ejpmr, 2020,7(7), 748-751

SJIF Impact Factor 6.222

EUROPEAN JOURNAL OF PHARMACEUTICAL AND MEDICAL RESEARCH

www.ejpmr.com

Research Article

ISSN 2394-3211

EJPMR

THE EFFECT OF 1000MG DAILY DAFLON TREATMENT ON SAPHENOFEMORAL JUNCTIONAL VALVE COMPETENCE AND REFLUX

Metin Onur Beyaz*[1] and Emin Can Ata[2]

Istanbul Medipol University Faculty of Medicine, Department of Cardiovascular Surgery.

***Corresponding Author: Dr. Metin Onur Beyaz**
Istanbul Medipol University Faculty of Medicine, Department of Cardiovascular Surgery.
DOI: 10.20959/ejpmr20207-8733

Article Received on 13/05/2020 **Article Revised on 03/06/2020** **Article Accepted on 24/06/2020**

ABSTRACT

Background: It has been shown in studies that there are symptomatic improvements in patients treated with Daflon 500, but studies on its effect on the venous valve are limited to experimental animal studies. In this study, the effect of Daflon 1000mg/day on saphenofemoral junctional (SFJ) valve competence and reflux was investigated. **Methods:** In this prospective study, 76 patients with insufficiency in the SFJ were treated with 1000mg Daflon daily. SFJ diameter and reflux degree of patients were evaluated and compared with venous Doppler ultrasound before and after 6 months of treatment. **Results:** The mean age was 46.2±8.6; the female was 48 (63.2%); the mean follow-up was 6.4±2.7 months. Pre- and post-treatment diameters of SFJ were 6.32±1.76 (3.8-10.5) and 5.78±1.61 (3.5-10) mm, respectively. This was not statistically significant (P=0.096). After the treatment, patients with SFJ reflux decreased from 100% to 82.9%, and 17.1% patients recovered from SFJ reflux. This was statistically significant (P=0.016, OR:0.031, 95% CI: 0.002-0.527). Similarly, the number of patients with severe GSV reflux decreased from 40.8% to 21%, this was also statistically significant (P=0.049 and P=0.009). Patients with leg pain decreased from 51.3% to 14.5%, this was statistically severely significant (P<0.001, OR:0.20, 95% CI:0.09-0.44). Patients suffering from ankle swelling and itching were also recovered in a significant number (P=0.0031 and P=0.0029). **Conclusion:** Six months' use of Daflon 1000mg/day reduces the reflux of SFJ and GSV, and provides symptomatic relief. In this study model, there is no significant improvement in the SFJ valve diameter.

KEYWORDS: Daflon; reflux; saphenofemoral junction; venous insufficiency.

INTRODUCTİON

Dysfunction or incompetence of the valves in the superficial venous system allows retrograde flow of blood, which is called "reflux" and serves to increase hydrostatic pressures. The earliest complaints or symptoms, as well as vessel wall deterioration, valve restructuring, and, eventually, varicose veins, result not only from elevation of pressure, but also from a cascade of biochemical events related to both the macro- and the microcirculation.[1,2] Leg heaviness, discomfort, itching, cramps, pain, paresthesia, and edema are the most frequent manifestations of CVD and a major reason for medical treatment.[3]

Daflon 500 (micronized purified flavonoid fraction [MPFF]) is an effective treatment for symptoms and edema in CVD as demonstrated in several randomized controlled studies.[3,4] The superiority of Daflon 500 mg over placebo about symptoms and objective signs was confirmed in the Reflux assEssment and quaLity of lIfe improvEment with micronized Flavonoids study (RELIEF).[5] This study included 5,052 patients in 23 countries, using a visual analog scale for evaluating pain, leg heaviness, cramps, and a sensation of swelling. All symptoms showed significant and progressive improvement. Based on high-quality evidence, MPFF is highly effective in improving leg symptoms, edema, and quality of life in patients with CVD.[3] These clinical findings support the strong recommendation for MPFF treatment found in the 2018 international guidelines for the management of CVD.[4,6,7]

In literature, there is still a lack of evidence of the direct effect of Daflon on the saphenofemoral valve competence and reflux. In this prospective study, we investigated Daflon 1000mg/daily treatment effect on saphenofemoral valve competency by measuring saphenofemoral junctional (SFJ) valve diameter and reflux using doppler US.

MATERIAL AND METHODS

Ethical consideration

This study was carried out after approval of the Istanbul Medipol University Ethics Committee (number: 10840098-604.01.01-E.2696). Informed consent forms were signed by each participant. Hospital authority and all the authors accepted the study results and publication of the study.

Study design

This prospective investigation was completed during February and December 2018 at Medipol Mega University Hospital. All the patients were evaluated for lower extremity venous insufficiency by two independent radiologists at the first admission. The primary endpoint of the study was SFJ evaluation by Doppler US after at least six months of Daflon 1000mg/day treatment, the secondary endpoint was saphenous vein ablation or stripping surgery due to advanced reflux and leg pain during the study period.

Inclusion and exclusion

Patients newly diagnosed with upper the knee great saphenous vein (GSV) insufficiency and reflux in SFJ were included in the study. All the diagnoses were confirmed by the independent radiologist after evaluating the superficial, perforating, and deep venous systems.

Patients over the ages of 65 years; who had arterial pathology (ABI<0.80), a history of deep vein thrombosis, and active chronic venous ulcers were excluded. Patients who have deep venous insufficiency without junctional and superficial venous insufficiency were also excluded. Table 1. Patients characteristics

Table 1: Patients characteristics.

	N=76	%
Age (year)	46.2±8.6	
Female	48	63.2
Male	28	36.8
Family history	21	27.6
Multiple child birth	13	17.1
Sedentary life	19	25.0
Obesity	14	18.4
SFJ reflux	76	100
GSV reflux (above the knee)	53	69.7
Deep venous insufficiency	16	21.0
Mean follow-up (month)	6.4±2.7	

GSV: great saphenous vein, SFJ: safeno-femoral junction

Statistical analysis

Statistical analysis was performed with the SPSS version 24.0 program (SPSS Inc. Chicago IL, USA). The normal distribution of the variables was examined by histogram graphs and the Kolmogorov-Smirnov test. Mean ± standard deviation values were used to present descriptive analyzes. Pearson Chi-Square and Fishers Exact Tests were compared with 2x2 tables. While normally distributed (parametric) variables were evaluated among the groups, Student T-test was used. Mann Whitney U test was used to evaluate nonparametric variables. Logistic regression tests were performed to find the odds ratio. P-values below 0.05 were evaluated as statistically significant results.

RESULTS

A total of 76 eligible patients were included, the mean age was 46.2±8.6, the female was 48 (63.2%). The demographic characteristics of the participants were given in Table 1. The mean follow-up was 6.4±2.7 months. Pre- and post-treatment diameters of SFJ were 6.32±1.76 (3.8-10.5) and 5.78±1.61 (3.5-10) mm, respectively. This difference was not statistically significant (P=0.096). All of the patients had SFJ reflux initially, after the treatment, patients with SFJ reflux were decreased to 63 (82.9%), and 13 (17.1%) patients recovered from SFJ reflux. This was statistically significant (P=0.016, OR:0.031, 95% CI: 0.002-0.527) (Table 2).

When analyzing the reflux grade of GSV, patients with no reflux increased from 23 to 39, and the number of patients with severe GSV reflux was decreased from 31 (40.8%)to 16 (21%), these changes were statistically significant (P=0.049 and P=0.009). The number of patients with moderate reflux were not changed significantly (Table 2).

In this study, we also investigated the effect of Daflon on the patients' symptoms. Leg pain during the night was the most common symptom of our series. Almost half of the patients (51.3%) were suffering leg pain at night before the treatment. After an average of six months of Daflon treatment, this symptom was decreased from 51.3% to 14.5%, this was statistically severely significant (P<0.001, OR:0.20, 95% CI:0.09-0.44). Similarly, patients suffering from ankle swelling and itching were recovered in a significant number after treatment (P=0.0031 and P=0.0029). Daflon 1000mg/day treatment was found to be effective in reducing symptoms caused by venous insufficiency (Table 2).

During the follow-up period, 3 (3.9%) patients had increased symptoms and GSV reflux. But this worsening was not statistically significant (P=0.192). All of these patients were treated by radiofrequency (RF) ablation in success.

Table 2: Pre- and post treatment changes.

	Pre-treatment	Post-treatment	P value
SFJ diameter (mm)	6.32±1.76	5.78±1.61	0.096
Reflux at SFJ	76 (100%)	63 (82.9%)	0.016
Changes in the Grade of GSV reflux			
Normal*	23 (30.3%)	39 (51.3%)	0.049
Moderate**	22 (28.9%)	21 (27.6%)	0.857
Severe***	31 (40.8%)	16 (21%)	0.009
Symptoms			
Leg Pain (night)	39 (51.3%)	11 (14.5%)	<0.001
Swelling (ancle)	31 (40.8%)	14 (18.4%)	0.0031
Itching	17 (22.4%)	3 (3.9%)	0.0027

*reflux duration of < 0.5 second
**reflux duration of 0.5-1 second
***reflux duration of > 1 second

DISCUSSION

The main findings of the study are that Daflon 1000mg/day monotherapy improves the life quality of the patients of venous insufficiency, these findings are consistent with the meta- analysis.[3,4] A different aspect of the study we found is that the junctional valve diameter diminished after Daflon treatment without a significant degree, but the change leads to significant reduction of venous reflux at the SFJ.

There are 4 phases of valve function which include opening, equilibrium, closing, and closed. The critical factors to valve function are axial vortical of blood flow opening the valve and vertical velocity in the valve cusp that increases mural pressure relative to the luminal pressure leading to valve closure.[8] Valve failure of the superficial veins may be primarily because of pre-existing weakness in the vessel wall or valve leaflets or secondary to direct injury, superficial phlebitis, or excessive venous distention resulting from hormonal effects or high pressure.[9] Failure of valves located at the junctions of the deep and superficial systems, at the saphenofemoral and saphenopopliteal junctions, can be a source of reflux leading to CVI. The incompetence of the valves of the superficial veins with reflux has been shown in ≤90% of patients presenting the CVD with reflux in the GSV, accounting for 70% to 80%, and in ≈84% of those presenting with venous ulcers.[10] Dysfunction of the deep vein valves has been shown to increase the rate of progression of venous disease with a higher rate of venous ulceration formation.[11] Takase et al. and Pascarella et al. conducted a study in a rat model using Daflon 500. Their study showed that venous hypertension caused by an arteriovenous fistula resulted in the development of venous reflux and an inflammatory reaction in venous valves culminating in their destruction. MPFF was able to delay the development of reflux and suppress damage to the valve structures in this rat model of venous hypertension.[12] In their rat model, the valve becomes incompetent by a combination of venous dilation and shortening of the valve leaflets due to venous hypertension. The valve leaflets are infiltrated with granulocytes, monocytes, and T-lymphocytes, and the endothelial cells express enhanced levels of P-selectin and ICAM-1. Decreased levels of granulocyte and macrophage infiltration into the valves were observed with the treatment of Daflon 500.[13] Nevertheless, investigation of valve morphology is not possible in the human study because of ethical reasons. An invasive method of intravascular ultrasound (IVS) is also not applicable to evaluate valve function due to the patient's failure to consent. The method described in this study is non-invasive, and it is very simple and detect to evaluate SFJ valve, since more than 90% of patients always have valves in SFJ.[14,15] Our study results indicate that the 1000mg/day Daflon decreases chronic elevation of venous pressure associated with an inflammatory reaction in venous valves, a process that may lead to their dysfunction, reflux, and upstream elevation of venous pressure.

CONCLUSIONS

Six month' use of micronized purified flavonoid fractions containing 90% diosmin and 10% hesperidin may reduce the reflux of SFJ and GSV, and provides symptomatic relief. In this study model, there is no significant improvement in the SFJ valve diameter. A combination with compression stocking may be reasonable to achieve better results.

ACKNOWLEDGMENT

We wish to thank M.D. Musa Ataseven and M.D. Yaşar Okay Sarıtaş for their enormous contribution of performing the radiological evaluation of venous pathology.

Conflict of interest: We declare no conflict of interest in this study.

Funding: We did not receive any funding during the study.

REFERENCES

1. Beebe-Dimmer JL, Pfeifer JR, Engle JS, Schottenfeld D. The epidemiology of chronic venous insufficiency and varicose veins. Ann Epidemiol**,** 2005; 15: 175–184.

2. Ferraz CR, Carvalho TT, Manchope MF, et al. Therapeutic Potential of Flavonoids in Pain and Inflammation: Mechanisms of Action, Pre-Clinical and Clinical Data, and Pharmaceutical Development. Molecules, 2020; 25(3): 762.
3. Kakkos SK, Nicolaides AN. Efficacy of micronized purified flavonoid fraction (Daflon®) on improving individual symptoms, signs and quality of life in patients with chronic venous disease: a systematic review and meta-analysis of randomized double-blind placebo-controlled trials. Int Angiol, 2018; 37(2): 143-154.
4. Ulloa JH. Micronized Purified Flavonoid Fraction (MPFF) for Patients Suffering from Chronic Venous Disease: A Review of New Evidence. Adv Ther., 2019; 36(1): 20-25.
5. Jantet G. Chronic venous insufficiency: worldwide results of the RELIEF study. Reflux assEssment and quaLity of lIfe improvEment with micronized Flavonoids. Angiology, 2002; 53(3): 245-256.
6. Hnátek L. Terapeutický potenciál mikronizované purifikované flavonoidní frakce (MPFF) diosminu a hesperidinu v rámci léčby chronického žilního onemocnění [Therapeutic potential of micronized purified flavonoid fraction (MPFF) of diosmin and hesperidin in treatment chronic venous disorder]. Vnitr Lek, 2015; 61(9): 807-814.
7. Bush R, Comerota A, Meissner M, Raffetto JD, Hahn SR, Freeman K. Recommendations for the medical management of chronic venous disease: The role of Micronized Purified Flavanoid Fraction (MPFF). Phlebology, 2017; 32: 3-19.
8. Lurie F, Kistner RL, Eklof B, Kessler D. Mechanism of venous valve closure and role of the valve in circulation: a new concept. J Vasc Surg, 2003; 38(5): 955-961.
9. Burnand KG. The physiology and hemodynamics of chronic venous insufficiency of the lower limb. In:, Gloviczki P, Yao JS, eds. Handbook of Venous Disorders, 2nd Edition. New York, NY: Arnold Publisher, 2001: 49–57.
10. Meissner MH, Moneta G, Burnand K, Gloviczki P, Lohr JM, Lurie F, Mattos MA, McLafferty RB, Mozes G, Rutherford RB, Padberg F, Sumner DS. The hemodynamics and diagnosis of venous disease**.** J Vasc Surg, 2007; 46(S): 4S–24S.
11. Labropoulos N, Gasparis AP, Tassiopoulos AK. Prospective evaluation of the clinical deterioration in post-thrombotic limbs. J Vasc Surg, 2009; 50: 826–830.
12. Pascarella L, Lulic D, Penn AH, et al. Mechanisms in experimental venous valve failure and their modification by Daflon 500 mg. Eur J Vasc Endovasc Surg, 2008; 35(1): 102-110.
13. Takase S, Pascarella L, Lerond L, Bergan JJ, Schmid-Schönbein GW. Venous hypertension, inflammation and valve remodeling. Eur J Vasc Endovasc Surg, 2004; 28(5): 484-493.
14. Nicolaides AN. Investigation of chronic venous insufficiency: a consensus statement. Circulation, 2000; 102: e126–e163.
15. Mühlberger D, Morandini L, Brenner E. Frequency and exact position of valves in the saphenofemoral junction. Phlebologie, 2007; 6: 3-7.