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Quantitative Evaluation of Venous Function Improvement After Entelon® Administration in Patients with Chronic Venous Insufficiency Using A 4D Flow MRI: A Pilot and Prospective Study

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Abstract

Background and objectives: Four-dimensional (4D) flow MRI was used to objectively assess changes in blood flow velocity in chronic venous insufficiency (CVI) patients who underwent stocking treatment and stocking combined with Entelon® (Hanlim Pharm Co. Ltd, Seoul, Korea) treatment.

Methods: Patients who were diagnosed with CVI were recruited from August 31, 2018 to December 31, 2020. A total of 23 participants were selected with 10 and 13 patients in the stocking treatment and stocking + Entelon® treatment groups, respectively. Blood flow velocity (Th-Plane peak and average velocities) was calculated using 4D flow MRI. Paired t-test was used to evaluate differences in the blood flow velocity before and after treatment.

Results: In the stocking treatment group, Th-Plane peak velocity increased by 2.48±5.05 after treatment ($p=0.155$). In the stocking + Entelon® treatment group, Th-Plane peak velocity increased by 4.85±5.57 after treatment ($p<0.001$).

Conclusion: This was the first study to quantitatively evaluate the increase in blood flow velocity in CVI patients using a 4D flow MRI. The blood flow velocity was significantly increased in participants who received Entelon®, highlighting the potential of Entelon® for CVI treatment.

Keywords: 4D flow MRI; CVI; Th-Plane Peak Velocity; Th-Plane Average Velocity; Venoactive drugs; GSPE (Grape Seed Proanthocyanidin extract); Proanthocyanidin

Introduction

Chronic venous insufficiency (CVI) comprises persistent ambulatory venous hypertension that affects the venous system of lower extremities. The condition causes various pathologies including pain, edema, skin changes, and ulcers [1] as well as symptoms of telangiectases (or spider veins), reticular veins, varicose veins, edema, pigmentation, eczema, lipodermatosclerosis, atrophie blanche, and venous ulceration [2]. Although the prevalence of CVI varies depending on the study population, anomalies of the lower extremity veins are observed in up to 50% of adults [3,4,5]. This does not only generate medical costs, but also negatively impacts the quality of life of affected individuals [6,7]. Risk factors of CVI include advancing age, family history of the disease, prolonged standing, obesity, smoking, sedentary lifestyle, lower extremity trauma, prior venous thrombosis, presence of an arteriovenous shunt, high estrogen levels, and pregnancy [3,8,9]. The prevalence of CVI in Korea is expected to increase due to under-diagnosis, increased prevalence of obesity, and aging of the population [2]. Currently, CVI is mainly diagnosed using ultrasound methods [10] or questionnaires on subjective symptoms of patients, such as a Chronic Venous Insufficiency Questionnaire (CIVIQ), Aberdeen Varicose Veins Questionnaire (AVVQ), Venous Clinical Severity Score (VCSS), and Venous Disability Score (VDS). Nevertheless, a correct diagnosis is a challenge as it depends on the equipment used as well as experience of the operator, the doctor interpreting the results, and subjective experiences of patients [11].

Recently, a time-resolved three-dimensional (3D) MRI called phase-contrast magnetic resonance imaging (PC-MRI) or four-dimensional (4D) flow MRI, has been developed and widely used for clinical evaluation of the blood flow [12,13]. This 3D measurement technique can assess the entire cardiovascular system, quantify the volume of blood flow at any angle, and conduct a retrospective analysis [14]. Unlike the conventional 2D PC-MRI, in which precise selection of the plane is of crucial importance, the 4D flow MRI can measure the entire vascular system at once and perform a retrospective analysis [15].

Vitis vinifera is a flavonoid polyphenolic compound extracted from grape seeds [16] is called "Grape seed proanthocyanidin extract (GSPE)". Various effects of GSPE have been reported, such as protection of early cerebrovascular injury caused by hypertension [17], antioxidant, reduction of inflammation and inhibition of progression of diabetic retinopathy [16,18] and improvement of vascular elasticity [19]. In addition, Entelon® (Hanlim Pharm Co. Ltd, Seoul, Korea) is an available venoactive drug for improvement of symptoms related to chronic venous insufficiecy as GSPE in Korea [20,21].

Therefore, this study used 4D flow MRI to objectively evaluate the improvement of blood flow velocity in CVI patients. To date, previous studies on objective evaluation of patients with CVI have not demonstrated uniform conclusions. This study used 4D flow MRI to compare changes in blood flow velocity before and after intervention in a group that underwent treatment using stockings and in a group that received Entelon® in addition to stocking treatment.

Methods

Study participants

This prospective study was conducted on patients diagnosed with CVI who did not have deep vein thrombosis and superficial vein regurgitation on Doppler ultrasonography after visiting the vascular surgery department between August 31, 2018 and December 31, 2020. A written consent form was obtained from each study participant, and MRI scans were performed before and 90 days after treatment for comparative analysis. Those who could not undergo MRI scans or were under prescription medications for venous insufficiency were excluded. The participants were randomly assigned to either the stocking treatment and stocking + Entelon® treatment groups using a random numbers. A total of 12 out of 37 participants dropped out of the study, and 2 participants, whose blood flow velocity could not be accurately measured during MRI scans due to shaking, were excluded. In the end, 23 participants were included in the final analysis with 10 and 13 participants in the stocking treatment and stocking + Entelon® treatment groups, respectively.

Measurement of blood flow velocity

To measure the blood flow velocity of the inferior vena cava (IVC), an 18-channel body coil was used in MAGNETOM Skyra 3T (Siemens Healthcare GmbH, Erlangen, Germany) MRI, and cross-sectional 3D phase-contrast images perpendicular to the IVC blood flow direction were obtained. The image parameters were as follows: TR = 5.5 msec, TE = 3.9 msec, Flip Angle = 7°, NEX = 2, FOV = 285 x 380 mm, acquisition matrix = 84 x 160, slice thickness = 2.5 mm, and receiver BW = 495 Hz/pixel. VENC was set in the range of 30-40 cm/s to eliminate aliasing artifacts and was applied in all directions of x, y, and z axes. During the scan, 11-12 frame images were acquired for every cycle with a time resolution of 50-55 msec, using prospective gating synchronized to the peripheral pulse, and the scan time was 12-14 minutes depending on the patient's cardiac cycle. The acquired data were analyzed using a prototype software (4D Flow version 2.4, Siemens Healthcare GmbH, Erlangen, Germany). A section through which blood flow passed in IVC was selected to calculate the flow rate and 4-pixel averaged peak velocity.

Definition of variables

The main outcome variable was blood flow velocity, which was assessed before and after 90 days of intervention. The blood flow velocity was defined as the Th-Plane peak velocity, which was the velocity at the pixel of the maximum peak of velocity in a cross-sectional curve. Th-Plane Peak Velocity and the mean velocity of the surrounding four pixels were defined as Th-Plane average velocity. Demographic characteristics of the participants including sex, age, height, weight, family history, history of surgery, and history of pregnancy, were assessed.

Statistical analysis

In general, summary statistics (mean, standard deviation) were presented for continuous variables. For categorical variables, the number of participants (N) and frequency (%) were presented. Paired t-test or Wilcoxon signed-rank exact test was conducted to evaluate the differences in blood flow velocity before and after treatment. All statistical analyses were performed using the statistical software R, version 4.1.0, and α=0.05 was considered statistically significant.

Ethics statement

This study was approved by the Institutional Review Board of the Pusan National University Yangsan Hospital (IRB No. 04-2018-020) and written consent was obtained from the participants before their enrollment.

Results

It shows the distribution of demographic characteristics of the study participants. The mean age of the participants was 56.83 years, and there were more women (15 participants; 65.22%) than men (8 participants; 34.78%).

The Th-Plane peak velocity was increased by 2.48±5.05 in the stocking treatment group after treatment (p=0.155). In the stocking + Entelon® treatment group, the Th-Plane peak velocity was increased by 4.85±5.57 (p<0.001). The Th-Plane average velocity was increased by 1.26±3.17 in the stocking treatment group after treatment (p=0.241). In the stocking + Entelon® treatment group, the Th-Plane average velocity was increased by 1.92±2.52 (p=0.006). Intragroup comparison of blood flow velocity before and after treatment showed that blood flood velocity was significantly increased in the stocking + Entelon® treatment group after intervention.

Discussion

This study compared differences in blood flow velocity before and after treatment in patients diagnosed with CVI, according to treatment with Entelon®, a venoactive drug. Th-Plane peak and average velocities were compared before and after treatment for each group. In the stocking treatment group, Th-Plane peak and average velocities increased following treatment by 2.48±5.05 and 1.26±3.17, respectively; however, the increase was not significant. In the stocking + Entelon® treatment group, Th-Plane peak and average velocities were increased following treatment by 4.85±5.57 and 1.92±2.52, respectively, and these changes was statistically significant.

The main pathophysiology of CVI is an increase in the venous pressure in the lower extremities. The main causes of the increase in the venous pressure include venous valve insufficiency, outflow venous obstruction, and insufficient muscle contractility [22]. The main mechanisms of action of venoactive drugs derived from natural extracts of synthetics are increased tension of the venous wall and reduced edema and pain [23]. Previous studies have reported the efficacy of various therapeutic agents [24,25,26] and the CVD treatment guidelines also recommend venoactive drug therapy for patients with C0s-C6 of CEAP classification [27,28,29]. In a previous study, Entelon® improved the symptoms of CVI [30], and GSPE was also shown to improve symptoms of edema by reducing capillar permeability [31,32]. In our study, blood flow velocity was significantly increased after treatment with Entelon®.

In clinical practice, 4D flow MRI is used to visualize the patterns of large and hepatic artery blood flow [12,13]. This study attempted to objectively evaluate CVI using 4D flow MRI and quantitatively measure blood flow velocity at an accurate location in blood vessels, which is not possible using the conventional 2D MRI. The flow rate can be calculated by multiplying the cross-sectional area of the blood vessel by the blood flow velocity. However, the cross-sectional shape and size of IVC before and after treatment was not identical in some patients. A previous study has reported that IVC diameter reflects changes related to intrathoracic pressure, abdominal pressure, and central venous pressure (CVP) [33]. Therefore, in this study, Th-Plane peak velocity, which shows the highest blood flow velocity within the diameter without being affected by the cross-sectional value, was used instead of the flow rate. In addition, Th-Plane average velocity, which can reduce variation in measurements while reflecting more pixels, was also calculated. As a result, blood flow velocity was significantly increased after treatment in the Entelon®-treated group.

The sample size of participants in this study is rather low, and this may affect the reliability of the presented results. However, this is an unavoidable limitation of pilot studies. Although the data was not shown in the study, there was no significant difference in the change of blood flow velocity between the two groups. This may be attributed to the small number of study participants. However, the novelty of the current study lies in the evaluation of the increase in blood flow velocity as an improvement in venous function using 4D flow MRI in CVI patients, who are mainly diagnosed using inaccurate ultrasound or questionnaire-based subjective assessment methods.

Conclusion

This was the first study to quantitatively evaluate the increase in blood flow velocity using 4D flow MRI in CVI patients. In the stocking + Entelon® group, the blood flow velocity of the participants was significantly increased after treatment, suggesting that Entelon® can improve venous function in CVI patients. Therefore, a large-scale follow-up study on venous function in CVI patients using 4D flow MRI is necessary to confirm our initial findings.

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