

ORIGINAL ARTICLE

Contact sensitivity in patients with venous leg ulcer: A multi-centric Indian study

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Venous leg ulcers are the most common form of non-healing leg ulcers. They are subjected to treatments such as topical medications, dressings, and compression therapies. This can lead to exposure to a number of allergens with subsequent sensitisation and contact dermatitis of the regional skin. This may contribute to the poor ulcer healing. To detect the various contact sensitisers in patients with venous leg ulcers through patch testing, patients from 6 centres across India with venous leg ulcers of longer than 6 weeks duration were enrolled for the study. They were patch tested using a special patch test kit with 27 antigens. A total of 172 patients were included in the study; 82 (48.2%) tested positive for at least 1 antigen. Among them, polyvalent sensitisation was noted in 71% of patients. Wood tar mix (10.4%) and the framycetin (8.7%) were the most common allergens. There is a high frequency of allergic sensitisation to various ingredients of topical therapies used in the venous ulcer management, which may interfere with wound healing. Avoiding them can help obtain a better therapeutic outcome.

KEYWORDS

contact dermatitis, patch test, venous ulcer

1 | INTRODUCTION

Venous ulcers are an important sequel of chronic venous insufficiency (CVI). They are known for protracted course and refractory healing. A multidisciplinary approach is required for their assessment and treatment, including proper wound management, compression, and surgical interventions. Persistence of the ulcer for a longer duration leads to exposure to numerous topical applicants and medicament-incorporated dressings. Contact with these medicaments by the barrier-disrupted skin and occlusive wound dressings can lead to contact sensitisation. This allergic contact dermatitis of the skin surrounding the leg ulcers is undesirable because it delays wound healing.

Contact sensitisation in leg ulcer patients is very frequently reported in published studies.^{1–7} The spectrum of allergens causing contact dermatitis in chronic leg ulcer patients depends on the wound care practices in a given area. In the majority of studies, a major group of sensitisers include fragrances, lanolin, antimicrobial agents, and rubber-related allergens. There is a high probability of polyvalent sensitisation, especially in ulcers of a longer duration. Patients with chronic leg ulcers, with or without associated dermatitis, should hence be patch tested to detect sensitisation to various allergens. This is an Indian study on the pattern of contact sensitisation in patients with chronic leg ulcers using special patch test series.

2 | METHODS

This is a prospective, multicentre, cross-sectional study conducted in 6 centres across India. Approval to conduct study was obtained from the respective institutional ethics committees. Consecutive patients who presented with chronic venous ulcers due to CVI persisting for 6 weeks and who consented to participate in the study were recruited. Patients with and without dermatitis of the surrounding skin were recruited for the study. Relevant clinical and demographic details were obtained. Local examination, including the morphology of ulceration, presence of dermatitis or other signs of CVI, and other relevant clinical findings, were also recorded. Those who were on immunosuppressive drugs, a steroid dose of 20 mg of prednisolone or equivalent, and those with dermatitis involving the back were excluded from the study. The study was conducted for a period of 1 year.

All patients included were patch tested using patch test series for leg ulcers obtained from the Chemotechnique Diagnostics, Modemgatan 9, SE-235 39, Vellinge, Sweden, which includes 27 allergens consisting of medicaments, preservatives, steroids, etc. Application of patch test series and patch test reading was performed according to the guidelines of the International Contact Dermatitis Research Group. The Finn chamber method was used to apply the allergens. Test patches were removed at 48 hours, and a patch test reading was performed. Readings were also taken at 72 to 96 hours and on the 7th day. Readings were recorded as negative (–), doubtful (?), weak/non-vesicular reaction (+), strong reaction (oedematous or vesicular) (++) and extreme reaction (bulla or ulceration) (+++). Patch testing was considered positive when recorded as (+), (++) or (+++) reactions during any reading. Findings from all 6 centres were obtained and tabulated. Univariate analysis was the statistical method followed.

3 | RESULTS

A total of 172 subjects participated in the study. Details of the subjects from various centres are given in Table 1. Most patients were middle aged or elderly; almost half of the patients were aged between 50 and 70 years (Table 2). Majority of the patients were males (142 out of 172). A total of 52% of our patients had an ulcer duration of less than a year (Table 3). Of 172 patients, 83 (48.2%) showed positive patch

TABLE 1 Subject enrolment

Centre 1	50
Centre 2	37
Centre 3	32
Centre 4	32
Centre 5	11
Centre 6	10
Total	172

Key Messages

- venous leg ulcers therapies, such as topical medications, dressings, and compressions, expose the patients to allergens, followed by sensitisation and contact dermatitis; patch testing them can identify these allergens, and avoiding these allergens is an integral part of successful wound healing
- venous leg ulcer therapies, such as topical medications, dressings, and compressions, expose the patients to various allergens leading to contact dermatitis; it can contribute to poor wound healing
- patch testing patients can identify these allergens; avoiding these allergens is an integral part of successful wound healing

TABLE 2 Demographic profile of the subjects

Age (years)	Gender		Total
	Male	Female	
18-20	1	2	3
21-30	10	1	11
31-40	20	7	27
41-50	29	4	33
51-60	34	7	41
61-70	35	8	43
71-80	9	1	10
81-90	4	0	4
Total	142	30	172

test reactions to 1 or more antigens (Table 3). Almost 50% of those showing positive reactions had disease duration of less than 1 year. A total of 29 % of the subjects demonstrated positive reaction to only 1 antigen and 27% to 2 antigens (Figure 1). One patient had positive reactions to 7 antigens.

Table 4 shows the various antigens that were patch tested. There were 183 positive reactions. Clinical relevance of the positive patch test reactions in these cases often remains questionable, but most positive reactions included antibiotics, antiseptics, solvents, and emulsifiers, which are components of the topical applicants. The most common allergen in our study was wood tar mix (19 patients). This was followed by framycetin sulphate (17 patients) and thiomersal and eosin (13 patients each). Twelve patients each

TABLE 3 Duration of disease with patch test positivity

Duration of ulcer (months)	Number of patients (%)	Number of patients with positive patch test	Percentage positivity (N = 83)
0-3	34 (19.8)	18	21.7
3-6	30 (17.4)	15	18.1
6-12	26 (15.1)	10	12.0
12-60	54 (31.4)	27	32.5
>60	28 (16.3)	13	15.7
Total	172 (100)	83 (48.2%)	100

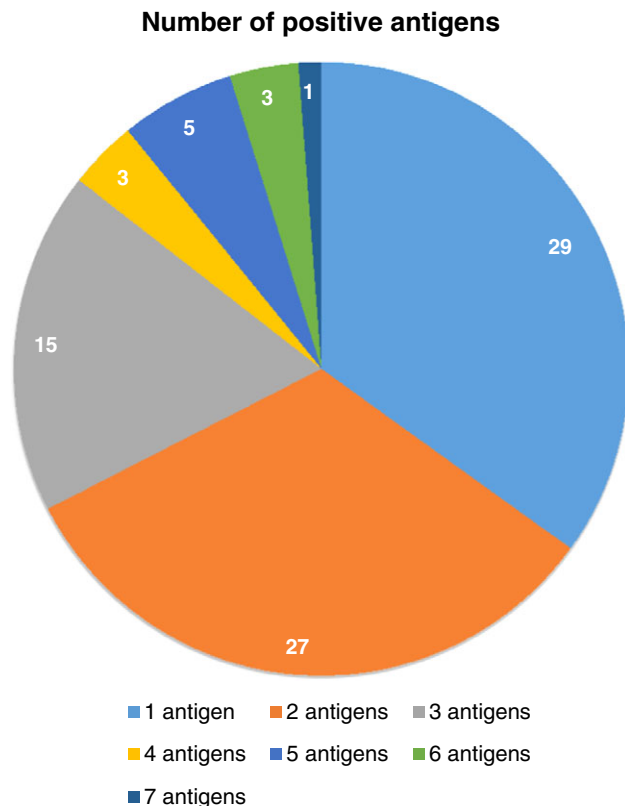


FIGURE 1 Number of positive antigens

showed positive patch test reactions to benzalkonium chloride and p-CHLORO-m-CRESOL (PCMC). All allergens except tixocortol pivalate showed at least 1 positive test reaction.

4 | DISCUSSION

Chronic venous ulcers are 1 of the common problems, with prevalence rates for open ulcers ranging from 0.12% to 1.1% of the population.⁸ Venous disease is the most frequent aetiology of leg ulcers, followed by arterial disease and other causes, such as diabetes.⁹ Prevalence of venous ulcers has reduced due to better management of CVI, but it continues to be a major health problem. Chronic course of the ulcers, local inflammation, skin barrier disruption, use of topical medicaments including “over the counter” preparations, and the use of occlusive bandages are the reasons patients get sensitised to many antigens.¹⁰ This leads to the onset of dermatitis, maceration of the surrounding skin, delayed wound healing, and bacterial infection. Allergic contact dermatitis may develop at distant sites other than the legs due to allergen exposure, dissemination from the ulcer site, or systemic spread.¹¹ Apart from poor wound healing, the presence of contact dermatitis of the surrounding skin will reduce the choices of therapy and local wound care.

Eczema was the most frequent manifestation of CVI, followed by leg ulceration.¹² Ulceration is an important determinant of the poor quality of life in venous disease.

Our study included all patients presenting with leg ulcers irrespective of the presence of eczema. We used the leg ulcer series commercially supplied by the Chemotechnique Diagnostics.

Our study included 172 patients; 83 (48.2%) patients demonstrated positive patch test reactions to at least 1 allergen (Table 3). Our study results are almost at par with the results of Smart et al, who reported positive patch test results in 46% of their patients.⁶ Higher positive results have been reported by Tavadia et al (68%), Saap et al (63%), Machet et al (75%), Lim et al (61.4%), and Jasmina et al (75%).^{1–5} Some of these studies tested a larger number of antigens, which could be the reason for higher positive reactions. For example, in the study by Saap et al, a standard North American Contact Dermatitis Group series and 54 supplemental antigens were used.² Contact sensitivity to various allergens was higher in their general population, thus yielding higher results. Artüz et al. recently reported their findings in a study involving 40 patients and 20 controls; reported patch test positivity in these groups was 77.5% and 50%, respectively.¹³ Management practices in our population may expose our patients to a lesser number of allergens, and this could have led to a lower percentage of positive reactions. In spite of all these factors, 48% positivity appears to be a high value and could play a role in the non-healing nature of the ulcers.

Among the 172 patients, 60% belonged to the age group of 30 to 60 years; another 30% were aged over 60 years. According to a population survey, 22% of the leg ulcers began before 40 years of age.¹⁴ Only 30 (17.4%) of our patients were females, which may be due to decreased hospital reporting by women. In a population-based study, women outnumbered men by a ratio of 2.8:1.¹⁵

The duration of the leg ulcer is an important factor in the development of contact sensitisation. Venous ulcers are usually chronic; 33% to 60% of the ulcers can persist beyond 6 weeks;¹⁶ 40 % of the ulcers may remain open for over 1 year.¹⁷ One can predict that there will be more patch test-positive reactions with increased duration of the ulcer. In our study, 48% of those who tested positive had an ulcer duration of 2 years or more (Table 3). Polyvalent sensitisation and higher mean number of allergen sensitisations were found more frequently in ulcers with a duration of more than 5 years.⁵

Polyvalent sensitisation has been reported consistently with leg ulcers.^{1–3,5} Studies have proven that the common sensitisers are the various ingredients of topical applicants, dressings, and bandages.¹⁸ Lanolin, antibiotics, antiseptics, preservatives, emulsifiers, resins, and latex were the principal sensitisers. A total of 71% of our patients were positive for more than 1 allergen (Table 4). One patient was found to have positive reactions to 11 allergens. A total of 183 positive reactions were found in our study (Table 4). The most common allergen in our patients was the wood tar mix, with 19 patients (10.4% of all positive reactions) showing

TABLE 4 List of allergens and positive reactions

S. No.	Antigens	Patients with positive reaction	Percentage (N = 183)
1.	Control	0	0
2.	Amerchol L 101	5	2.7
3.	Fusidic acid sodium salt	4	2.2
4.	Chlorhexidine digluconate	5	2.7
5.	Benzalkonium chloride	12	6.6
6.	Nitrofurazone	6	3.3
7.	Bacitracin	4	2.2
8.	Cetearyl alcohol	4	2.2
9.	2,6-Ditert-butyl-4-cresol (BHT)	3	1.6
10.	Chloramphenicol	7	3.8
11.	Benzoyl peroxide	2	1.1
12.	Propylene glycol	9	4.9
13.	Propolis	6	3.3
14.	Thimerosal (Merthiolate)	13	7.1
15.	Sorbic acid	3	1.6
16.	Eosin	13	7.1
17.	4-Chloro-3-cresol (PCMC)	12	6.6
18.	Budesonide	3	1.6
19.	Triethanolamine	8	4.4
20.	Framycetin sulphate	16	8.7
21.	Sorbitan sesquioleate	4	2.2
22.	Tixocortol-21-pivalate	0	0
23.	Sorbitan monooleate (span 80)	5	2.7
24.	Phenyl mercuric acetate	6	3.3
25.	Chloroacetamide	2	1.1
26.	Diazolidinyl urea (Germall ii)	4	2.2
27.	Imidazolidinyl urea (Germall 115)	7	3.8
28.	Wood tar mix	19	10.4
	Total	183	100

positive reactions. This was followed by framycetin (16 patients, 9%), eosin (13 patients, 7.5%), *p*-CHLORO-*m*-CRESOL or PCMC (12, 7%), and benzalkonium chloride (12 patients, 7%). Other important allergens include propylene glycol, triethanolamine, chloramphenicol, imidazolidinyl urea, and phenyl mercuric acetate (Table 4). The majority of these reactions were relevant. There was no sensitisation to tixocortol pivalate. A venous eczema study utilising Indian standard series has been published by Jindal et al; they found 50% of positive results, with fragrance mix, *p*-phenylene diamine, wool alcohol, and nickel being the other common detected allergens.¹⁹

Wood tar mix was 1 of the most frequent (20%) allergens also found in the study by Saap et al.² In their study, sensitivity to balsum of Peru and bacitracin were the most frequent. Wood tar sensitisation was also 1 of the common sensitisers in a large study involving 1883 patients with allergic contact dermatitis.²⁰ Wood tar is used in the flavouring of certain food. A high degree of cross-allergy between wood tars and fragrance mix can occur. Framycetin is a common antibacterial agent used for ulcer care in India;

hence, sensitisation to this agent is highly relevant. In spite of lack of evidences of the efficacy of framycetin or other antibiotics, the practice of topical antibiotic usage widely prevails in wound care.²¹ We have known about very high framycetin sensitisation in leg ulcer patients for decade.^{22,23} A number of antibiotic- and antiseptic-impregnated dressings are also used in ulcer management.²⁴ Eosin sensitisation has been reported in 2 studies.^{25,26} In one of those studies, a very high rate of contact sensitivity (82.5%) has been reported, with eosin being positive in 5%. Eosin is an acid red dye used in lipsticks, nail polish, textiles, and antiseptics. Patch test positivity is thus relevant in patients with leg ulcers. PCMC and benzalkonium chloride are compounds used as an antiseptic and disinfectant. Both are known for their potential for allergic contact dermatitis.^{27,28} Saap et al. have reported 13% patch test positivity to benzalkonium chloride in their study.² We detected many other allergens with low frequency, and the relevance of such positive reactions cannot be determined.

Compression therapy using various bandages and stockings is an integral part of management and prevention of venous ulcers.^{29,30} Allergic contact dermatitis to synthetic rubber, neoprene, in compression stockings has been reported.^{32,33} Modern dressing-related contact dermatitis is infrequent but has also been reported.³¹⁻³⁴ Usage of these modern dressings is infrequent in Indian patients, and hence, sensitisation may be a rare occurrence. Many indigenous and traditional home remedies are used, and their sensitisation potential has also been explored in a few studies.^{10,35}

The most important limitation of this study was the non-inclusion of a control group. Inclusion of a control group with healthy volunteers was not considered in order to avoid the discomfort involved in patch testing. There was no uniformity in the number of patients recruited from the various centres. Indian standard series patch testing could have been performed in addition to the leg ulcer series.

Venous insufficiency and ulcers are problems Indian patients experience because of occupations that involve prolonged standing. There may be a genetic predisposition to varicose veins in many patients. It affects people during their prime of life as our study inferred. It is more common in men, who are the breadwinners in most Indian households, thus causing health as well as economic burden. The pattern of sensitisation appears to be related to treatment practices. Allergens and their frequencies in Indian patients with venous disease were almost similar to those reported from other parts of the world.^{1-4,19} Common allergens in many of those studies were the fragrance mix, antibacterials, wood tar mix, and lanolins. Sensitisation to fragrance mix was very high, and a significant number were sensitive to topical corticosteroids in the study by Tavadia et al. We found wood tar mix and the antibacterials (framycetin) among the common allergens, and we found no sensitisation to corticosteroids.

Studies have inferred that patients with chronic wounds of the lower extremity experience functional disability and

emotional distress, with negative influences on quality of life. Apart from physical and psychosocial functioning, treatment-related issues also can have an impact.^{36,37} A review of the literature and calculated sensitisation rates of a pool of 3043 patients extracted from 24 series, and their own, has shown a significant increase in sensitisation in recent times.³ Contact allergy to the various topical treatments employed in leg ulcer management can contribute to or worsen eczema and can impede ulcer healing. Thus, it can be a major reason of poor quality of life. Modern dressings with lower allergenic potential may be used as wound dressing. It is better to avoid antiseptics and antibiotics in the absence of infection, and it should be used for a limited period. This should be known by all health care personnel involved in managing venous leg ulcers.

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