Sulodexide improves capillary blood flow and the quality of life in patients with Raynaud syndrome – a pilot study

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SULODEXIDE IMPROVES CAPILLARY BLOOD FLOW AND THE QUALITY OF LIFE IN PATIENTS WITH RAYNAUD SYNDROME – A PILOT STUDY.

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Short title: Sulodexide in Raynaud Syndrome.

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Conflict of interest: none declared
**Introduction**

Raynaud Syndrome (RS) is one of the most common diseases of microcirculation. It is characterized by pathological reactions of blood vessels, involving vasoconstriction in response to selected factors, including cold, stress or vibrations [1]. Calcium antagonists, angiotensin-converting enzyme (ACE) inhibitors and α1-blockers are currently the most commonly used pharmacotherapy of RS [2,3]. The aim of this study was to estimate a potential usefulness of Sulodexide in the treatment of RS, by evaluation of the drug influence on capillary blood flow and the quality of life in patients with RS.

**Patients and methods**

*Patients*

34 patients were recruited (24 females and 10 males, aged 27-55 years). The average duration of RS symptoms prior to the baseline examination was 11±10 years. The inclusion criterion was presence of clinical symptoms of RS in fingers in response to exposure to cold. Exclusion criteria were: age over 70, systemic connective tissue disease, diabetes, a history of hemorrhagic stroke, venous or arterial thrombosis diagnosed within three months before baseline, and treatment with diuretics, hypotensive or psychotropic drugs, α-adrenolytics, calcium channel blockers, β-blockers, steroids, heparin or non-steroidal anti-inflammatory drugs.

*Outline of the study*

Prior to the administration of the drug, a baseline examination of capillary vessels in fingers of both hands was undertaken, and the quality of life (QOL) was assessed with a questionnaire. The dose of 1000 LSU of Sulodexide (Vessel Due F, Alfasigma) was administered daily for 20 consecutive days. Between days 20 and 70 of the study, the daily
dosage was reduced to 500 LSU. At the end of the day 70 the drug was discontinued. The assessment of capillary flow in middle fingers of both hands and the QOL evaluation were completed on days 1, 20, 70, and 100 of the study in all patients.

*Measurements of the capillary blood flow*

Laser Doppler Flow measurements were done using the PeriFlux-6000 device and the Laser-Thermal probe (Perimed, Sweden) fixed to nails of middle fingers of both hands. In all patients capillary blood flow was measured at room temperature (20-25°C) and followed by two consecutive measurements at 10°C and 44°C. A response to cold was assessed at 10°C. Measurements at 44°C were done to exclude other vascular diseases (e.g. microangiopathy).

The preliminary (resting) measurement was performed at ambient temperature (20-25°C). In order to obtain thermal stability, the patient remained in this temperature for 30 minutes prior to the examination. The probe was attached to the middle finger of the hand. When the record was stable, its registration was activated. A 30-second-long perfusion reading was selected from the registered recording just before putting the hand in icy water.

The patient would then put his hand into an ice-water container (10°C, measurement standardized with an external thermometer) for 2 minutes. A 1-minute fragment was selected from the received recording just before removing the hand from the vessel. The patient subsequently took his hand out of the ice-water container, and the probe was activated at 44°C. Results were given in perfusion units (PU*sec), as percentages (%), and as the area under the curve (AUC). Perfusion changes in capillaries, on days 20, 70 and 100 were presented as % change in relation to baseline flow values registered on day 1 of the study (before the drug administration).

*The QOL assessment*
The number of episodes of RS during the entire study (100 days) was assessed. The QOL was assessed subjectively during each episode of RS. The Visual Analogue Scale (VAS) 0-10 [0-lowest possible, 10-highest possible] was used to evaluate the QOL as well as the pain intensity [0-no pain, 10-strongest possible pain].

Statistical analysis

The Shapiro-Wilk test were used to verify normal distribution. Results obtained in individual measurements (on days 1, 20, 70, and 100) were compared using the Friedman’s test, the Dunn-Bonferroni’s post-hoc test and the Page’s trend test. The analysis of QOL and pain intensity during RS episodes were completed with the Student t-test. The level of significance was set at p < 0.05. Statistical analyses were performed using the PQStatv.1.6.6.246.Software.

Bioethics Committee

The study was approved by the Bioethics Committee of the Centre of Postgraduate Medical Education with the Resolution of March 25, 2009.

Results

Statistically significant (p<0.01) improved blood flow values were found in subsequent measurements at 10°C. Perfusion in capillary vessels after administration of Sulodexide was improved by 193% in the right hand and by 174% in the left one. Statistically significant differences (p<0.05) were also found in the AUC analysis, with an increasing trend observed in subsequent measurements.

The improvement of capillary blood flow in both hands was observed at room temperature (right – by 121%, left – by 145%) and at +44°C (right – by 106%, left – by 102%). However, differences between subsequent measurements taken at room temperature in both hands and at
44°C in the left hand were not statistically significant. Only differences between consecutive measurements taken in right hands at 44°C were statistically significant ($p<0.05$). We hypothesize that dominating character of the right hand (higher strength and better training) could be the reason. [Table I]

A significant QOL improvement (93.5%, $p<0.05$) was observed after 20 days of Sulodexide therapy. Despite the decrease of the drug dose on the day 20 of treatment and its discontinuation at the end of the day 70, the improved QOL (32.3%) was observed on the day 100, compared to baseline values.

Frequency of RS episodes per week decreased from 2.03 (0.16) before the first Sulodexide dose to 1.47 (0.27) at the end of the study.

The lowest number of pain episodes per week 0.61 (0.59) was observed after 20 days of Sulodexide administration.

The VAS revealed a significant reduction in pain intensivity after 20 days of Sulodexide administration, with a sustained pain reduction at the end of the study (compared to the baseline). [Table S1]

**Discussion**

Sulodexide is a mixture of glycosaminoglycans (GAGs): heparan sulfate (approx. 80% vol) and dermatan sulfate (approx. 20% vol). GAGs are components of arterial wall (basal membrane) and extracellular matrix. They influence function and activity of heparin-binding proteins. Many factors influence GAGs distribution on the surface of endothelial cells. Shear stress generating blood flow has been shown to increase the production of GAGs on the endothelial surface [4]. A reduced thickness of glycocalyx on the endothelial surface leads to its impaired reaction to shear stress, that may induce a pathological response, including reduced nitric oxide production [5]. Moreover, permeability of the endothelium, and consequently of the microvascular wall, may be increased, resulting in abnormal exchange of
fluids and molecules between the endovascular and extravascular space [6]. For this reason various actions are taken, including modification of oxidative stress, the use of substances inhibiting the inflammatory reaction, and actions aimed at the maintenance of a physiological level of plasma albumin, to stabilize the glycocalyx on the surface of endothelial cells and prevent endothelial cell dysfunction [7]. Results of this study indicate that Sulodexide improves capillary blood flow in fingers. A statistically significant increase in blood perfusion in capillary vessels (193% in the right hand and 174% in the left hand (p<0.01) was observed. Moreover, a significant improvement in the patients’ QOL, as well as reduction of frequency of pain episodes and decrease of pain intensity during the episodes were recorded. To our knowledge, this is the first study assessing the effect of Sulodexide on capillary flow in patients with RS. Therefore, the results of the study can only be compared with therapeutic effects of other medications.

Assessments of efficacy of various drugs in the treatment of RS were based on the subjective scale of QOL as evaluated using the VAS, and on the incidence of recurrent RS episodes. The meta-analysis of efficacy of calcium channel blockers in the treatment of primary Raynaud’s phenomenon (Cochrane Review 2016) was based on 7 randomized controlled clinical trials involving 296 patients treated with nifedipine or nicardipine. No evidence was found that these drugs reduced frequency of RS symptoms (only nifedipine was found effective in a single analysis) [8]. Another meta-analysis showed a statistically significant decrease of SM episodes frequency after treatment with nifedipine.

Type-5 phosphodiesterase (PDE5) inhibitors are another group of drugs potentially useful in RS treatment. They support cyclic guanosine monophosphate (a compound that induces vasodilatation). The 2014 meta-analysis of 6 randomized control studies, including 244 patients with secondary RS treated with PDE5 inhibitors, demonstrated a statistically significant reduction in the severity and duration of RS episodes [9].
No data on the cumulative benefits of calcium channel blockers combined with PDE5 inhibitor therapy in RS treatment are available.

None of the above mentioned studies showed a decreased incidence of RS episodes as soon as after 20 days of a drug administration. Our study of Sulodexide demonstrated that efficacy.

**Conclusions**

Preliminary results of our study indicate that the treatment of RS with Sulodexide results in long-term improvement of capillary flow and reduces frequency of RS relapses. Moreover, a significant improvement of QOL was observed during the Sulodexide therapy, including a decrease in recurrence of RS episodes as well as reduced pain sensitivity.

**Contribution statement:** GM, JOT, PG contributed to the design of the research. PG and JOT performed main statistical analyses. PG, AE, JOT, MJ wrote the paper. GM, MJ, AE, JOT, WZ and PG provided a critical review of the manuscript. All authors contributed to this work and approved the manuscript for submission.
References


<table>
<thead>
<tr>
<th>Temp. 10°C</th>
<th>Right hand</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Day of treatment</td>
<td>1 day</td>
<td>20 days</td>
</tr>
<tr>
<td><strong>Perfusion units [PU * sec]</strong></td>
<td>6 (0–31)</td>
<td>14 (3-43)</td>
</tr>
<tr>
<td><strong>AUC</strong></td>
<td>428 (0-1900)</td>
<td>856 (171-2534)</td>
</tr>
<tr>
<td><strong>Increase of perfusion in capillary vessels [%]</strong></td>
<td>100</td>
<td>156</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Temp. 10°C</th>
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<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Day of treatment</td>
<td>1 day</td>
<td>20 days</td>
</tr>
<tr>
<td><strong>Perfusion units [PU * sec]</strong></td>
<td>7 (0-52)</td>
<td>8 (2-35)</td>
</tr>
<tr>
<td><strong>AUC</strong></td>
<td>423 (0-2960)</td>
<td>478 (66-1914)</td>
</tr>
<tr>
<td><strong>Increase of perfusion in capillary vessels [%]</strong></td>
<td>100</td>
<td>111</td>
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<table>
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<tr>
<th>Temp. 44°C</th>
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<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Day of treatment</td>
<td>1 day</td>
<td>20 days</td>
</tr>
<tr>
<td><strong>Perfusion units [PU * sec]</strong></td>
<td>60 (12-144)</td>
<td>67 (24-163)</td>
</tr>
<tr>
<td><strong>AUC</strong></td>
<td>7426 (1389-16065)</td>
<td>8065 (2910-19160)</td>
</tr>
<tr>
<td><strong>Increase of perfusion in capillary vessels [%]</strong></td>
<td>100</td>
<td>127</td>
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<table>
<thead>
<tr>
<th>Temp. 44°C</th>
<th>Left hand</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Day of treatment</td>
<td>1 day</td>
<td>20 days</td>
</tr>
</tbody>
</table>
Values were expressed as median and range.*

Table I

Evaluation of perfusion in capillary vessels at 10°C and 44°C during treatment with Sulodexide.

<table>
<thead>
<tr>
<th>Perfusion units [PU * sec] *</th>
<th>48 (10-163)</th>
<th>50 (16-138)</th>
<th>50 (20-107)</th>
<th>54 (25-110)</th>
<th>P = 0.95</th>
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<tbody>
<tr>
<td>AUC *</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>5829 (1389-16065)</td>
<td>5955 (1927-16499)</td>
<td>5937 (2471-12764)</td>
<td>6464 (2782-13104)</td>
<td>P = 0.79</td>
<td></td>
</tr>
<tr>
<td>Increase of perfusion in capillary vessels [%]</td>
<td>100</td>
<td>105</td>
<td>103</td>
<td>102</td>
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