

ORIGINAL ARTICLE

Low molecular weight heparin improves healing of chronic venous ulcers especially in the elderly

Raffaele Serra^{1,2}, Gianluca Buffone¹, Vincenzo Molinari¹, Rossella Montemurro¹, Paolo Perri¹, Domenico M Stillitano¹, Bruno Amato^{2,3} & Stefano de Franciscis^{1,2}

1 Department of Medical and Surgical Science, University Magna Graecia of Catanzaro, Viale Europa, Località Germaneto, Catanzaro, 88100, Italy

2 Interuniversity Center of Phlebology, International Research and Educational Program in Clinical and Experimental Biotechnology, University Magna Graecia of Catanzaro, Viale Europa, Località Germaneto, Catanzaro, 88100, Italy

3 Department of General, Geriatric, Oncologic Surgery and Advanced Technologies, University "Federico II" of Naples, Via Pansini, Naples, 5-80131, Italy

Key words

Chronic venous disease; Chronic venous leg ulcers; Elderly; Low molecular weight heparin; Wound healing

Correspondence to

Raffaele Serra, MD, PhD
Department of Medical and Surgical Science
University Magna Graecia of Catanzaro
Viale Europa, Località Germaneto 88100
Catanzaro, Italy
E-mail: rserra@unicz.it

doi: 10.1111/iwj.12071

Serra R, Buffone G, Molinari V, Montemurro R, Perri P, Stillitano DM, Amato B, de Franciscis S. Low molecular weight heparin improves healing of chronic venous ulcers especially in the elderly. *Int Wound J* 2015; 12:150–153

Abstract

Venous ulcers are common, especially in the elderly, accounting for more than 50% of all lower extremity ulcers with important socioeconomic problems. Improving extracellular matrix functioning, by heparin administration, seems to be a way to support wound healing. A total of 284 patients with venous ulcers were recruited in a 4-year period. All patients were subjected to the most appropriate treatment after considering their preference (compression therapy followed or not by vein surgery). Patients were randomised into two groups of 142 persons in each (group A and group B as cases and controls, respectively). Patients of group A, in addition to the basic treatment as described earlier, received administration of nadroparin 2850 IU/0.3 ml through subcutaneous injection once a day for 12 months, whereas group B patients received basic treatment alone. Healing was assessed by means of direct ulcer tracing with computerised planimetry. Group A showed a healing rate of 83.80% at 12 months, whereas that of group B was 60.56%. Results by age group surprisingly showed that the group of older patients took the most advantage from long-term treatment with low molecular weight heparin; this group also had lowest recurrence rate.

Introduction

Venous leg ulcers are responsible for more than half of lower extremity ulcerations, with an overall prevalence ranging up to 2% in the general population. Furthermore, venous ulcers seem to have an increased healing rate in older age groups, with a peak between 60 and 80 years (1,2). Venous ulcerations tend to be a chronic or recurrent problem resulting in diminished quality of life, frequent hospitalisations and health care provider visits, increased morbidity with consequent significant economic cost and psychological impact (2–4). Treatment of venous stasis ulcers varies from multiple surgical procedures to the use of various topical agents combined with compression therapy (5).

Chronic wounds, as venous ulcers, exhibit deficiencies or dysfunction in the extracellular matrix (ECM) that cannot support healing (6–8) and some studies describe the effects of heparin in regulating ECM proteins (9) and also in improving

wound healing (10). The aim of this work is to demonstrate the efficacy of low molecular weight heparin (LMWH) in accelerating healing of venous leg ulcers, as a support to basic treatment.

Key Messages

- venous ulcers are common, especially in the elderly, resulting in diminished quality of life and frequent hospitalisations
- complete healing is often difficult to achieve and recurrence is extremely common
- heparin administration appears to accelerate healing of chronic venous leg ulcers, especially in elderly patients

Methods

This is an open-label study comprising a total population of 284 patients [63 males (32.18%), 221 females (77.82%), age range 48–91 years, mean age 69.5 years] at their first admission for venous ulcers of the lower limbs, secondary to primary chronic venous insufficiency, according to C6 of Clinical-Etiology-Anatomy-Pathophysiology (CEAP) Classification for chronic venous disorders (11). These patients were recruited in a 4-year period (1 January 2003–31 December 2006), whose demographics and clinical characteristics are shown in Table 1.

Venous leg ulcers were selected after clinical and ultrasound examinations [all patients of this study had evidence of superficial veins and/or calf perforating veins reflux, but none had deep venous reflux or evidence of deep vein thrombosis (DVT)] and by exclusion of other causes of ulceration, especially arterial insufficiency. Only ulcers lasting more than 6 weeks were included in this study, as chronic leg ulcers are defined as those wounds lasting longer than 6 weeks (4).

All patients were subjected to the most appropriate treatment after considering their preference. The typology of surgery, when it was accepted, was chosen according to the anatomical level of vein incompetence: superficial venous surgery [Cure Conservatrice et Haemodynamique de l'Insuffisance Veineuse en Ambulatoire procedure (CHIVA)

procedure is the procedure of choice at our institutions in these cases] and/or subfascial endoscopic perforating surgery (Table 1).

All patients, regardless of whether surgery was performed or not, were treated with third-class medical compression stocking (36–50 mmHg) for 12 months and then with second-class medical compression stocking (25–40 mmHg) for the remaining period of the study (48 months). Compliance with elastic stockings was optimal in all patients. All patients had adopted local care according to the typology of the wound. Patients were randomised into two groups of 142 persons in each (group A and group B). Patients of group A, in addition to the basic treatment described earlier, were administered nadroparin at the dosage of 2850 IU/0.3 ml through subcutaneous injection, once a day for 12 months. All patients of group A had no documented bleeding risk factors (such as uncontrolled hypertension, thrombocytopaenia, coagulopathy or recent gastrointestinal bleeding).

Patients of group A were evaluated every week for 5 years. In the first year of heparin therapy, blood samples were taken monthly for assessment of anti-Xa activity, activated partial thromboplastin time and blood cell counts.

Patients of group B (control group) received only basic treatment according to their clinical conditions and were evaluated every week for 5 years. Institutional Review Board (IRB) approval was obtained and informed consent was received from all patients.

Healing was assessed by means of direct ulcer tracing onto clear plastic sheet and subsequent computerised planimetry. Healing was calculated by subtracting the final ulcer area from the initial area and dividing by the number of weeks that the patient had been observed to obtain the total area healed per week. The follow-up was 5 years for both groups and was terminated for all patients on 31 December 2011.

Table 1 Baseline Patient Characteristics

Parameters	Group A	Group B	Total
Number of patients	142	142	284
Sex (M/F)	31/111	32/110	63 (32.18%)/ 221 (77.82%)
Age			
Range (years)	48–91	49–86	48–91
Mean (years)	69.5	72.5	69.5
48–64 years	42 (29.57%)	39 (27.46%)	81 (28.52%)
65–79 years	62 (43.66%)	67 (47.18%)	129 (45.42%)
80+ years	38 (26.76%)	36 (25.35%)	74 (26.05%)
Duplex ultrasound findings			
Superficial vein incompetence	131 (92.25%)	128 (90.14%)	258 (90.84%)
Perforating vein incompetence	7 (4.92%)	12 (8.45%)	19 (6.69%)
Superficial + perforating incompetence	4 (2.81%)	2 (1.40%)	6 (2.11%)
Surgery			
Superficial vein surgery	124 (87.32%)	121 (85.21%)	245 (86.27%)
SEPS	2 (1.41%)	6 (4.22%)	8 (2.82%)
Superficial vein surgery + SEPS	1 (0.70%)	1 (0.70%)	2 (0.70%)
Concomitant conditions			
Arterial hypertension	52 (36.61%)	65 (45.77%)	117 (41.19%)
Obesity	43 (30.28%)	38 (26.76%)	81 (28.52%)
Ulcer features			
Area (range, cm ²)	2.9–19.5	3.1–21.5	2.9–21.5
Area (mean, cm ²)	12.7	14.7	13.5

SEPS, subfascial endoscopic perforator surgery.

Results

All patients completed the follow-up. No side effects related to heparin treatment occurred in group A (no heparin-induced thrombocytopaenia, no osteoporosis, no bleeding). Healing rates at 12 months (Table 2) was 83.80% for group A and 60.56% for group B. The mean total ulcer area rate of healing for group A was of 1.3 cm²/week and 0.87 cm²/week for group B.

Considering the results by age group (Table 3), it is surprising that the group of older patients took the most advantage from the treatment with LMWH. In fact, 87.09% of patients aged between 65 and 79 years and 91.10% of patients aged over 80 years achieved and maintained healing at 1 year during heparin treatment. On the other hand, in group B, the

Table 2 Healing rates at 12 months

	Group A	Group B
Healed ulcers	119 (83.80%)	86 (60.56%)
Mean area healing per week (cm ² /week)	1.3	0.87
Non-healing ulcers	23 (16.19%)	58 (40.84%)
<i>P</i> value	<0.00001	

Table 3 Healing rates at 12 months according to age range

	Group A	Group B
Healed ulcers		
48–64 years	30/42 (71.42%)	37/39 (94.87%)
65–79 years	54/62 (87.09%)	39/67 (58.20%)
80+ years	35/38 (91.10%)	10/36 (27.77%)
Non-healing ulcers		
48–64 years	12/42 (28.57%)	9/39 (23.07%)
65–79 years	8/62 (12.90%)	31/67 (46.27%)
80+ years	3/38 (7.89%)	17/36 (47.22%)
P value		
48–64 years	<0.322	
65–79 years	<0.0001	
80+ years	<0.00001	

Table 4 Recurrence rate of venous ulcers at 5 years

	Group A	Group B
	Total recurrence 38/142 pts (26.76%)	Total recurrence 84/142 pts (59.15%)
Age range		
48–64 years	18/42 (42.85%)	17/39 (43.58%)
65–79 years	12/62 (19.35%)	38/67 (56.71%)
80+ years	8/38 (21.05%)	29/36 (80.55%)
P value		
48–64 years	<0.003	
65–79 years	<0.002	
80+ years	<0.002	

Table 5 Recurrence rate versus type of surgery

Type of surgery	Group A	Group B
SPV	36/131 (27.48%)	78/128 (60.93%)
SEPS	1/2 (50%)	4/6 (66.66%)
SPV + SEPS	1/1 (100%)	1/1 (100%)

SPV, superficial vein surgery; SEPS, subfascial endoscopic perforator surgery.

greatest benefit was achieved by patients aged between 48 and 64 years. Also with regard to the recurrence rate (Table 4), the results were better for group A. In group A, recurrences occurred only in 26.76% of the cases, whereas in group B the rate of recurrence was of 59.15%. Also in the case of recurrences, older patients of group A showed a lower rate than those of the same category of group B (19.35% versus 56.71% in age range 65–79 years; 21.05% versus 80.55% in age range 80+ years). Recurrence rate according to the type of surgery was lower for group A especially for superficial venous surgery (Table 5).

Discussion

Compression therapy and surgical correction of superficial venous incompetence are the main methods currently employed in the treatment for venous ulcers. Graduated external compression to the lower extremity has resulted in accelerated healing of venous ulcers and has become the mainstay of treatment, while superficial venous surgery

appears to be associated with rates of ulcer healing similar to those by compression alone, but with less recurrence (12).

Healing is often delayed and once healed, many patients with chronic venous ulcers have a recurrence, which is reported to be as high as 72% of treated subjects (1,2,5).

Heparin has been studied to determine its effects on wound healing. The role of heparin in wound healing has been demonstrated in some studies. Heparin appears to be associated with rapid and effective endothelial cell repair, having anti-inflammatory properties and enhanced angiogenesis and neovascularisation (10).

Previous studies (13,14) showed that venous ulceration may be associated with microvascular thrombosis displaying depressed fibrinolytic activity, increased red cell aggregation, endothelial cell damage, expression of adhesion molecules and cytokine release and in this context, heparin has a role in limiting these adverse events.

In a previous study (10), long-term treatment with LMWH appears to have improved early and late results of patients who underwent reconstructive surgery (skin grafting) for difficult-to-heal chronic venous ulcer.

In the present study, it was shown that the use of LMWH is also useful in the initial treatment of venous leg ulcers and is free from risks and side effects. Moreover, it appears that the greatest advantage of LMWH use occurs in older patients, both in terms of healing as well as maintenance of results at 5 years but the reason is, however, not clear.

A suggestive hypothesis could be that in the initial stages of formation of a venous ulcer, phenomena of inflammation and hypoxia predominate in ECM. In the maintaining stage, phenomena of local thrombosis in ECM may predominate instead and this makes the ulcer increasingly irreversible. These states go hand in hand with the evolution of pro-thrombotic state that characterise the age-related physiological changes of an elderly patient. In addition heparin, with its antithrombotic and anticoagulant effects, may interrupt the natural history of an ulcer that leads to irreversibility, increasing its chances of recovery. The main disadvantage of the present study is the absence of placebo, as it is an open-label trial not supported by external funding, and therefore further studies, may be of double-blind typology, with placebo are needed to clarify these issues.

Conclusions

The data from this study suggest that long-term LMWH therapy may expedite the healing of chronic venous leg ulcers especially in older patients. These initial results suggest future clinical investigations to conduct larger studies with more prolonged follow-up to confirm their validity.

Acknowledgement

The authors declare that they have no competing interests.

References

1. Callam MJ, Ruckley CV, Harper DR, Dale JJ. Chronic ulceration of the leg: extent of the problem and provision of care. *Br Med J (Clin Res Ed)* 1985;290:1855–6.

2. Margolis DJ, Bilker W, Santanna J, Baumgarten M. Venous leg ulcer: incidence and prevalence in the elderly. *J Am Acad Dermatol* 2002;**46**:381–6.
3. Reichenberg J, Davis M. Venous ulcers. *Semin Cutan Med Surg* 2005;**24**:216–26.
4. Serra R, Buffone G, de Franciscis A, Mastrangelo D, Molinari V, Montemurro R, de Franciscis S. A genetic study of chronic venous insufficiency. *Ann Vasc Surg* 2012;**26**:636–42.
5. Neglen P; Writing Group II of the Pacific Vascular Symposium 6, Eklöf B, Kulwicki A, Davies A, Deschamps T, Garcia M, Gloviczki P, Labropoulos N, Nicolaides A, Partsch H, Perrin M, Rabe E, Wittens C. Prevention and treatment of venous ulcers in primary chronic venous insufficiency. *J Vasc Surg*. 2010;**52**(5 Suppl):15S-20S
6. Clark RA. Biology of dermal wound repair. *Dermatol Clin* 1993;**11**:647–66.
7. Galvan L. Effects of heparin on wound healing. *J Wound Ostomy Continence Nurs* 1996;**23**:224–6.
8. Longo C, Serra R, Mastrangelo D, de Franciscis S. VEGF as a biological marker of the venous disease-associated ulcers natural history in the elderly: preliminary data. *BMC Geriatr* 2010;**10**(Suppl 1):A64.
9. Serra R, Buffone G, Falcone D, Molinari V, Scaramuzzino M, Gallelli L, de Franciscis S. Chronic venous leg ulcers are associated with high levels of metalloproteinases-9 and neutrophil gelatinase associated lipocalin. *Wound Repair Regen* In press. DOI: 10.1111/wrr.12035.
10. Serra R, Buffone G, de Franciscis A, Mastrangelo D, Vitagliano T, Greco M, de Franciscis S. Skin grafting followed by low-molecular-weight heparin long-term therapy in chronic venous leg ulcers. *Ann Vasc Surg* 2012;**26**:190–7.
11. Eklöf B, Rutherford RB, Bergan JJ, Carpentier PH, Gloviczki P, Kistner RL, Meissner MH, Moneta GL, Myers K, Padberg FT, Perrin M, Ruckley CV, Smith PC, Wakefield TW. Revision of the CEAP classification for chronic venous disorders: consensus statement. *J Vasc Surg* 2004;**40**:1248–52.
12. Howard DP, Howard A, Kothari A, Carpentier PH, Gloviczki P, Kistner RL, Meissner MH, Moneta GL, Myers K, Padberg FT, Perrin M, Ruckley CV, Smith PC, Wakefield TW. The role of superficial venous surgery in the management of venous ulcers: a systematic review. *Eur J Vasc Endovasc Surg* 2008;**36**:458–65.
13. Bradbury AW, MacKenzie RK, Burns P, Fegan C. Thrombophilia and chronic venous ulceration. *Eur J Vasc Endovasc Surg* 2002;**24**:97–104.
14. de Franciscis S, De Sarro G, Longo P, Buffone G, Molinari V, Stillitano DM, Gallelli L, Serra R. Hyperhomocysteinemia and chronic venous ulcers. *Int Wound J* 2013. DOI: 10.1111/iwj.12042.