

The Role of Topical Traditional Chinese Medicaments as Contact Sensitisers in Chronic Venous Leg Ulcer Patients

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Abstract

Introduction: Leg ulcers are a chronic condition affecting the older population. In Singapore, the use of topical traditional Chinese medicaments (TTCM) is common amongst those older than 65 years of age. We study the role of TTCM as contact sensitisers in patients with chronic venous leg ulcers and its impact in the clinical management of these patients. **Materials and Methods:** Patients with chronic leg ulcers attending the Wound and Ulcer Clinic at the National Skin Centre (NSC) between October 2005 and April 2006 were patch-tested to the NSC TTCM series. They were also patch-tested for other allergens from the NSC Standard Series, Medicament Series, Steroid Series and wound dressings. **Results:** A total of 44 patients were patch-tested. Seventeen of the 44 (38.7%) patients were using or had used at least 1 TTCM. Seven patients (15.9%) had at least 1 positive patch test (PT) reading to TTCM, giving a sensitisation rate of 41% (7 of 17). A significantly high proportion of the patients, 94.1% (16 of 17) with a positive history of TTCM usage had at least 1 positive PT reading compared to those without a history of TTCM usage, 45.8% (11 of 24). **Conclusion:** TTCM play an important role as contact sensitisers in our patients with chronic venous leg ulcers and may be a significant factor in non- or poor-healing leg ulcers. In such patients, a history of TTCM usage should be sought for and patch testing should include the commonly used TTCM where relevant.

Ann Acad Med Singapore 2007;36:942-6

Key words: Allergic contact dermatitis, Stasis ulcers, Traditional Chinese medicines

Introduction

Leg ulcers are a chronic condition affecting 1% to 7% of the population above 65 years.¹ Allergic contact dermatitis poses a significant problem to the healing of leg ulcers and local skin care, affecting up to 78% of patients.²⁻⁷ A recent study by our group found a high overall contact sensitisation rate of 61.4% in patients with chronic venous leg ulcers.⁸ The pattern of allergens involved constantly evolves according to local wound care practice. Previous studies from the West highlight aminoglycoside antibiotics, balsam of Peru, fragrance mix and lanolin alcohol as a few of the most frequent allergens.^{1,3,5-7}

In Singapore, the use of topical traditional Chinese medicaments (TTCM) is common as self- or Chinese physician-directed remedies. In a cross-sectional analysis of a cohort of community-living adults aged above the age of 65 years in Singapore, the prevalence of Chinese herbal medicines use was 25.3%, among whom 52% reported concurrent use of Western prescription medicines.⁹ In this

paper, we focus on TTCM as contact sensitisers in our study patients and its role in the clinical management of recurrent venous leg ulcers.

Materials and Methods

Eligible patients with chronic leg ulcers attending the Wound and Ulcer Clinic at the National Skin Centre (NSC) between October 2005 and April 2006 were patch-tested. Patients with a clinical and/or histological diagnosis of chronic venous (or mixed venous and arterial) leg ulcers were recruited. Patients with leg ulcers due to other causes, on systemic immunosuppression or had contraindications to patch testing were excluded. The NSC TTCM series (Table 1) used for patch testing in this study was developed based on a previous study which identified the 10 most commonly used TTCM by local patients seen at the NSC Contact Dermatitis Clinic.^{10,11} The ingredients of the respective TTCM as listed by their manufacturers are shown in Table 2.¹⁰ Apart from TTCM, the study patients

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Table 1. Topical Traditional Chinese Medicament (TTCM) Series Used for the Patch Test

Allergen/(concentration/vehicle)	Sensitisation rate as % of all patients (no. of patients)
Axe Brand Oil (as is)	0 (0)
Green Grass Oil (20% olive oil)	4.5 (2)
Tiger Balm (10% yellow soft paraffin)	6.8 (3)
Tjin Koo Lin (20% olive oil)	6.8 (3)
Wong Cheung Wah U1 oil (5% olive oil)	2.3 (1)
Eagle Brand Medicated Oil (50% olive oil)	4.5 (2)
Saw Hong Choon Skin Ointment (as is)	11.3 (5)
Tiger Oil (as is)	2.3 (1)
White Flower Oil (as is)	4.5 (2)
Zhen Gu Shui (Yulin) (as is)	4.5 (2)

were patch-tested to the NSC standard series, steroid series, medicament series and to their individual wound dressing products.⁸

Allergens were applied to back skin on Finn Chambers (Epitest Ltd, Oy, Tuusula, Finland) under Airpore tape (Qiagen Inc., Valencia, CA, United States). Standard allergens were obtained from Chemotechnique Diagnostics, Malmö, Sweden. The patch tests were removed after 48 hours and read on Day 2 (D2) and/or Day 3 (D3). A further reading on Day 7 (D7) was done to detect delayed reactions.¹² As per International Contact Dermatitis Research Group guidelines, readings of + and above were taken as positive.

Comparison of means for statistical significance was done using the Mann-Whitney U test and comparison of

proportions was done using the chi-square test. Statistical analysis was performed using SPSS version 13.0 (SPSS Inc., Chicago, Illinois, USA). *P* values of <0.05 were taken as statistically significant.

Results

A total of 44 patients with a mean age of 63 years (range, 33 to 86; median, 62.5) were tested.⁸ There was a slight male predominance (male-to-female ratio of 1.2:1). The average duration of their leg ulcers was 43.8 months (range, 2 to 480; median, 19.5). A high prevalence of 61.4% (27 of 44) of the patients tested had at least 1 positive patch test reaction with 31.8% (14 of 44) having multiple positive readings. In our study, the common sensitizers and their rates of sensitization were antimicrobials (18.2%), TTCM (15.9%), colophony (11.3%) and Balsam of Peru (9.1%).⁸

At the time of patch testing, 38.7% (17 of 44) of our patients were using or had used at least 1 TTCM, 6.8% (3 of 44) were unsure or unable to recall TTCM usage and 54.5% (24 of 44) denied having ever used it. Amongst the patients with a history of TTCM usage, there were a higher proportion of females compared to males (12:5). The mean age of the patients with a history of TTCM usage was 61.1 years and their average duration of disease was 34.8 months. This was not statistically significantly different from the patients without a history of TTCM usage (mean age, 64.2 years; *P* = 0.366, average duration of disease, 49.5 months; *P* = 0.544). A high proportion of the patients, 94.1% (16 of 17) with a positive history of TTCM usage had at least 1 positive PT reading compared to those without a history of TTCM usage, 45.8% (11 of 24). This was statistically significant (*P* <0.01). The non-TTCM

Table 2. Ingredients of the Individual TTCM

Name	Ingredients
Axe Brand Oil	Methol crystals 20%, eucalyptus oil 12%, camphor 5%
Eagle Brand Medicated Oil	Mineral oil 36.15%, menthol 28.5%, methyl salicylate 18.6%, chlorophyll 1.15%, other essential oils 15.6%
Green Grass Oil	Extract rheum palmatum and base to 100%, camphor 23.8%, menthol 3.5%
Saw Hong Choon Skin Ointment	Salicylic acid 5%
Tiger Balm	Wax and petrolatum 36.8%, camphor 24.9%, peppermint oil 15.9%, cajuput oil 12.9%, menthol 8%, clove oil 1.5%
Tiger Oil	Methyl salicylate 38%, white oil 25%, camphor 17.5%, menthol 8%, eucalyptus oil 6%, lavender spike 5%, chloroform BP 0.5%
Tjin Koo Lin	Wintergreen 10%, ethanol 10%, cinnamon oil 4%, clove oil 4%, nutmeg oil 4%, camphor 4%, peppermint oil 2%, cassia oil 2%, methyl salicylate, and others
White Flower Oil	Wintergreen oil 40%, menthol crystals 30%, eucalyptus oil 18%, camphor 6%, lavender oil 6%
Wong Cheung Wah U I Oil	Peppermint oil 20%
Zhen Gu Shui	Radix pseudoginseng 25%, Croton tiglium 18%, Cinnamomum camphora nees et Eberm 15%, Radix angelicae 13%, Moghania macrophylla 12%, Inula cappa 12%, menthol 3%, camphor 2%

Table 3. Characteristics of Patients With and Without a History of TTCM Usage

	Positive TTCM usage (n = 17)	Negative TTCM usage (n = 24)
Mean age (y)	61.1	64.2
Male:female ratio	0.42:1	2.38:1
Disease duration (mo)	34.8	49.5
Positive PT reading (n, %)	16 (94%)	11 (46%)
Positive PT reading to TTCM	7	0

TTCM: topical traditional Chinese medicament
Statistically significant

allergens that patients with a history of TTCM usage tested positive for included colophony, Balsam of Peru, neomycin, fragrance mix, flavine, 4-phenylenediamine (PPD), thiuram mix, wool alcohols, gentamicin and miconazole. Table 3 summarises the characteristics of the patients with and without a history of TTCM usage.

Seven out of the 44 patients (15.9%) had at least 1 positive reading for TTCM. Although the mean age of these patients was older (68.4 years) compared to those who had at least 1 positive patch test reading for sensitisers other than TTCM (63.2 years), this difference was not

statistically significant ($P = 0.422$). The sensitisation rates of the individual TTCM in our series are as shown in Table 1. Amongst users (current and past) of TTCM, the sensitisation rate was 41% (7 of 17). Most of these patients (5 of 7) had positive reactions to more than 1 TTCM allergen with another 3 patients also having positive reactions to allergens other than TTCM. Table 4 describes the characteristics and clinical relevance of the 7 patients with positive reaction/s to TTCM.

Discussion

Allergic contact dermatitis remains a major morbidity for patients with chronic leg ulcers. Not only can it contribute to periwound eczema and maceration, it can result in complications such as delayed wound healing and secondary bacterial infection such as cellulitis. This can have a significant adverse impact on the quality of life of these patients.

TTCM may play one or more of the following roles in motivating patients to use them: contributing to a common whole; satisfying a demand not met by conventional Western medical practices; or diversifying the conceptual framework of medicine.¹³ As yet, there are no published reports or studies showing the benefits of TTCM in the management

Table 4. Details of Patients With at Least One Positive Reaction to TTCM

Patient no.	Disease length (mo)	Contact allergens (TTCM)	Contact allergens other than TTCM	Clinical relevance
1	72	Tiger Balm, Eagle Brand Medicated Oil, Tjin Koo Lin, Zhen Gu Shui	Balsam of Peru, fragrance mix	Past
2	9	White flower oil, Green grass oil	–	Present relevance: Recurrent infected stasis leg ulcers not responding to treatment and compression stockings. Advised to stop TTCM application with subsequent resolution of recurrent ulcers after 6 weeks.
3	15	Saw Hong Choon ointment, Tjin Koo Lin	–	Past
4	5	Saw Hong Choon ointment, Tiger Balm	Balsam of Peru, povidone iodine	Present relevance: Leg ulcers for 5 months with long-standing stasis eczema. Initial response to treatment poor. Advised to stop TTCM application with resultant satisfactory healing after 4 weeks.
5	6	Saw Hong Choon ointment	–	Past
6	48	Saw Hong Choon ointment	–	Past
7	3	Saw Hong Choon ointment, Tiger Balm, Tjin Koo Lin, Eagle Brand Medicated oil, green grass oil, white flower oil, Zhen Gu Shui (Yulin), Tiger oil, Wong Cheung Wah Ul oil	Balsam of Peru, fragrance mix, colophony, povidone iodine, DUODERM CGF	Present relevance: Stasis ulcers treated by a Chinese physician. Subsequently worsened with bleeding from ulcers. Advised to stop TTCM. Wound dressed and compression stockings used, resulting in satisfactory healing after 3 weeks.

TTCM: topical traditional Chinese medicament

of chronic venous leg ulcers. Instead, TTCM are important contact sensitisers in our group of patients with chronic venous leg ulcers, representing the second commonest sensitisers as a group in our series.⁸ These findings highlight the importance of taking the local as well as the patient's personal practices into context when assessing the possible sensitisers in a case of allergic contact dermatitis in venous leg ulcer patients.

There was some difficulty in determining the clinical relevance of the positive reactions in our group of patients due to the chronicity of the disease, a reluctance to reveal current or previous usage of TTCM, as well as being unable to recall the actual duration of TTCM usage. However, as illustrated by the 3 short clinical scenarios (patient nos. 2, 4, 7) in Table 4, avoidance of the putative allergens in combination with appropriate wound care had a significant clinical impact on the healing of the chronic leg ulcers. There was gradual reepithelialisation of the ulcers with a decrease in periwound maceration and erythema.

The high sensitisation rate of TTCM (41%) amongst its users in our series was surprising as a previous study from our centre showed a sensitisation rate of only 4.5% (4 of 89) when users were tested to the same panel of topical Chinese medicaments.¹⁰ In this earlier report, only a small percentage of the study participants had stasis eczema, compared to the majority of the patients in this study who had stasis ulcers. The presence of large quantities of activated Langerhans cells in early stasis eczema skin may explain the importance of stasis eczema as a risk factor for the development of allergic contact dermatitis.¹⁴ The sensitising potential of TTCM should not be disregarded as well. In our study, nearly all the patients (94.1%) who had a history of TTCM usage had at least 1 positive PT reading.

High rates of cross-sensitivity between the individual TTCM, as well as between TTCM and fragrance mix, Balsam of Peru or colophony have been well reported.^{10,11,15} Interestingly, despite the high sensitisation rates of both colophony (11.3%) and TTCM (15.9%) in our study, only 1 case (patient no. 7) tested positive to both these sensitisers. Previous analysis of the individual topical Chinese medicaments in our series for dehydroabietic acid (DHAA) and abietic acid (AA) content, the main components of colophony responsible for skin sensitisation, revealed that only the Eagle brand medicated oil contained high contents of both these putative allergens.^{16,17}

False-positive irritant reactions need to be considered in the interpretation of any patch test reading. Irritant contact dermatitis to TTCM is not uncommon with reports associated with the use of Zhen Gu Shui and white flower oil among others.¹¹ In the development of our TTCM series that was previously reported, the commonly used TTCM were identified by interviewing patients and patch testing

of these selected preparations was done at stepwise concentrations varying from 1% to 50% in each respective vehicle and as is. The highest concentration at which no irritant contact reaction was elicited was determined for each medicament.¹⁰ In this series, there were 2 positive readings to White flower oil (patients 2 and 7) and 2 positive readings to Zhen Gu Shui (patient 1 and 7). In patients 1 and 7, multiple sensitivities to other TTCM, as well as to allergens such as Balsam of Peru, fragrance mix and colophony were found as well. In these 3 cases (patients 1, 2, 7), the Day 7 delayed reading remained positive for the above allergens (data not shown); hence, decreasing the possibility of a false-positive irritant reaction. The sensitisation rate to Saw Hong Choon ointment (11.3%) was the highest amongst the TTCM in our study. This is surprising as contact sensitisation to the ointment has not been previously reported.¹⁰ In 4 of the 5 positive reactions to Saw Hong Choon ointment, the Day 7 readings remained positive (data not shown), decreasing the possibility of an irritant reaction.

In conclusion, TTCM play an important role as contact sensitisers in our patients with chronic venous leg ulcers. Allergic contact dermatitis or contact irritation from the application of TTCM may be a significant factor in non- or poor-healing leg ulcers. In our local setting, a thorough history of TTCM usage should be sought for and patch testing should include the commonly used TTCM where relevant.

Acknowledgements

We would like to thank our nurses, Cindy Choi and Agnes Chong, as well as our research assistant, Hwee Bing Kuik, for their invaluable assistance.

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