a randomised protocol. A blocked randomisation scheme was used to allocate patients in equal proportions to the herbal or placebo groups. Both the clinicians and the patients were completely blinded to the study medications. Unlike the preliminary study during which the herbal drinks were acquired from a Shanghai hospital, the innovative herbal formulation was prepared locally, very much based on the Shanghai experience.[2] The formula consisted of 12 herbs, viz: Radix astragali, Rhizoma atractylodis marcocephalae, Radix stephaniae tetrandrae, Radix polygoni multiflori, Radix rehmanniae, Radix smilax china, Fructus corni, Rhizoma dioscoreae, Cortex moutan, Rhizoma alismatis, Rhizoma smilacis glabrae, and Fructus schisandrae. The relative proportions of the herbs were used as described in the previous report.[1] The decoction made from the formula was converted into user-friendly granules which were given twice daily in a drink. The placebo was made with starch and colouring material. The herbal items were all in common use, and none belonged to any toxic group of medicinal herbs. To ensure safety, contaminants such as heavy metals, insecticides, and microbes had been eliminated, according to regulations set out by the Hong Kong Department of Health.[3]

The study protocol was screened and approved by the Clinical Research Ethics Committee of the Chinese University of Hong Kong. All patients were required to give written informed consent before registration.

The primary outcome measures were: limb salvage and healing of ulcers. At the same time, the rate of ulcer healing, changes in the surface temperature, and oxygen consumption of the surrounding skin were taken as supportive outcome parameters. Skin temperature was measured with a digital thermometer (Fisher Scientific, US) and oxygen consumption by a transcutaneous oxygen tension detector (MicroGas 7650, Linde Medical Sensors AG, Switzerland) at fixed points around the ulcer. Adverse events were recorded, and liver and renal function tests monitored at baseline and 4 weekly thereafter. Tumour necrotising factor–alpha (TNF-α) was also checked to evaluate the state of inflammation before and 4 weeks after treatment.

Intervention

Standard antidiabetic treatment was given to each patient, according to what they were using before they were recruited. Broad-spectrum antibiotics were given, according to results of sensitivity tests to control any infection in the chronic ulcer. The ulcers were cleaned daily with antiseptics, and de-sloughing was performed at the same time. The herbal adjuvant therapy was given orally twice a day.

Statistical analyses

Eighty patients were recruited from the target population, assuming that the difference in the outcomes between the herbal treatment and placebo treatment would reach 30%. For the granulation maturation time, a survival analysis (Kaplan-Meier) was used and the difference in the time taken was tested by using Breslow method. Paired *t* tests were used to compare changing within patient: skin temperatures, skin oxygen consumption, and the state of inflammation (by TNF-α measurements). All the analyses were based on an intention-to-treat principle. All patients adhered to their assigned trial treatment, regardless of any other treatment they actually received, and regardless of subsequent withdrawal from the study, whatever the reason.

Comparison of results from the two groups was conducted using analysis of variance (ANOVA) according to the Statistical Package for the Social Sciences (Windows version 14.0; SPSS Inc, Chicago [IL], US).

Results

The study took 4 years, ending in April 2006. Patient demographics and ulcer characteristics are shown in

TABLE 1. Baseline demographic characteristics of the patients

Characteristic	Herbal treatment (n=40)*	Placebo (n=40)*	P value (herbal vs placebo)
Sex			
Male	25	22	0.496
Female	15	18	
Age (years)			
Mean±SD	66.3±12.6	68.5±11.1	0.408
Range	40-85	49-86	
Diabetes duration (years)	8.4±7.6	12.4±8.8	0.034
Ulcer duration (weeks)	7.8±8.2	12.9±24.6	0.296
Ulcer size (cm^2)	28.7±31.3	26.7±27.3	0.789
Diabetes types			
Type I	5/40 (13)	9/39 (23)	0.218
Type II	35/40 (88)	30/39 (77)	
Current medication for diabetes			
Oral hypoglycaemic	28/40 (70)	26/40 (65)	0.891
Insulin injection	7/40 (18)	8/40 (20)	
Diet control	5/40 (13)	6/40 (15)	
Diabetes control (blood check)			0.321
Good (steady)	19/37 (51)	17/35 (49)	
Fair (occasionally fluctuating)	14/37 (38)	17/35 (49)	
Poor (fluctuating)	4/37 (8)	1/35 (3)	
Smoking			
Smoker (3 cigarettes per day)	13/40 (33)	16/40 (40)	0.485
Non-smoker	27/40 (68)	24/40 (60)	
Ulcer bed			
Infected with slough	28/35 (80)	30/36 (83)	0.171
Oedematous with patchy necrosis	6/35 (17)	4/36 (11)	
Relatively clean	1/35 (3)	2/36 (6)	
Gangrenous tissue			
Dry	12/38 (32)	8/31 (26)	0.274
Wet	19/38 (50)	12/31 (39)	
None	7/38 (18)	11/31 (35)	
Nutritional state			
Body weight (kg)	59.1±12.3	61.2±12.3	0.601
Serum albumin level (g/L)	31.7±4.5	32.2±4.2	0.647

* Data are shown in mean±standard deviation or No. (%)

Table 1. In all, 80% of the ulcers were accompanied with gangrene in different segments of associated toes. Double blinding was maintained as long as there was no obvious deterioration, which was considered to threaten patient survival. Whenever sepsis or extensive gangrenous changes occurred, failure was regarded as inevitable and emergency amputation was carried out. Whenever there was no progress over the first 4 weeks, and yet the deterioration was not bad enough to justify amputation, patients assigned to placebo were changed to herbal supplement though they still remained blinded to the medication. This was done to offer the best opportunity for limb salvage until either improvement or sacrifice of the limb could be properly determined. Table 2 summarises early failures (herbal 3, placebo 3), rescue after continuing on or changing to herbal treatment (herbal 6/6, placebo 6/12) and the total failure cases (12/80). Ulcer duration in the amputated limbs was 1 to 4 weeks for the herbal treatment and 4 to 24 weeks for the placebo group.

The steadily improving ulcers were watched for granulation tissue growth which took varying periods to mature. The duration taken for maturation

TABLE 2. Outcome of poor responders*

Group	Amputation because of rapid deterioration in the first 4 weeks	No improvement in the first 4 weeks		Limb salvaged after herbal treatment	Amputation in spite of herbal treatment	Total No. of amputations
Herbal treatment	3	6	After shifting to herbal treatment	6	0	3
Placebo	3	12		6	6	9
Total	**6**	**18**		**12**	**6**	**12**

* Outcomes in the treatment and placebo groups compared according to the intention-to-treat principle, the difference in amputation rates was nearly statistically significant (P=0.057)

TABLE 3. Time taken for maturation of granulation (before skin grafting)

Group	Time to healing (weeks)
Herbal treatment	
Mean±SD	5.9±1.4
Median	3.4
Placebo	
Mean±SD	9.2±1.9
Median	6.9
P value	0.147

TABLE 4. Tumour necrosis factor–alpha (TNF-α) levels in serum after each visit

Group	TNF-α (pg/mL)			
	Week 0 (baseline)	Week 2	Week 4	% Change at week 4*
Herbal treatment	48±116	36±76	28±62	-42
Placebo	44±83	41±68	39±64	-10
P value	0.841	0.433	0.703	-

* Comparison of the two groups in terms of % change from baseline to week 4 by paired *t* test (P=0.037)

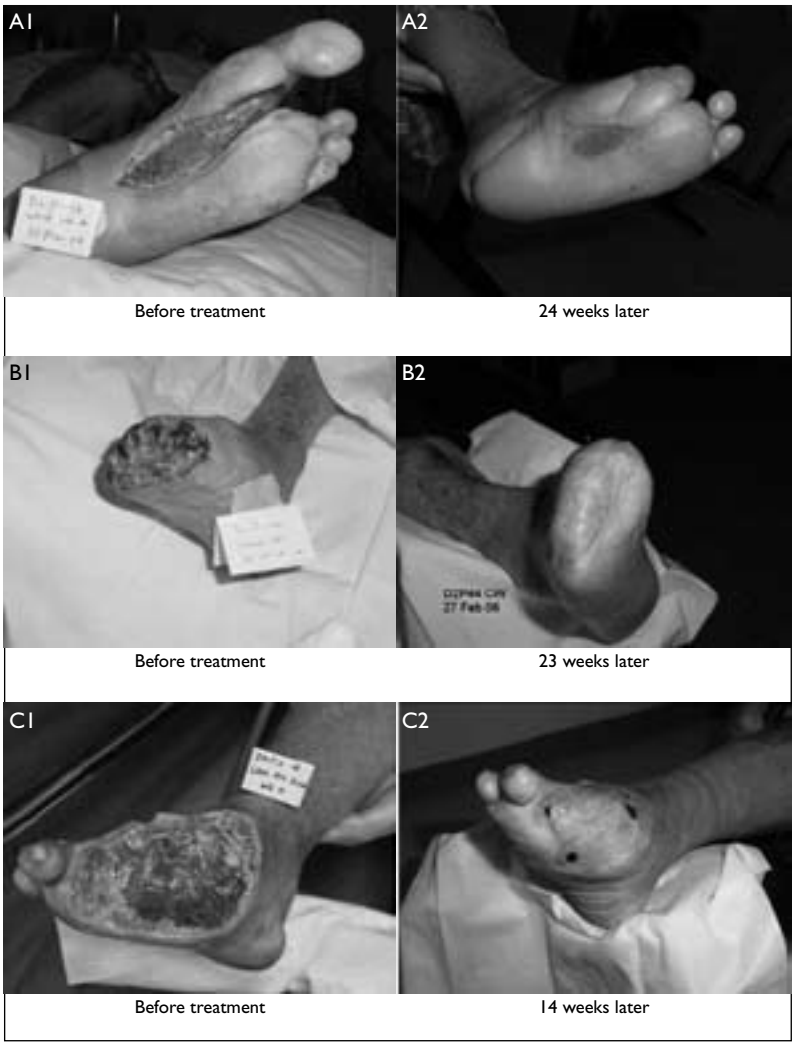

FIG. Diabetic foot ulceration of three patients before and after herbal treatment

to enable skin grafting in the two groups is shown in Table 3. Skin grafts took well as a rule (Fig). The changes in skin temperature and surface oxygen consumption around the ulcers were recorded. The results were positive only for surface oxygen consumption.

During the 24 weeks of treatment, some self-limiting adverse events (epigastric pain, dry month, and diarrhoea) were experienced. Liver and renal functions were not affected. Consumption of the herbal supplement, therefore, could be considered safe.

Analysis of TNF-α values in serum declined as the ulcers healed. On comparing the percentage change from the baseline in the two groups at week 4 by paired *t* test, the decline was faster in patients assigned to the herbal treatment (P=0.037; Table 4).

Discussion

This study was a development of the previous cohort study reported in 2001,[1] which had shown encouraged results. The current randomised, double-blind controlled trial further supports the efficacy of the herbal supplement. The treatment group showed superiority over the placebo group in terms of: limb salvage, appearance of granulation tissue, and overall assessment of wound healing (P=0.007 and 0.031, respectively). Importantly, the study further supported the safety of the herbal formulation. However, the treatment group somehow enjoyed more favourable pre-treatment (baseline) characteristics in terms

TABLE 5. Patients 18 to 48 months after limb salvage (n=21)

Foot condition	No. of patients
Ambulation state	
Independent walking	8
Walking with aids	11
Wheel chair–bound	2
Foot wear	
Ordinary	16
Special	4
Orthosis	1
Diabetic control	
Good	10
Fair	7
Poor	4
Recurrent ulcer	
Nil	19
Ulcer over sole	2
Circulation	
Dorsalis pedis pulse present	8
Posterior tibial pulse present	6
Sensation	
Protective sensation present	19
Protective sensation absent	2

of: diabetes duration, prior duration of ulcers, and the proportion with type II diabetes. Nevertheless, common to all cases, they were all scheduled for amputation by orthopaedic surgeons. Regrettably, more detailed analysis of other factors (numbers of ulcerated/ischaemic toes, numbers of debridements performed, dressing procedures) that could have provided supplementary evidence was not obtained.

Although the active components from the herbs and the pharmacology of the herbal formulation are still unknown, our laboratory experiments have shown that some of the constituents promote wound healing in-vitro and in-vivo. Thus, using fibroblasts cultures, we found that Rehmanniae glutinosa, a component of the formulation, promoted cell division.[4] Using an in-vivo diabetic rat model, herbal feed induced faster and better healing of foot ulcers.[5] Other experiments showed that the formulation was not working through any glycaemic control.[6] The formulation therefore has the potential to be developed into an effective agent for promoting wound healing in diabetic and non-diabetic ulcers.

Tumour necrosis factor–alpha is a molecular marker of inflammation in the process of tissue healing. Previous studies have demonstrated this relationship to wound healing.[7,8] Decline of TNF-α values was taken to be a favourable feature, indicating control of inflammation and hence progressive wound healing, which could also be taken to provide further support that consumption of the herbal formulation was beneficial.

Preserving limbs in patients enduring chronic unhealing ulcers has been criticised as being over-conservative, because the salvaged limb with a defective foot might remain disabled and could be a nuisance. However, late follow-up (after 18 to 48 months) of 21 patients (Table 5), who underwent limited tissue removal and toe amputations in the pursuit of limb salvage, appeared to enjoy having an intact limb though it was obviously defective. Recurrence of ulceration ensued in only two patients. Only 21 patients were reassessed as 10 (5 assigned to placebo and 5 to herbal treatment) had died and the rest could not be contacted or refused reassessment.

Acknowledgements

This study was supported by the University Grants Council of Hong Kong, and is part of a project entitled Area of Excellence in the Study and Development of Chinese Medicine.

References

1. Wong MW, Leung PC, Wong WC. Limb salvage in extensive diabetic foot ulceration—a preliminary clinical study using simple debridement and herbal drinks. Hong Kong Med J 2001;7:403-7.
2. Shi JY, Zhou SL. Diabetic teno-necrosis—a clinical study [in Chinese]. Shanghai J Trad Chin Med 1996;5:27-31.
3. Regulations on medicinal herbal preparations. Hong Kong SAR: Department of Health; 2004.
4. Lau TW, Chan YW, Lau CP, et al. Investigation of the effects of Chinese medicine on fibroblast viability: implications in wound healing. Phytother Res 2007;21:938-47.
5. Lau TW, Sahota DS, Lau CH, et al. An in vivo investigation on the would healing effect of two medicinal herbs using an Animal Model of Diabetic Foot Ulcer. Eur Surg Res. In press.
6. Chan CM, Chan YW, Lau CH, et al. Influence of an anti-diabetic foot ulcer formula and its component herbs on tissue and systemic glucose homeostasis. J Ethnopharmacol 2007;109:10-20.
7. Goren I, Müller E, Schiefelbein D, et al. Systemic anti-TNFalpha treatment restores diabetes-impaired skin repair in ob/ob Mice by inactivation of macrophages. J Invest Dermatol 2007;127:2259-67.
8. Lee RH, Efron DT, Tantry U, et al. Inhibition of tumor necrosis factor-alpha attenuates wound breaking strength in rats. Wound Repair Regen 2000;8:547-53.