

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

Grzegorz Madycki¹, Jolanta Obidzińska-Trościanko¹,
Michał Juszyński¹, Wojciech Zgliczyński², Piotr Glinicki²

¹ Department of Vascular Surgery and Angiology, Centre of Postgraduate Medical Education, Warsaw, Poland

² Department of Endocrinology, Centre of Postgraduate Medical Education, Warsaw, Poland

Introduction Raynaud syndrome (RS) is one of the most common diseases of microcirculation. It is characterized by blood vessel abnormalities, involving vasoconstriction in response to selected factors, such as cold, stress, or vibrations.¹ Calcium antagonists, angiotensin-converting enzyme inhibitors, and α_1 -blockers are currently the most common medications in the pharmacotherapy of RS.^{2,3} The aim of this study was to assess the usefulness of sulodexide in the treatment of RS by evaluating the effect of the drug on capillary blood flow and the quality of life in patients with this syndrome.

Patients and methods **Patients** The study included 34 patients (24 women and 10 men; age, 27–55 years). The mean (SD) duration of RS symptoms prior to the baseline examination was 11 (10) years. The inclusion criterion was the presence of clinical symptoms of RS in the fingers following exposure to cold. The exclusion criteria were age over 70 years, systemic connective tissue disease, diabetes, a history of hemorrhagic stroke, venous or arterial thrombosis diagnosed within 3 months before enrollment, and treatment with diuretics, antihypertensive or psychotropic drugs, α_1 -blockers, calcium channel blockers, β -blockers, steroids, heparin, or nonsteroidal anti-inflammatory drugs.

Outline of the study Prior to drug administration, the capillary vessels in the fingers of both hands were examined and the quality of life (QoL) was assessed using a questionnaire. The dose of 1000 lipasemic units (LSU) of sulodexide (Vessel Due F, Alfasigma SpA, Milano, Italy) was administered daily for 20 consecutive days. Between days 20 and 70, the daily dose was reduced to 500 LSU.

At the end of day 70, the drug was discontinued. The capillary flow in the middle fingers of both hands and the QoL were evaluated on days 1, 20, 70, and 100 in all patients.

Measurement of the capillary blood flow Laser Doppler flow measurements were done using the PeriFlux 6000 device and laser thermal probe (Perimed, Järfälla, Sweden) fixed to the nails of the middle fingers of both hands. In all patients, the capillary blood flow was measured at room temperature (20°C–25°C) and followed by 2 consecutive measurements at a temperature of 10°C and 44°C. Response to cold was assessed at 10°C. The measurements at 44°C were performed to exclude other vascular diseases (eg, microangiopathy).

The preliminary (resting) measurement was performed at ambient temperature (20°C–25°C). To obtain thermal stability, the patient remained in this temperature for 30 minutes prior to examination. The probe was attached to the middle finger of the hand. When the recording was stable, its registration was activated. A 30-second perfusion reading was selected from the registered recording just before the hand was placed in icy water. The patient would then put his or her hand in an ice-water container (10°C, measurement standardized with an external thermometer) for 2 minutes. A 1-minute fragment was selected from the obtained recording just before removing the hand from the container. The patient would then take his or her hand out of the container, and the probe was activated at 44°C. The results were presented as perfusion units (PU*s), percentages (%), and the area under the curve (AUC). Perfusion changes in capillaries on days 20, 70, and 100 were presented as

Correspondence to:
Piotr Glinicki, BSc, MSc, PhD,
Department of Endocrinology,
Centre of Postgraduate Medical
Education, Bielanski Hospital,
ul. Ceglowska 80, 01-809 Warszawa,
Poland, phone: +48 22 56 90 293,
email: piotr.glinicki@bielanski.med.pl
Received: September 12, 2019.
Revision accepted: October 31, 2019.
Published online: November 5, 2019.
Pol Arch Intern Med. 2020;
130 (1): 79–81
doi:10.20452/pamw.15053
Copyright by Medycyna Praktyczna,
Kraków 2020

TABLE 1 Perfusion in capillary vessels at a temperature of 10°C and 44°C during treatment with sulodexide

Parameter		Day of treatment				P value
		1	20	70	100	
10°C						
Right hand	Perfusion units, PU*s	6 (0–31)	14 (3–43)	15 (3–53)	15 (3–106)	<0.001
	AUC	428 (0–1900)	856 (171–2534)	918 (138–3067)	885 (92–6561)	<0.001
	Increase of perfusion in capillary vessels, %	100	156	163	193	–
Left hand	Perfusion units, PU*s	7 (0–52)	8 (2–35)	13 (3–48)	17 (2–51)	0.03
	AUC	423 (0–2960)	478 (66–1914)	878 (155–2798)	1052 (194–3017)	0.001
	Increase of perfusion in capillary vessels, %	100	111	143	174	–
44°C						
Right hand	Perfusion units, PU*s	60 (12–144)	67 (24–163)	58 (24–120)	57 (22–155)	0.04
	AUC	7426 (1389–16 065)	8065 (2910–19 160)	6836 (2840–14 504)	6877 (2636–18 788)	0.03
	Increase of perfusion in capillary vessels, %	100	127	105	106	
Left hand	Perfusion units, PU*s	48 (10–163)	50 (16–138)	50 (20–107)	54 (25–110)	0.95
	AUC	5829 (1389–16 065)	5955 (1927–16 499)	5937 (2471–12 764)	6464 (2782–13 104)	0.79
	Increase of perfusion in capillary vessels, %	100	105	103	102	–

Data are presented as median (range) unless otherwise indicated.

Abbreviations: AUC, area under the curve

% change in relation to baseline flow values registered on day 1 (before drug administration).

Quality-of-life 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, with 0 indicating the lowest possible and 10 the highest possible QoL) was used to evaluate the QoL and pain intensity (0, no pain; 10, strongest possible pain).

Statistical analysis The Shapiro–Wilk test was used to verify normal distribution of variables. Results obtained in individual measurements (on days 1, 20, 70, and 100) were compared using the Friedman test, Dunn–Bonferroni post hoc test, and Page trend test. The QoL and pain intensity during RS episodes were analyzed with the *t* test. The level of significance was set at a *P* value of less than 0.05. Statistical analyses were performed using the PQStat v.1.6.6.246 software (PQStat Software, Poznań, Poland).

Ethics approval The study was approved by the Bioethics Committee of the Centre of Postgraduate Medical Education in Warsaw.

Results An increase in blood flow values was observed on subsequent measurements at 10°C (*P* < 0.01). Perfusion in capillary vessels after administration of sulodexide increased by 193% in the right hand and by 174% in the left hand. Significant differences were also noted in the AUC analysis, with an increasing trend observed on subsequent measurements.

The improvement of capillary blood flow in both hands was observed at room temperature (right hand, by 121%; left hand, by 145%) and at 44°C (right hand, by 106%; left hand, by 102%). However, only differences between consecutive measurements taken in the right hand at 44°C were significant. A possible reason for this might be that the right hand is generally stronger and better trained (TABLE 1).

An improvement in the QoL (93.5%, *P* < 0.05) was observed after 20 days of sulodexide treatment. Despite a reduction in the drug dose on day 20 and drug discontinuation on day 70, an improved QoL (32.3%) was observed on day 100, as compared with baseline.

The mean (SD) frequency of RS episodes per week decreased from 2.03 (0.16) at baseline to 1.47 (0.27) at the end of the study.

The lowest number of pain episodes per week (mean (SD), 0.61 [0.59]) was observed after 20 days of sulodexide treatment.

The VAS revealed a significant reduction in pain intensity after 20 days of treatment, with a sustained pain reduction at the end of the study, as compared with baseline (Supplementary material, Table S1).

Discussion Sulodexide is a mixture of glycosaminoglycans: heparan sulfate (approx. 80% vol) and dermatan sulfate (approx. 20% vol). Glycosaminoglycans are components of the arterial wall (basal membrane) and extracellular matrix. They influence the function and activity of heparin-binding proteins. Numerous factors affect the distribution of glycosaminoglycans on the surface of endothelial cells. Shear stress-generating blood flow has

been shown to increase the production of glycosaminoglycans on the endothelial surface.⁴ A reduced thickness of the glycocalyx on the endothelial surface leads to its impaired reaction to shear stress, which may induce a pathologic response, including reduced nitric oxide production.⁵ Moreover, the permeability of the endothelium and, consequently, of the microvascular wall, may be increased, resulting in an abnormal exchange of fluids and molecules between the endovascular and extravascular space.⁶ For this reason, various actions are undertaken, including the modification of oxidative stress, use of anti-inflammatory agents, and attempts at maintaining the physiological plasma albumin levels, in order to stabilize the glycocalyx on the surface of endothelial cells and prevent endothelial cell dysfunction.⁷ Our results indicate that sulodexide improves the capillary blood flow in the fingers. A significant increase in blood perfusion in the capillary vessels was observed. Moreover, a significant improvement in the patients' QoL was noted, together with a reduction in the frequency of pain episodes and a decrease of pain intensity during the episodes. To our knowledge, this is the first study assessing the effect of sulodexide on the capillary flow in patients with RS. Therefore, our results may only be compared with the therapeutic effects of other medications.

The efficacy of various drugs in the treatment of RS has been assessed on the basis of the subjective QoL measures (VAS) as well as on the incidence of recurrent RS episodes. A meta-analysis investigating the efficacy of calcium channel blockers in the treatment of primary Raynaud phenomenon (Cochrane Review 2016¹) included 7 randomized controlled trials involving 296 patients treated with nifedipine or nicardipine. No evidence was found that these drugs reduced the frequency of RS symptoms (only nifedipine was shown to be effective in a single report).⁸ Another meta-analysis revealed a significant decrease in the frequency of Reynaud secondary symptom episodes after treatment with nifedipine.

Phosphodiesterase type 5 (PDE5) inhibitors are another class of drugs potentially useful in RS treatment. These drugs prevent the breakdown of cyclic guanosine monophosphate (a compound that induces vasodilation). A meta-analysis of 6 randomized controlled trials, including 244 patients with secondary RS treated with PDE5 inhibitors, demonstrated a significant reduction in the severity and duration of RS episodes.⁹ No data on the cumulative benefit of calcium channel blockers combined with PDE5 inhibitors in RS treatment are currently available.

None of the studies cited above showed a lower incidence of RS episodes already after 20 days of drug administration. On the other hand, our study of sulodexide demonstrated such an effect.

Conclusions Preliminary results of our study indicate that sulodexide treatment of RS results in

a long-term improvement of capillary flow and reduces the frequency of RS relapse. Moreover, a significant improvement of the QoL was observed with sulodexide, including a decrease in the recurrence of RS episodes as well as reduced pain intensity.

SUPPLEMENTARY MATERIAL

Supplementary material is available with the article at www.mp.pl/paim.

ARTICLE INFORMATION

CONTRIBUTION STATEMENT GM, JO-T, and PG contributed to study design. PG and JO-T performed the main statistical analyses. PG, AE, JO-T, and MJ wrote the manuscript. GM, MJ, AE, JO-T, WZ, and PG contributed to a critical review of the manuscript. All authors contributed to this work and approved the final manuscript for submission.

CONFLICT OF INTEREST None declared.

OPEN ACCESS This is an Open Access article distributed under the terms of the Creative Commons Attribution NonCommercial ShareAlike 4.0 International License (CC BY-NC-SA 4.0), allowing third parties to copy and redistribute the material in any medium or format and to remix, transform, and build upon the material, provided the original work is properly cited, distributed under the same license, and used for noncommercial purposes only. For commercial use, please contact the journal office at pamw@mp.pl.

HOW TO CITE Madyski G, Obidzińska-Trościanko J, Juszyński M, et al. Sulodexide improves capillary blood flow and the quality of life in patients with Raynaud syndrome: a pilot study. *Pol Arch Intern Med.* 2020; 130: 79-81. doi:10.20452/pamw.15053

REFERENCES

- Gregorczyk-Maga I, Frolow M, Kaczmarczyk P, Maga P. Microcirculation disorders of the oral cavity in patients with primary Raynaud phenomenon. *Pol Arch Intern Med.* 2019; 129: 36-42. [↗](#)
- Prete M, Fatone MC, Favoino E, Perosa F. Raynaud's phenomenon: from molecular pathogenesis to therapy. *Autoimmun Rev.* 2014; 13: 655-667. [↗](#)
- Flavahan NA. A vascular mechanistic approach to understanding Raynaud phenomenon. *Nat Rev Rheumatol.* 2015; 11: 146-158. [↗](#)
- Arisaka T, Mitsumata M, Kawasumi M, et al. Effects of shear stress on glycosaminoglycan synthesis in vascular endothelial cells. *Ann N Y Acad Sci.* 199; 748: 543-554. [↗](#)
- Brower JB, Targovnik JH, Caplan MR, Massia SP. High glucose-mediated loss of cell surface heparan sulfate proteoglycan impairs the endothelial shear stress response. *Cytoskeleton.* 2010; 67: 135-141. [↗](#)
- Becker BF, Chappell D, Jacob M. Endothelial glycocalyx and coronary vascular permeability: the fringe benefit. *Basic Res Cardiol.* 2010; 105: 687-701. [↗](#)
- Becker BF, Chappell D, Bruegger D, et al. Therapeutic strategies targeting the endothelial glycocalyx: acute deficits, but great potential. *Cardiovasc Res.* 2010; 87: 300-310. [↗](#)
- Shapiro SC, Wigley FM. Treating Raynaud phenomenon: beyond staying warm. *Cleve Clin J Med.* 2017; 84: 797-804. [↗](#)
- Roustit M, Blaise S, Allanoire Y, et al. Phosphodiesterase-5 inhibitors for the treatment of secondary Raynaud's phenomenon: systematic review and meta-analysis of randomized trials. *Ann Rheum Dis.* 2013; 72: 1696-1699. [↗](#)