



A randomized trial of surgery alone versus surgery plus compression in the treatment of venous leg ulcers in patients with primary venous insufficiency

Randomizovano ispitivanje efikasnosti hirurškog tretmana naspram kombinacije hirurškog i kompresivnog tretmana u lečenju venskih ulceracija kod bolesnika sa primarnom venskom insuficijencijom

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Abstract

Background/Aim. Venous leg ulcers (VLU) are a significant health problem worldwide. It is well known that VLU are difficult to treat and that they have high tendency for recurrence. Compression therapy is the preferred treatment modality but there is growing evidence that correction of underlying venous disorder in early stages of the disease in addition to compression treatment may improve ulcer healing and reduce recurrence rate. **Methods.** An open, prospective, randomized, single-center study, with a 6-months follow-up was performed to determine the efficacy of two different treatment modalities (surgery alone versus surgery plus compression) in the treatment of VLU in patients with primary venous insufficiency. Patients with secondary venous insufficiency and/or thrombosis were excluded from the study. Overall, 71 patients were randomized (37 men, 34 women; mean age 60 years) into two groups: the group A – 34 patients who underwent surgical intervention (stripping) and postoperatively were treated with simple wound dressing only, and the

group B – 37 patients who underwent surgical intervention (stripping) and wore a heelless open-toed elastic class III compression device knitted in tubular form – Tubulcus® (Laboratoires Innothera, Arcueil, France). All patients in group B were instructed to wear compression device continuously during the day and night. The study was performed at the Clinic for Cardiovascular and Transplant Surgery, Clinical Centre Niš (Serbia) with primary endpoint of the study being complete ulcer healing at 180 days. **Results.** The healing rate was 29.41% (10/34) in the group A, and 56.76% (21/37) in the group B ($p < 0.01$). Mean healing time in the group A was 141 ± 15 days, and in the group B it was 98 ± 12 days (Log-rank life table analysis: $p < 0.001$). **Conclusion.** This study suggests that for VLU in patients with primary venous insufficiency, surgery plus compression therapy provides higher healing rate and faster healing time compared to surgery only.

Key words:

varicose ulcer; vascular surgical procedures; stockings, compression; treatment outcome.

Apstrakt

Uvod/Cilj: Venske ulceracije nogu (VUN) predstavljaju široko rasprostranjen zdravstveni problem. Poznato je da se VUN teško leče i da postoji visoka stopa recidiva. Kompresivna terapija predstavlja terapiju izbora, ali postoji sve veći broj dokaza da korigovanje osnovnog venskog oboljenja u ranom stadijumu bolesti, uz kompresivnu terapiju, može poboljšati zarastanje ulceracija i smanjiti stopu recidiva. **Metode.** U cilju utvrđivanja efikasnosti dva različita načina lečenja (samo hirurgija *vs* hirurgija plus kompresivna terapija) venskih ulceracija, kod pacijenata sa primarnom ven-

skom insuficijencijom, sprovedena je otvorena, prospektivna, randomizirana studija, sa šestomesečnim praćenjem. Bolesnici sa sekundarnom venskom insuficijencijom i/ili venskom trombozom su bili isključeni iz studije. Studijom je obuhvaćeno ukupno 71 bolesnika (37 muškaraca i 34 žene), podeljenih u dve grupe: grupu A – 34 bolesnika kod kojih je urađena operacija (*stripping*) i koji su postoperativno tretirani samo običnim previjanjem rane, i grupu B – 37 bolesnika kod kojih je urađena operacija (*stripping*) i koji su postoperativno nosili elastičnu čarapu III klase kompresije, sa otvorenim prstima, satkanu u tubularnoj formi – Tubulcus® (Laboratoires Innothera, Arcueil, France). Svim bolesnicima iz

grupe B je objašnjeno da kompresivnu čarapu nose konstantno tokom dana i noći. Bolesnici su tretirani ambulantno, na Klinici za kardiovaskularnu i transplantacionu hirurgiju, Klinički Centar Niš (Srbija), sa primarnim ciljem da do zarastanja ulceracije dođe unutar 180 dana. **Rezultati.** Stopa zarastanja ulceracija je bila 29,41% (10/34) u grupi A i 56,76% (21/37) u grupi B ($p < 0.01$). Srednje vreme zarastanja ulceracija je bilo 141 ± 15 dana u grupi A, a u grupi B, 98 ± 12 dana (Log-rank analiza: $p < 0,001$). **Zaključak.** Re-

zultati studije su pokazali da lečenje venskih ulceracija kod bolesnika sa primarnom venskom insuficijencijom, hirurškom metodom u kombinaciji sa kompresivnom terapijom daje veću uspešnost i kraće vreme zarastanja, u poređenju sa samo hirurškom metodom.

Ključne reči:
venska ulceracija; hirurgija, vaskularna, procedure; čarape, kompresivne; lečenje, ishod.

Introduction

Venous leg ulcers (VLU) are a significant health problem worldwide. The treatment costs are very high and many patients due to this condition experience early retirement. It is well known that VLU are difficult to treat and that they have high tendency for recurrence. Compression therapy is the preferred treatment modality and has been used in different forms (compression hosiery, elastic or inelastic bandages usually applied as either two or multilayer bandaging systems)¹⁻⁴. Healing rates of VLU obtained with compression treatment vary widely from 40%–95%⁵⁻⁷. Despite the widespread use of compression therapy, recurrence rates of VLU remain high, between 25%–70%⁸⁻¹⁰. During the last couple of years published data suggest that correction of underlying venous disorder in early stages of the disease in addition to compression treatment may improve ulcer healing and reduce recurrence rate¹¹⁻¹².

Methods

An open, prospective, randomized, single-center study, with a 6-months follow-up was performed to determine the efficacy of two different treatment modalities (surgery alone versus surgery plus compression) in the treatment of VLU in patients with superficial venous reflux. Patients with secondary venous insufficiency and/or thrombosis were excluded from the study.

Population

Patients aged at least 18 years with VLU and primary venous insufficiency present on ultrasound examination were screened for inclusion in the trial. Significant arterial disease, pregnancy, rheumatoid disease, malignancy, restricted range of ankle motion and diabetes mellitus were exclusion criteria from the study.

Before randomization, all patients were examined by Color Duplex Scan investigation (CDS). In order to establish significant arterial diseases ankle brachial pressure index (ABPI) measurements were performed. For ultrasound investigation a Siemens Sonoline Sienna device with a 7 MHz probe was used. Exclusion of venous thrombosis was determined by assessing venous compressibility and establishing flow characteristics. The flow direction was determined during a Valsalva maneuver in the 20–30° reverse Trendelen-

burg position. The reflux was induced using a rapid cuff deflation in the standing position. The presence of reflux was confirmed if the reflux time was > 0.5 seconds.

Sample size

With a power of 80% and a confidence level of 95%, assuming VLU healing rates of at least 20% in the group A and 40% in the group B, a total of 70 patients were needed for this study. One hundred and eleven patients were examined for potential participation in this study. Of these, seventy-one were accepted and randomized.

Randomization

Randomization was computer generated and, in total, 71 patients were randomized (37 men, 34 women; mean age 60 years) into two groups: the group A – 34 patients who underwent surgical intervention (*stripping*) and postoperatively were treated with simple wound dressing only, and the group B – 37 patients who underwent surgical intervention (*stripping*) and wore a heelless open-toed elastic class III compression device knitted in tubular form-Tubulcus® (Laboratoires Innothera, Arcueil, France). All patients in the group B were instructed to wear compression device continuously during the day and at night. This study was performed at the Clinic for Cardiovascular and Transplant Surgery, Clinical Centre Niš (Serbia) with the primary endpoint of the investigation being complete VLU healing at 180 days.

The relevant authorities approved the study protocol and all patients who were included in the study gave their written consent.

Study protocol

All patients included in the study were treated and monitored by the same clinical team comprising of three doctors and three medical nurses. Patients were treated and monitored on the ambulatory basis at the Clinic for Cardiovascular and Transplant Surgery, Clinical Centre of Niš (Serbia) (3 visits per week for the 6 months period). The surgical procedure was performed on all patients and included crossectomy with stripping of the great saphenous vein. The patients were operated in local anesthesia and received 2 g of cephalosporine intraoperatively.

Treatment regimen

The local treatment regimen for ulcers was the same for all patients included in the study. The dressings were changed in regard to amount of wound exudation (from 1 to 7 days). The patients did not receive any additional local or systemic therapy. No medication including antibiotics or venous-active drugs were used. Simple mechanical debridement was performed at each patient's visit using sterile gauze to remove dead tissue and slough. After this, ulcers were covered by sterile gauzes and one layer of creep bandage was applied to affected leg. The patients in the group B received tubular compression device knee-high (Tubulcus®). This elastic stocking is classified as a compression device Class 3 that exerts the interface pressure of 35–40 mmHg. The interface pressure achieved with this device is graduated and the highest pressure is exerted at the ankle in the region of medial malleoli, diminishing upwards towards the knee. Tubulcus® elastic stocking comes in 5 different sizes (S, M, L, XL and XXL) and the size for each patient was determined according to the circumference of the affected leg. Two measures of the affected leg were taken: one at the ankle and the second at the largest part of the calf. One pair of elastic stockings were changed after the 6 months period and the circumference of the affected leg was remeasured in order to provide elastic stockings of adequate size. The Tubulcus® elastic stockings were placed on the affected leg over the local dressing using the special positioner. After slipping over the Tubulcus® device over the positioner, the stocking was placed to the desired position. The positioner was then removed by pulling it down using special handle³. The patients in the group B were instructed to wear Tubulcus® elastic stockings all the time during the day and at night.

Outcomes

Primary endpoint of our study was complete ulcer healing at 180 days. The ulcer closure was defined as the point at which complete epithelialization of the affected leg occurred.

Statistical analyses

After the 6 months follow up, data were collected and statistically analyzed. Our primary analysis compared time to ulcer healing on an intention-to-treat basis using the Kaplan-Meier survival analysis with log rank comparisons. In order to determine whether covariates (age, gender, body mass index – BMI, ulcer size, duration of venous ulceration) significantly influenced the ulcer healing rate, Cox regression analysis with backward method was used.

The χ^2 test was used to compare categorical parameters between the groups. Differences in median values between the two groups were analyzed with the Mann-Whitney *U* test.

The Fisher exact tests and Mantel-Haenszel χ^2 -test were used to compare the frequencies. In order to compare means between the examined groups, an independent samples *t*-test was used. Single variable logistic regression was performed to calculate odds ratios (ORs) with 95% confidence intervals

(CIs). The age was considered as a continuous, and other monitored factors as a categorical variables. Calculated *p* values were represented by the estimated regression coefficient divided by its standard error.

Statistical package SPSS 16.0 was used for the analyses (SPSS Inc., Chicago, Ill), with *p* values less than 0.05 considered as significant.

Results

One hundred and eleven patients were examined for possible inclusion onto this study and 71 were recruited and randomized.

The study excluded 40 patients: patients with diabetes mellitus (seven patients), heart insufficiency (one patient), pregnancy (one patients), malignant disease (two patients), patients with significant arterial disease (six patients), and patients who had secondary venous insufficiency and/or thrombosis (twenty-three patients).

Overall, 71 patients (37 men, 34 women; mean age 60 years) completed the study. The two study groups were comparable in terms of age, gender, general medical history, previous episodes of ulceration, size and duration of the ulcer (Table 1).

Table 1
Characteristics of the treatment and control groups
(median, range)

Parameter	Group A (n = 34)	Group B (n = 37)	<i>p</i>
Male : female ratio	16 : 18	21:16	0.480
Age (years)	60 (33–80)	61 (40–77)	0.853
BMI, kg/m ²	28 (23–34)	29 (22–35)	0.903
Size of the ulcer (cm ²)	52.7 (11–134)	46.6 (8–142)	0.698
Duration of the ulcer (years)	5.1 (0.7–12)	4.4 (0.7–11)	0.484

Group A – patients treated by surgery only; Group B – patients treated by surgery plus compression.

BMI – body mass index.

The clinical, etiologic, anatomic and pathophysiologic (CEAP) classification was presented as follows: clinical – all patients included in the study had an active VLU (C6); etiologic – all patients had primary CVI; anatomic – superficial vein reflux was present in all 71 patients included in the study; pathophysiologic – reflux was the pathophysiology established in all 71 patients included in the study.

Ulcer characteristics

The median size of the ulcer in the group A was 52.7 cm² (range, 11.0–154.0 cm²) and in the group B it was 46.6 cm² (range, 8.0–142.0 cm²), (Table 1). The ulcer median duration time in the group A was 5.1 years (range, 7 months–12 years) and in the group B it was 4.4 years (range, 7 months–11 years) (Table 1).

Time to healing and healing rate

The healing rate was 29.41% (10/34) in the group A, and 56.76% (21/37) in the group B ($p < 0.01$). Mean healing time in the group A was 141 ± 15 days, and in the group B it was 98 ± 12 days (Log-rank life table analysis: $p < 0.001$), (Figure 1).

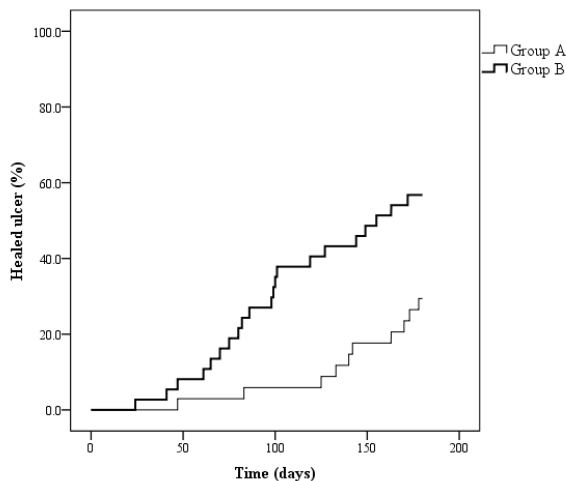


Fig. 1 – Cumulative healing rate of venous leg ulcers in the combined treatment group (surgery plus compression – the Group B) and the control group (surgery only – the Group A).

Age, gender, ulceration size, duration of the ulcer, body mass index are not independent parameters of success or failure of compression treatment (Table 2).

Table 2
Covariates entered in Cox regression model with enter method

Variables not in the equation	OR	95% CI	<i>p</i>
Age	0.988	0.951–1.026	0.517
Sex	1.504	0.717–3.155	0.280
Ulceration surface	1.006	0.997–1.015	0.202
Time since ulcer onset	0.981	0.895–1.076	0.687
Body mass index	1.003	0.913–1.102	0.948

CI – confidence interval; OR – odds ratio.

Discussion

Venous leg ulcers develop as a result of ambulatory venous hypertension. There are two main reasons for this: venous reflux and obstruction. As a result of ambulatory venous hypertension, inflammation process and leukocytes activation are triggered which leads to skin changes, at first and, in time, skin brake appears usually below the knee in the region of medial malleoli¹³.

The aim of compression treatment in patients with VLU is ulcer healing, prevention of ulcer recurrences and reduction of pain and edema¹⁴. Regrettably, a large number of ve-

nous leg ulcers remain refractory to compression therapy and it is evident that healed venous ulcers have a high tendency for recurrence.

Compression therapy is the preferred treatment modality and has been used in different forms (compression hosiery, elastic or inelastic bandages usually applied as either two or multilayer bandaging systems)¹⁻⁴. However, there is growing evidence supporting conclusion that surgical correction of underlying venous disorder in addition to compression may improve ulcer healing and reduce the rate of ulcer recurrences^{11-12, 15}. There are many published studies comparing the efficacy of different compression systems, efficacy of surgery treatment in addition to compression compared to compression alone, but, there are no studies that compare contemporary surgical treatment alone to compression systems.

Our study clearly demonstrated the superiority of compression therapy plus surgery in the treatment of active venous ulcers compared to surgical treatment only.

This study could not verify risk factors for VLU healing rate and healing time based on patient's basic characteristics (age, sex, BMI, previous operations, medical history).

Interestingly, a recently published study by Gohel et al.¹⁵ showed that treating venous ulcers early with endovenous ablation could significantly improve healing times and delay the recurrence of ulcers. In this study the patients were treated with compression as an addition to surgery which is in concordance with our finding that compression plus surgery achieves better results compared to surgery alone.

Our study also clearly demonstrated that surgical correction of venous reflux may resolve ulcer healing in small ulcers of short duration only. Large ulcers of long duration may be successfully treated with compression only. The inflammation lasted a long time and pathological skin changes were more profound compared to patients with small ulcers of short duration. These results show that patients with venous ulcers should be surgically treated as soon as venous ulcers develop in order to accelerate ulcer healing and provide a longer length of time free from ulcers (ulcer-free time). Surgical correction of underlying venous disorder, whenever is possible, is mandatory to abolish ambulatory venous hypertension and prevent continuous inflammation.

Among other risk factors, Nelson et al.¹⁰ identified previous ulcers as a risk factor for VLU healing and recurrence rates. We could not confirm this finding in our study. This is probably because most of the patients included in our study had never been treated with compression previously. High percentage of our patients had an active venous ulcer for decades and previous ulcers were recognized only during the initial phase of venous ulcer development when they experienced spontaneous wound closure without compression treatment.

The ESCHAR study^{11, 12} reported that patients who were surgically treated in addition to compression had a lower ulcer recurrence rate at 4 years compared to patients who were treated with compression only. However, healing rate and healing time was the same in both examined groups.

One of our previously published studies ⁷ found that high-compression systems healed more ulcers than compression systems with low or moderate compression. This trial is in concordance with these findings and it supports the premise that compression systems are mandatory in the treatment of venous leg ulcers.

Conclusion

The results obtained in this study suggest that compression therapy plus surgery provide statistically significant higher healing rate and faster healing time compared to surgery alone.

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