Treatment of venous leg ulcers with sulodexide

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Keywords
Sulodexide, venous leg ulcers

Summary
Aim: The study of the influence of sulodexide in the treatment of venous leg ulcers. Patients and method: 44 patients with chronic venous ulceration were randomly divided into two groups. Group I: 21 patients (ulceration area: 12.7-18.9 cm²); Group II: 23 patients (ulceration size: 12.1-20.3 cm²). Both groups were treated by using Unna’s boot. This dressing was changed every seven days until the ulcer had healed. Additionally, the patients in group II received the systemic pharmacological treatment with sulodexide.

Results: After 7 weeks of treatment ulcers of seven patients (35%) from group I had healed, and 3 weeks later the ulceration of two more patients had healed completely. After further 7 weeks the ulcers of 12 patients had healed completely. Whereas in group II after 7 weeks of treatment ulceration of 16 (70%, p <0.05) patient had healed completely and after further 3 weeks the ulcers of the remaining 7 patients had healed, too.

Conclusion: The use of sulodexide in patients with chronic venous leg ulcers accelerates the healing process.

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Persisting high blood pressure in macro-circulation is inevitably transposed to microcirculation. At this stage possible observations are:
- adhesion, migration, and excitation of leukocytes,
- release of harmful factors such as cytokines and leucotriens,
- appearance of free oxygen radicals derived from leukocytes, proteolytic enzymes, thrombocyte activating factor (in tissues).

As a result blood plateles are activated and microthromboses formed (8, 12, 22). Over a longer period of time this leads to the formation of ulcerated wounds. Regular dressing of such wounds, which is considered to be the standard treatment of varicose ulceration, helps to close the ulceration. However, the process is time-consuming requiring a few months or even a few years.

For improvement of microcirculation and acceleration of the healing process drugs are administered to assist this process. They primarily are used to protect the endothelium and to prevent morphotic blood elements aggregation (1, 4, 9, 13). A drug characterized by such properties is sulodexide. It is a glycosaminoglycan consist-
ing of 80% heparin with high affinity for antithrombin III and 20% of dermatansulfate with high affinity for heparin cofactor II. Heparin contained in sulodexide is weaker in its antithrombotic properties in comparison with its counterpart, the non-fractionated heparin. However, its half-life is relatively long. Dermatansulfate inhibits the activation of factor Xa as well as blood platelet activation and adhesion. It also exerts a reducing effect of the plasminogen activator inhibitor which leads to the reduced concentration fibrinogen in plasma.

The aim of this study was the evaluation of the influence of sulodexide in the treatment of venous leg ulceration.

Patients and methods

Patients

Our research comprised 44 patients with chronic venous ulceration (inclusion criteria) who were randomly divided into two groups. Each ulcer was diagnosed as a venous ulcer by using Doppler sonography (Logiq 500, General Electric, USA). All patients were chosen at random from those who applied for consultation by surgery doctor. Group I included patients with odd numbers, group II included patients with even numbers. The numbers were determined by the surgeon.

Group I (Tab. 1) consisted of 12 women and 9 men aged 52-68 years (on the average 57.8 years). The ulceration area of these patients varied from 12.7 to 18.9 cm² (on the average 15.8 cm²). The ulcer location in 9 people was on the left crus, and in 12 cases on the right one. The duration of the wound was from 1 year to 6 years (on the average 3.2 years). Seventeen patients had full mobility and 4 women suffered from a limitation in mobility. Body mass index (BMI) ranged from 21 to 37.8 kg/cm² (on the average 26.5 kg/cm²). The BMI was >30 kg/cm² in 4 women and 1 man. None of the patients suffered from diabetes mellitus or atherosclerosis of the lower limbs (exclusion criterion). Ankle/arm pressure ratio was ≥0.8.

Group II (Tab. 1) consisted of 14 women and 9 men (age: 53-66 years; on the average 58.2 years). The ulceration area of these patients varied from 12.1 to 20.3 cm² (on the average 16.2 cm²) and the duration of the wound from 18 months to 7 years (on the average 4.1 years). In 10 patients ulcers were located on the left crus, and in 13 patients on the right one. The full mobility was given in 18 patients, it was limited in 5 patients. BMI ranged from 19.8 to 36.9 kg/cm² (average 25.8 kg/cm²). The BMI was >30 kg/cm² in 3 women. None of the patients was suffering from diabetes mellitus or atherosclerosis of the lower limbs (exclusion criterion). Ankle/arm pressure ratio was ≥0.8.

On the basis of clinical and sonography findings all patients were classified using the classification and grading (CEAP) of chronic venous disease (Tab. 2) (18). All patients from both groups had previously been treated by traditional methods, such as hydrogel and hydrocolloid dressing. Nevertheless, the healing of their wound was not promoted.

Methods

Patients from both groups underwent a treatment by using Unna’s boot (1). Earlier, the necrotic tissues had been removed from the ulcerations either by surgery or with the use of enzyme-containing ointment. After rinsing the wound with physiological salt solution Unna’s rigid paste bandages were tied round the limbs from below the toes up to the knee. This dressing was changed every seven days until the ulcer was healed.

Additionally, the patients in the group II received the systematic pharmacological treatment with sulodexide (Vessel Due F, Alfa Wassermann, Italy). The drug was administered to the patients according to the following dosage scheme:

<table>
<thead>
<tr>
<th>CEAP Class</th>
<th>group I</th>
<th>group II</th>
</tr>
</thead>
<tbody>
<tr>
<td>C0 E0   A0.4</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>C0 E0   A0.4/10  P1</td>
<td>4</td>
<td>3</td>
</tr>
<tr>
<td>C0 E0   A0.4/18  P1</td>
<td>4</td>
<td>4</td>
</tr>
<tr>
<td>C0 E0   A0.4/18  P1</td>
<td>4</td>
<td>4</td>
</tr>
<tr>
<td>C0 E0   A0.4/18  P1</td>
<td>3</td>
<td>4</td>
</tr>
</tbody>
</table>

Tab. 1 Patient’s demographic data (n/s: not significant; BMI: body mass index; ABPI: ankle-brachial pressure index)
one intramuscular administration of 600 lipoprotein lipase releasing units (LRU) per day for 20 consecutive days
followed by 500 LRU divided into two oral administrations per day until the ulcer was healed.

Prior to the treatment, as well as before each change of dressing bandages all the patients had the bacterial swab from the ulcers taken. All the same time the area of the ulcers was measured. The procedure was as follows:

First, homothetic congruent projections of the ulcers were plotted onto transparent foil.

Then the planimetric measurements of the wounds were taken with the use of digitizer Mutoh Kurta XGT-1218 A3 (USA).

The ulcers were measured once a week, every week, until the wounds were healed completely.

In order to estimate the speed of the changes in the ulceration area, the following formula was worked out

\[ v_I = \frac{S_i - S_{i-1}}{t} \]

\( S_i \): ulceration area at the time of the previous measurement, \( S_{i-1} \): ulceration area on the day of a given measurement, \( t \): time in days in which the ulceration area was changing from \( S_{i-1} \) to \( S_i \); \( i \): I, II: number of the group.

All the patients underwent ambulatory treatment. Also, they were examined by the physician every week, until the ulceration healed completely. The obtained results were analyzed by using Mann-Whitney U-test. A p-values <0.05 were considered statistically significant.

Results

In the patients of group I after seven days of treatment the average ulceration area decreased by 1.2 cm², and the speed at which it decreased equalled \( v_I = 0.171 \) cm² per day (Tab. 3, Fig. 1). In the three consecutive weeks of further treatment it withdrew by 0.4, 0.3, 0.2 cm², respectively, leading to the measurement of 13.7 cm². At the same time the speed of ulceration withdrawal amounted to

\[ v_I = 0.057 - 0.043 - 0.029 \text{ cm}^2/\text{d} \]

At this stage one woman’s ulceration was healed (Tab. 4). After the next three weeks six more patients had their ulceration healed. The average ulcer area diminished to 10.9 cm² with \( v_I = 0.171 \text{ cm}^2/\text{d} \). In the three consecutive weeks two more patients’ ulcer were healed completely and the average ulcer area in the remaining patients
equalled 6.5 cm\(^2\). The speed of ulceration withdrawal was equal to \(v_I = 0.171\) cm\(^2\)/d.

The following two weeks brought successful treatment of three more patients and the average ulceration area was estimated to 4.3 cm\(^2\). At that time the speed of ulcer withdrawal remained the same (\(v_I = 0.171\) cm\(^2\)/d). After further two weeks the ulcerations of four patients were healed completely. The wound area decreased by 2.1 cm\(^2\), and the speed \(v_I = 0.143\) cm\(^2\)/day. The ulcers of the remaining two women and three men were healed completely after a few weeks of treatment. In that period of time the speed of ulceration withdrawal equalled

\[ v_I = 0.157 - 0.155\ \text{cm}^2/\text{d} \]

In patients from group II after seven days of treatment the average ulcer area diminished by only 0.4 cm\(^2\) with the speed of the wound withdrawal equaling \(v_{II} = 0.129\) cm\(^2\)/d. In the following three weeks of treatment the ulcer area decreased by 1.9, 1.4, and 1.5 cm\(^2\), respectively, and the speed of ulcer withdrawal amounted to

\[ v_{II} = 0.200 \pm 0.200 \pm 0.214\ \text{cm}^2/\text{d} \]

After that time ulcers of three women were healed, and the average ulceration area in the remaining patients was equal to 11.0 cm\(^2\). After further two weeks of treatment five patients’ wounds healed completely. The speed at which the ulceration decreased equalled to 0.214 – 0.229 cm\(^2\)/d. In eight patients’ ulcers were healed completely after the next seven days and the average ulcer area in the other patients was equal to 6.3 cm\(^2\). The ulcers of the remaining patients healed completely after the following three weeks. The speed at which the ulcer area was decreasing amounted to 0.229, 0.329, 0.343 cm\(^2\)/d, respectively.

**Discussion**

Venous ulceration in the leg is a chronic condition in which the healing of the ulcer is dependent on the size of the ulcer, the age of the patient and the mode of treatment (13). The standard treatment of venous leg ulcers of the lower limbs consists in topical administration of medicines and compression therapy. Compression therapy is crucial for the healing of venous leg ulcers, but local therapy may also improve the healing rate. There are five basic types of occlusive dressings: hydrogels, hydrocolloids, films, alginates, and foams (1, 13).

**Tab. 3 Mean ulceration area (cm\(^2\)) according to the duration of treatment**

<table>
<thead>
<tr>
<th>group</th>
<th>duration of treatment (weeks)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0</td>
</tr>
<tr>
<td>I</td>
<td>X</td>
</tr>
<tr>
<td>SD</td>
<td>3.1</td>
</tr>
<tr>
<td>II</td>
<td>X</td>
</tr>
<tr>
<td>SD</td>
<td>4.1</td>
</tr>
</tbody>
</table>

**Statistical significance**

| p     | <0.005 | <0.005 | <0.005 | <0.005 | <0.005 | <0.005 | <0.005 | <0.005 | <0.005 | <0.005 | <0.005 | <0.005 | <0.005 | <0.005 | <0.005 | <0.005 | <0.005 |

**Fig. 1 Time relationship of the ulcer areas (\(s\)) for both groups**
Hydrocolloid dressings are known since last century when in 1896 Unna presented this method of treatment for the first time. These dressings are used to gently stimulate tissue granulation and can be left on the wound for several days at a time. They inhibit bacterial overgrowth due to their physical barrier properties and by providing an acidic environment (17). However, it takes a long time to heal the wound: This process may last from a few months to a few years. Therefore, in order to shorten the time various drugs are used (4, 8, 9). These are said to improve the peripheral circulation and microcirculation.

Such a drug is sulodexide (Vessel Due F. Alpha Wassermann, Italy). It is a glycosaminoglycan containing 80% heparin characterized by its high affinity to antithrombin III and 20% of dermatansulfate possessing high affinity to heparin cofactor II. This antithrombotic activity in the arterial and venous vessels results from the inhibition activation of factor Xa and thrombin as well as inhibition of the thrombolytic aggregation. Also, this drug activates the fibrinolytic system through the increase in plasminogen activity, the decrease of the plasminogen activity inhibitor and the decrease in blood viscosity (11, 16, 19).

In our study Unnas' boot was used in the treatment of venous leg ulcers in all patients, in group II we additionally used sulodexide. After seven weeks of treatment ulcers of seven (35%) patients from group I were healed, and after further three weeks the ulcerations of two more patients healed completely. After the following seven weeks the ulcers of the remaining 12 patients were healed. Whereas, in group II after seven weeks of treatment ulcerations of 16 (70%) patients were healed completely and after further three weeks the ulcer of the remaining seven healed, too.

Similar results were achieved by Scondotto et al. (20), who examined the influence of sulodexide on the healing process of the venous ulcers of the lower limbs. For all patients they ordered compression therapy, additionally in half of the cases they administered sulodexide. They showed that after eight weeks of treatment the ulcers were completely healed in 58% of the patients who were receiving the additional drug, and only 36% of the cases who underwent the compression therapy.

Recently, the Italian research from venous arm of the Sulodexide Arterial Venous Italian Study Group (5) reported their results of effect of sulodexide in the treatment of venous leg ulcers. Approximately 71% of their patients had the ulceration area ≤10 cm² and approximately 24% ≥10 cm². All patients used high compression badges (example 4-layer bandages). 120 patients were treated with sulodexide drug and 110 people with placebo. The Italian researcher showed that after two months the completely ulcer healing was reached by 35.0% in patients with sulodexide group and 20.9% in case of placebo. After three months of treatment the ulcer healed in 52.5% patients who were receiving the additional drug and 32.7% in patients with placebo. We obtained similar results even though our patients had larger ulcer (12.1–20.3 cm²).

According to the “Consensus Paper on Venous Leg Ulcer” (10) it is advisable to accept as the final point of treatment first of all the complete healing of the wound and as second choice the ulcer decrease in the stated time. For comparison of the results of treatment

- the daily decrease of the ulceration area in mm² (or the percentage of the initial area),
- the duration of ulcers until the healing process is complete,
- the percentage of the tissue healed in the time function

are needed as parameters. We estimated the effectiveness of venous leg ulceration treatment taking into consideration two parameters, that is

- speed of healing the ulceration in cm² per day as well as
- decrease of the ulceration area.

The speed of decreasing of ulcers in group I varied from 0.029 to 0.171 cm²/d whereas in group II it equalled 0.200 to 0.343 cm²/d. The comparison of the results from both groups showed that vs of patients from group II was much higher than that vs of patients from group I. Our results are similar to those presented by Martin (15), who observed the speed of ulcer decrease at around 0.24 cm²/d; whereas Margalis et al. (14) stated that the average weekly speed at which the ulceration area was decreasing varied from 0.065 to 0.181 cm², which corresponds 0.093 to 0.259 cm²/d.

It is impossible to compare how fast the healing process occurs taken into consideration the ulcer area decrease in mm² per day if the values are not compatible. Analysing the parabolic run of the ulcer area decrease, it seems that if the ulceration is large the reduction in size is bigger than in the case of small ulcers. This regularity was confirmed in our research. In 1971 Stember (21), who compared ulcers bigger than 2.8 cm², had a similar problem in interpreting the speed of ulcer healing.

The duration of the healing process can also be interpreted as a positive or negative effect of treatment. Big ulcers need more time to heal than small ones. That is why comparing ulcers of different sizes give different results. The ulcerations of the patients in our research were more or less of the same in size (group I: 15.8 cm², group II: 16.2 cm²). The ulcers of the patients who received treatment by the sulodexide healed 49 days earlier than wounds of the patients in group II.

<p>| Tab. 4 Number of patients exhibiting successful ulcer healing according to the duration of treatment |
|--------------------------------------------------|------------------|------------------|------------------|------------------|------------------|------------------|------------------|</p>
<table>
<thead>
<tr>
<th>group</th>
<th>duration of treatment (weeks)</th>
<th>2</th>
<th>4</th>
<th>6</th>
<th>7</th>
<th>10</th>
<th>12</th>
<th>14</th>
<th>17</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td></td>
<td>-</td>
<td>1</td>
<td>2</td>
<td>4</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>II</td>
<td></td>
<td>-</td>
<td>3</td>
<td>5</td>
<td>8</td>
<td>7</td>
<td>-</td>
<td>-</td>
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</tr>
</tbody>
</table>
Conclusion

The use of sulodexide in patients with chronic venous leg ulcers accelerates the healing process.

References


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