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LETTER TO THE EDITOR

Comparison of the efficacy and safety of oligomeric proanthocyanidins and nifedipine in patients with primary Raynaud's phenomenon: An open-label, randomized, prospective pilot study

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Raynaud's phenomenon (RP) is reversible vasospasm of peripheral arteries caused by cold temperatures or emotional stress.[1] Oligomeric proanthocyanidins, a major component of Entelon®, a potent antioxidant and anti-inflammatory agent, reduce vascular permeability and improve capillary strength, vascular function, and peripheral circulation in the treatment of

Table 1. Demographic and baseline characteristics of the study population

	Entelon® (n=9)				Nifedipine (n=9)				
	n	%	Median	IQR	n	%	Median	IQR	*p*
Age (year)			51.00	17			52.00	22	0.931
Sex									
Female	7	77.8			5	55.56			0.620
Body mass index (kg/m^2)			22.00	5.8			22.90	2.75	0.796
Smoking	0	0			1	11.1			1.000
Raynaud phenomenon									
Disease duration (months)			48.0	144			60.0	96	0.931
Attack frequency (times/day)			5.0	6			4.0	4	0.535
Attack duration (min)			15.0	55.2			10.0	12.0	0.297
Raynaud condition score			5.5	2.5			6.0)	2.3	0.796
Medication use (n, %)									
Steroid	0	0			0	0			
Calcium channel blockers	0	0			0	0			
ACEi/ARB	0	0			0	0			
Aspirin	0	0			0	0			
Oral contraceptive	1	11.1			0	0			
Statin	1	11.1			0	0			

IQR: Interquartile range; ACEi: Angiotensin converting enzyme inhibitors; ARB: Angiotensin II receptor blocker.

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Table 2. Changes in clinical outcomes of RP before and after treatment with Entelon® and nifedipine

	Entelon® (n=9)					Nifedipine (n=9)					Change score				
	Baseline		2 weeks			Baseline		2 weeks			Entelon®		Nifedipine		
	Median	IQR	Median	IQR	*p*	Median	IQR	Median	IQR	*p*	Median	IQR	Median	IQR	*p*
Attack frequency (times/day)	5.0	6.0	1.0	5.25	0.008	4.0	3.5	3.5	4.75	0.007	-2.5	4.0	-0.5	2.25	0.063
Attack duration (min)	15.0	55.2	11.07	29.04	0.008	10.0	12.0	5.3	12.68	0.011	-3.93	30.81	-3.25	6.48	0.402
Raynaud condition score	5.5	2.5	4.0	2.0	0.007	6.0	2.3	4.0	4.25	0.007	-1.5	2.25	-2.0	4.0	0.893
	Entelon® (n=6)					Nifedipine (n=8)					Change score				
	Baseline		6 weeks			Baseline		6 weeks			Entelon®		Nifedipine		
	Median	IQR	Median	IQR	*p*	Median	IQR	Median	IQR	*p*	Median	IQR	Median	IQR	*p*
Attack frequency (times/day)	5.5	6.7	1.5	4.81	0.027	4.5	3.75	2.5	4.69	0.012	-3.0	4.19	-1.37	1.88	0.081
Attack duration (min)	17.5	82.05	12	51.53	0.249	8.0	13.4	4.6	7.98	0.017	-2.85	79.9	-2.7		1.000
Raynaud condition score	5.5	3.25	4	5.13	0.074	6.0	2.4	2.3	4.9	0.012	-2.5	4.9	-2.5	3.4	0.897

RP: Raynaud's phenomenon; IQR: Interquartile range.

venous insufficiency and non-proliferative diabetic retinopathy.[2-4] Previous studies have suggested that the levels of reactive oxygen species increase, and those of antioxidant ascorbic acid decrease, in patients with primary RP.[5] These findings support the notion that oxidative stress has a role in primary RP. This open-label, randomized, prospective pilot study assessed the safety and efficacy of Entelon® compared to nifedipine in patients with primary RP.

Between January and June 2018, we recruited adult patients with primary RP according to the international consensus criteria for the diagnosis of RP who had at least three attacks of RP a week, described as color change and paresthesias.[6] We excluded patients with secondary RP, severe cardiopulmonary and renal disorder, epilepsy, edema from causes such as diabetes, chronic inflammatory disease, hypothyroidism, liver diseases, anemia and malnutrition.

The patients were randomized into experimental (Entelon® 150 mg twice a day) and control (nifedipine 30 mg once daily) groups in an open-label trial. The patients recorded a daily RP attack diary regarding the number of RP attacks and the duration of each RP attack. They also completed the Raynaud's Condition Score (RCS) which is a daily self-assessment of RP activity (0-10 scale).[7] As primary endpoints, RCS, frequency and duration of RP attack were evaluated after six weeks of treatment. Adverse events (AEs) within the study period of six weeks, changes in patterns of nailfold capillaroscopy (NFC) baseline and six weeks of treatment were also assessed. Changes from baseline after two and six weeks were compared using the Wilcoxon signed-rank test. A p value of <0.05 was considered statistically significant.

In total, 18 patients were enrolled with nine in each group. Table 1 shows the demographic characteristics of the study population. After two-week treatment, both nifedipine and Entelon® groups showed a significant improvement of RP clinical outcomes. After six-week treatment of nifedipine, the duration and frequency of RP attack significantly decreased (p=0.012, and p=0.017, respectively) and RCS improved (p=0.012). In the Entelon® group, the RP frequency significantly decreased (p=0.027) after six weeks of treatment (Table 2). No significant

differences in the absolute changes of duration and frequency of RP, and RCS per time point between two groups was observed. No unexpected AEs were noted, and one patient in the Entelon® group experienced diarrhea. Abnormal NFC pattern was not observed at baseline and six weeks in both groups.

In conclusion, this pilot study showed that Entelon® reduced the RP attack frequency compared to nifedipine in patients with primary RP. In patients with intolerability of nifedipine, Entelon® may be an alternative therapeutic option. Further large-scale, long-term studies are needed to investigate the efficacy and safety of Entelon®.

Ethics Committee Approval: The trial was approved by the Institutional Review Board for Human Research (SCH 2016-08-023). The study was conducted in accordance with the principles of the Declaration of Helsinki.

Patient Consent for Publication: A written informed consent was obtained from each patient.

Data Sharing Statement: The data that support the findings of this study are available from the corresponding author upon reasonable request.

Author Contributions: Analysis and/or interpretation, literature review, writing the article: K.A.L.; Data collection and/or processing: S.H.J.; Data collection and/or processing: J.S.K.; Idea/concept, design, control/supervision, references and funding: H.S.K.

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