Clinical value of interwoven silver fibres in class II compression stockings: results from a crossover trial

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Abstract
Objective: The aim of the study was to show whether silver fibres interwoven into regular compression stockings will enhance the nutritive capillary perfusion in chronic venous insufficiency (CVI) patients.
Methods: Double-blind, randomized crossover trial with two 10-day treatment phases and an intermediate three-day wash-out in 20 CVI patients (7 males, 13 females, median age: 65 years), comparing regular and silver fibres containing class II compression stockings. Primary endpoint: tcpO2 measurement at 44°C probe temperature in the peri-malleolar region of the reference leg.
Results: In the overall study population, the ’end-of-treatment-phase’ minus ’start-of-treatment-phase’ tcpO2 differences were negative for the regular hosiery (median [MAD]: −6.75 [8.5] mmHg, supine leg position; −7.25 [5.75] mmHg, dependent leg position), but positive for the silver fibre containing fabric (median [MAD]: 4.0 [7.75] and 2.5 [8.5] mmHg for the supine and the dependent leg position). The intergroup differences in the overall data were not statistically significant. Analysis of a core data-set, excluding data points above the 90% and below the 10% percentile, approached (P=0.052, supine leg position) or reached statistical significance (P=0.023, dependent leg position).
Conclusions: The study provides first evidence that using interwoven silver fibres in class II compression stockings results in clinical benefit for CVI patients.

Keywords: Chronic venous insufficiency; compression therapy; silver fibres; tcpO2

Introduction

Chronic venous insufficiency (CVI) is a common medical condition with major socioeconomic impact. In total 25–33% of women and 10-20% of men are affected by varicose veins.1,2 The annual incidence of varicosity is 2.6% and 1.9% in women and men, respectively, as seen in the Framingham study.3 The prevalence of CVI-related peripheral oedema and skin changes such as hyperpigmentation reported in literature ranges between 3% and 11%.1,4 Moreover, the prevalence of severe CVI with active or healed ulcers is 1% of an adult Western population.5,6 Annual recurrence rates range between 5% and 15%.7,8 It is estimated that up to 12.5% of the working age patients will apply for early retirement because of CVI and continued disability.9 Health economic data from the 1990s suggest that the annual (direct and indirect) costs created by CVI and its consequences amount to approximately $1 billion (USD) for European countries such as Germany, France and the UK.10,11

In view of the magnitude of the medical and the socioeconomic problem, effective conservative treatment is required. As proven by two meta-analyses, clinically efficient standard regimens include mechanical compression, either as compression bandaging or hosiery.12,13

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Recently, a silver fibre containing fabric was introduced to the market, possibly improving microcirculatory perfusion by a Joule’s effect. Since a first pilot trial from our institution in healthy volunteers has given evidence that this hypothesis may indeed be true,14 a double-blind, randomized comparison of regular hosiery and silver fibre containing stockings was performed in CVI patients (present study).

Methods

Patients

Thirty-seven patients were screened between June 2003 and May 2004. Fourteen did not match all the selection criteria and 23 patients were randomized; three patients dropped out because of private but not medical reasons. Thus, seven male and 13 female patients finished the study. The demographic data are summarized in Table 1.

Selection criteria

Patients presenting with CVI up to CEAP C4 and a clear indication for compression therapy were allowed to participate. Patients with peripheral oedema of non-venous origin, patients with peripheral arterial disease, cardiac failure (NYHA III, IV), decompensated chronic obstructive pulmonary disease and patients with cutaneous lesions of diabetic origin were excluded.

Definition of the reference leg

In cases of bilateral CVI, the more diseased leg was defined as the reference leg. If both legs were affected to a similar degree, the reference leg was determined empirically.

Study design

Prospectively planned, double-blind, randomized, crossover study with two 10-day treatment periods and a three-day wash-out in-between.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Mean</th>
<th>SD</th>
<th>Median</th>
<th>MAD</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
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<td>15.1</td>
<td>65</td>
<td>5.5</td>
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<tr>
<td>Height (cm)</td>
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<td>7.7</td>
<td>—</td>
<td>—</td>
<td>154-180</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>74.0</td>
<td>12.8</td>
<td>—</td>
<td>—</td>
<td>54-99</td>
</tr>
<tr>
<td>Systolic BP (mmHg)</td>
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<td>20.0</td>
<td>130</td>
<td>10</td>
<td>110-195</td>
</tr>
<tr>
<td>Diastolic BP (mmHg)</td>
<td>79.5</td>
<td>10.6</td>
<td>80</td>
<td>7.5</td>
<td>60-110</td>
</tr>
<tr>
<td>ABI right</td>
<td>1.15</td>
<td>0.10</td>
<td>—</td>
<td>—</td>
<td>0.97-1.36</td>
</tr>
<tr>
<td>ABI left</td>
<td>1.12</td>
<td>0.12</td>
<td>—</td>
<td>—</td>
<td>1.0-1.44</td>
</tr>
</tbody>
</table>

SD, standard deviation; MAD, median absolute deviation; BP, blood pressure; ABI, ankle brachial pressure index

Medication

Pairs of regular, knee-high but custom-fitted compression stockings (Venasan®) and seemingly identical custom-fitted compression stockings with interwoven silver fibres (Venasan 5000®), both manufactured by Salzmann AG, St Gallen, Switzerland.

Endpoints

The primary endpoint was the tcpO2 measured at 44°C in the peri-malleolar region of the reference leg. Secondary endpoints included the laser Doppler flux (LDF) and the hosiery wearing comfort measured with a visual analogue scale (VAS).

Measurements

Measurements of tcpO2 and LDF were performed as follows: patients initially lay in a supine position for a period of 10 min in an air-conditioned room with a temperature between 20-22°C, wearing the stockings. The stockings were then taken off to apply the tcpO2 and LD-probes 2 cm dorso-cranially from the medial malleolus. Measurements were performed in a supine and seated (dependent) position. TcpO2 measurements were taken at 44°C probe temperatures, LDF measurements at physiological skin temperature.

Instrumentation

The tcpO2 and the LDF were measured using a Servomed Oxyapnomonitor (Hellige Ltd, Freiburg, Germany) and a MOOR DRT LD with a wavelength of 780 nm (MOOR Instruments Ltd, Devon, UK), respectively. The LD parameter ‘flux’ was calculated by the MOOR DRT4 WIN software. The tcpO2 monitor was calibrated against air and a zero-solution, according to the manufacturer’s instructions. The LD probe was calibrated using the manufacturer’s standard solution.

Ethical aspects

All participants were appropriately informed about the trial and signed a written informed consent form. The study protocol was evaluated and approved by the ethics committee of the University of Basel (EKBB).

Randomization and statistics

Patients were randomized in blocks of two. Custom-fitted stockings were fax-ordered from the manufacturer who was supplied with a
randomization plan. Stockings were delivered labelled with the patient number, the patient's initials and birth date, and the study phase (crossover phase 1 or 2).

The study was classified as an explorative pilot study. Since no pre-published data were available to calculate the sample size, it was set empirically. Data were analysed using a per protocol (PP) analysis. The PP population only consisted of patients with a full set of data; 20 sets were complete. Data were analysed using descriptive statistics. Non-parametric statistics were generally applied as the number of volunteers was low and the probability high for a non-normal data distribution. The Wilcoxon signed rank test was used to compare for differences emerging from both treatment phases. Statistical significance was defined by alpha and beta errors of 5% and 20%, respectively. Analysis of covariance modelling was used to test for influences of patient demographics or haemodynamic variables on the results. The overall data contained a few outlier values that, because of low patient numbers, substantially affected the study results. To show essential trends of change between the two crossover phases, a more stable 'core data-set' was generated by excluding data points above the 90% and below the 10% percentile of the overall data-set. Data were analysed using the StatView 5.0 statistical package (SAS Institute Inc., Cary, NJ, USA).

Results

Behaviour of tcpO2 and LDF in supine and dependent leg positions

Lowering the leg from a supine into a dependent position increased the mean baseline tcpO2 values (44°C) from 60.4 (13.6 standard deviation [SD]) to 75.0 (11.5 SD) and 58.1 (16.8 SD) to 72.6 (15.9 SD) in the Venosan and the Venosan 5000 groups, respectively. Correspondingly, LDF values decreased from 15.5 (6.9 SD) to 10.3 (9.7 SD) for Venosan and 12.2 (2.9 SD) to 8.3 (4.9 SD) for Venosan 5000. Changing the leg position from supine to dependent at the end of each treatment phase augmented the tcpO2 values from 59.9 (13.9 SD) to 72.4 (13.2 SD) and 60.9 (9.8 SD) to 74.1 (10.5 SD) mmHg in the Venosan and the Venosan 5000 groups, respectively. Corresponding LDF values were 15.5 (7.1 SD) to 9.7 (7.6 SD) and 16.0 (8.1 SD) to 10.2 (7.0 SD).

Primary endpoint

PP population

The different tcpO2 values (tcpO2_end of treatment phase—tcpO2_start of treatment phase) for the leg in the supine and dependent position are given in Table 2. The median differences between the group results were 10.75 and 9.75 mmHg in favour of Venosan 5000 for the leg in a supine and a dependent position ($P = 0.25, 0.19$).

Core data

Core data, as defined in the statistics section differed from the PP data by the exclusion of four data points per data-set, two data points from above the 90% percentile and two data-points from below the 10% percentile of the overall data of the two groups.

The differences of tcpO2 values (tcpO2_end—tcpO2_start) for the leg in a supine and a dependent position are given in Table 3. The median differences between the group results were, as in the PP data, 10.75 and 9.75 mmHg in favour of Venosan 5000 for the leg in a supine and a dependent position ($P = 0.052, 0.023$). Results from the PP and the core data-set are illustrated and compared in Figure 1.

Secondary endpoints

Laser doppler flux

With the leg in a supine position, LDF tended to increase slightly in both groups (data not shown);

<table>
<thead>
<tr>
<th>Table 2</th>
<th>Differences in tcpO2 (tcpO2_end of treatment phase—tcpO2_start of treatment phase) measured at 44°C for the reference leg in supine and dependent position: PP population</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean</td>
<td>SD</td>
</tr>
<tr>
<td>tcpO2 supine (mmHg)</td>
<td></td>
</tr>
<tr>
<td>Venosan</td>
<td>-3.58</td>
</tr>
<tr>
<td>Venosan 5000</td>
<td>1.10</td>
</tr>
<tr>
<td>tcpO2 dependent (mmHg)</td>
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</tr>
<tr>
<td>Venosan</td>
<td>-3.70</td>
</tr>
<tr>
<td>Venosan 5000</td>
<td>1.53</td>
</tr>
<tr>
<td>SD, standard deviation; MAD, median absolute deviation</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Table 3</th>
<th>Differences in tcpO2 (tcpO2_end of treatment phase—tcpO2_start of treatment phase) measured at 44°C for the reference leg in supine and dependent position: core data</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean</td>
<td>SD</td>
</tr>
<tr>
<td>tcpO2 supine (mmHg)</td>
<td></td>
</tr>
<tr>
<td>Venosan</td>
<td>-4.44</td>
</tr>
<tr>
<td>Venosan 5000</td>
<td>1.91</td>
</tr>
<tr>
<td>tcpO2 dependent (mmHg)</td>
<td></td>
</tr>
<tr>
<td>Venosan</td>
<td>-6.78</td>
</tr>
<tr>
<td>Venosan 5000</td>
<td>1.53</td>
</tr>
<tr>
<td>SD, standard deviation; MAD, median absolute deviation</td>
<td></td>
</tr>
</tbody>
</table>


with the leg in a dependent position, both the intra- and inter-group differences were around zero. None of the measured changes were statistically significant.

**Hosiery wearing comfort**

The hosiery wearing comfort was measured by a 100mm VAS at the end of each treatment phase. VAS results ranged between 31 and 100mm and were grouped as follows: 31-53mm, moderate; 54-76mm, good; 77-100mm, excellent. The majority of patients judged the wearing comfort for both treatments as excellent (Venosan 60%, Venosan 5000 65%). Eighty per cent (Venosan) and 85% (Venosan 5000) of patients agreed that the wearing comfort was at least good and only a small minority of patients were not satisfied with either product.

**Discussion**

This study was the first trial in CVI patients to compare regular compression stockings with fabrics containing interwoven silver threads. The study gave evidence, in agreement with the results of a pilot trial in healthy volunteers, that interwoven silver fibres result in a substantial improvement of the nutritive skin perfusion as shown by tcpO₂ measurements. This is of clear medical relevance, particularly if seen in context with the major socioeconomic problem, caused by CVI and its complications.

There is little discussion on the need and the usefulness of compression therapy in CVI patients. A recent initiative of the International Union of Phlebology summarized this evidence and listed and discussed the most important evidence level A and B studies. However, in contrast to trials on the clinical outcome, information on the effects of compression on the nutritive capillary flow in CVI patients remains limited. There is agreement that appropriate compression will reduce venous pooling by reducing the venous capacity, will augment the venous drainage and overall, lead to a reduction of the venous pressure. Thus, the venous pooling and capacity-dependent deleterious effects of leukocyte (polymorph nuclear) activation and its sequelae may be reduced. Furthermore, the arterio-venous (AV)-pressure gradient over the capillary bed may rise, enhancing the cutaneous nutritive perfusion, particularly in case of capillary rarefaction and other conditions of tissue oxygen deficiency.

However, any form of skin compression may as well result in a mechanical reduction of the nutritive capillary flow and thus in a redistribution of flow towards deeper cutaneous structures (AV-shunts). From a theoretical point of view, there is, despite all positive effects on the venous macro-circulation, the possibility of a compression-related negative net balance of the capillary perfusion. Results from Fromy et al. support this hypothesis. In their own material, the tcpO₂ decreased by 5–10% over the treatment period when using regular compression stockings, whether or not this difference is of clinical relevance remains unknown, although, overall positive effects of compression seem to outweigh negative ones as shown by clinical outcome studies. Still, the question remains whether the positive results of outcome studies could be more impressive if the negative effects of compression therapy were avoided.

Regular class II compression stockings with interwoven silver fibres may offer this advantage. The use of Venosan 5000 led to a median increase of the tcpO₂ of 4 mmHg over the treatment period, with a total oxygen pressure difference from Venosan of approximately 11 mmHg. If this difference and particularly the positive O₂-net-pressure-balance can be translated into clinical benefit in future prospective randomized long-term outcome studies, silver fibres containing
hosiery would become the compression standard. Even at present, there is little reason not to give preference to the new product as wearing comfort and costs of both fabrics are in a comparable range.

**Strengths and limitations**

This is the second study to give positive evidence that silver fibre containing compression stockings may be superior to regular hosiery. Results were consistent from a hypothesis-proving-phase IIa study in volunteers to this explorative pilot trial in CVI patients. This study was prospectively planned and randomized and was performed in consecutive CVI outpatients, fulfilling the selection criteria.

The small number of patients and the fact that statistically significant results were only achieved in retrospectively defined core data, excluding data points above the 90% and below the 10% percentile of the overall data, are the main drawbacks. The analysis of core data may be criticized, but the relevance of the conclusions is supported by the fact that median results are identical and median absolute deviations are almost identical for both the PP and the core datasets.

**Conclusion**

This study provides first evidence in CVI patients that the use of silver fibre containing hosiery results in clinically relevant advantages over regular compression stockings.

**Acknowledgements**

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