Evaluation of D-dimer after radiofrequency ablation or foam sclerotherapy of lower limb varicose: D-dimer is not good marker of venous thromboembolism after this procedure

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Abstract
Varicose veins are the most common human vascular disease. For the past two decades, intravenous destruction techniques, laser therapy, radiofrequency ablation (RFA), and ultrasound-guided foam sclerotherapy (UGFS) are some of these intravenous techniques which have been used as an alternative to the surgical removal of saphenous varicose veins. This cross-sectional analytical study was performed on 35 patients with venous insufficiency of the lower extremities who were referred to Razi Hospital Vascular Surgery Clinic, during the first 6 months of 2019. Patients were treated with RF and UGFS which were performed by a vascular surgeon. A checklist with necessary information was prepared for patients individually. The sexual frequency of patients with 25 cases (71.4%) was male and 10 cases (28.6%) were female. Totally, 25 cases (71.4%) were treated by sclerotherapy method and 10 cases (28.6%) were treated by RF. The results of our study showed that there was no significant difference in D-dimer within 24 hours before the surgery (P = 0.625) but the mean of D-dimer one week and two weeks after surgery showed a significant difference between the two groups (P<0.05). The results of our study showed that the level of D-dimer 24 hours before the surgery was not significantly different between the two treatment methods, however, one and two weeks after the surgery, the level of D-dimer was significantly higher in patients receiving sclerotherapy and RF with no difference in the final side effects of the two treatment methods.

Keywords: Varicose Veins, Sclerotherapy, Radiofrequency

Introduction
Varicose veins are an extremely common medical condition. The most common estimates of the prevalence of varicose veins have been between 5% and 30% in the adult population [1]. The findings in patients may include dilated and tortuous veins, telangiectasias, and fine reticular varicosities[2]. Patients may complain of heaviness, aching, and extremity fatigue or burning pain [3]. More severe signs include thrombophlebitis, hyperpigmentation, lipodermatosclerosis, ulceration, and bleeding from attenuated vein clusters [2]. Risk factors for varicose veins include female sex, older age, family history, obesity, a history of phlebitis, high number of pregnancies and prolonged standing [4]. Additional behavioral factors such as smoking, physical inactivity, and low-fiber diets have also been suggested to play a role [4].

Varicose veins are the most common appearance of chronic venous disease touching 25-33% of adult women and 10-20% of adult men [2]. The clinical manifestations of varicose veins vary among patients. Some patients are asymptomatic, and if diagnosed so, symptoms are usually limited to areas on the varicose
veins. However, the veins may be so wide that they cover the lower limbs diffusely [3]. Common symptoms include pain in the legs, heaviness, and swelling of the legs, and a burning and itching sensation [4]. Symptoms are often more severe at the end of the day, especially after long periods of standing up, and often are resolved after the patient sits down and raises the legs. Lower extremities veins insufficiencies lead to increased venous pressure, which eventually will lead to skin-form changes and severe wounds in the advanced stages [5]. Its worst symptoms include thrombophlebitis, hyperpigmentation, lipodermatosclerosis, ulceration, and bleeding from a thinned vein [6, 7]. For the past two decades, intravenous destruction techniques have been used as an alternative to the surgical removal of saphenous varicose veins. Laser therapy, RA, and UGFS are some of these intravenous techniques. These techniques are less invasive and have fewer complications than invasive surgical procedures [8, 9]. Endovenous radiofrequency (RF) is relatively new and minimally invasive [10] which is associated with fewer postoperative complications [11]. UGFS has mainly replaced liquid sclerotherapy in the treatment of superficial venous insufficiency [12]. The purpose of this procedure is to cause damage to the endothelium and terminate the venous wall. In this technique, sodium tetradecyl sulfate (STS) and polidocanol are commonly used in a foam form to treat varicose veins and vascular abnormalities [13]. D-dimer and fibrin monomer represent the activation of coagulation [14]. It was found in preliminary studies that D-dimer increases after EFS and it was suggested that this activation in coagulation plays a central role in sclerotherapy efficacy, yet, it might be associated with thrombosis adverse effects [15]. D-dimer is not normally present in human blood plasma, except when the coagulation system is activated, for example, due to thrombosis or coagulation diffuse within the membrane [13]. Because of its high sensitivity, performing D-dimer reduces the need for unnecessary tests in people suspected of thromboembolic diseases [16]. One of the treatment complications with the two mentioned methods is the development of thromboembolic disorders, and this complication can cause significant disability and even mortality in patients. On the other hand, the D-dimer test as a sensitive and diagnostic test can help the therapist in the early stages to take appropriate therapeutic actions. The results of this study can be instructive and guiding. Therefore, it is hoped that the achieved results of the present study, while revealing the thrombotic consequences of these two methods, would be able to provide the possibility of choosing a method with minimal complications for varicose veins treatments for vascular surgeons and pave the way for further research in this area.

**Materials and Methods**

**Patients**

This cross-sectional analytical study was performed on 35 patients with venous insufficiency of the lower extremities that were referred to Razi hospital, Vascular Surgery Clinic, in the north of Iran during the first 6 months of 2019. The study was performed by the declaration of Helsinki and approved by the Ethics Committee of Guilan University of Medical Sciences (IR.GUMS.REC.1398.338). Patients between the ages of 18 and 60, who required invasive treatment intervention due to large or small saphenous vein insufficiency, were included in the study. These patients were excluded because of known hypersensitivity to
Table 1. Demographic characteristics

|                | Number | percent |
|----------------|--------|---------|
| **Gender**     |        |         |
| Man            | 25     | 71.4%   |
| Female         | 10     | 28.6%   |
| **Side involved** |      |         |
| Right          | 10     | 28.6%   |
| Left           | 25     | 71.4%   |
| Great Saphenous| 35     | 100     |
| **Treatment**  |        |         |
| Sclerotherapy  | 10     | 28.6%   |
| RF & Sclerotherapy | 25   | 71.4%   |

|                | Number | mean     | Standard deviation |
|----------------|--------|----------|---------------------|
| **Age**        | 35     | 44.77    | 14.5                |
| **BMI**        | 35     | 27.65    | 2.68                |
| **Volume of sclerosing material** | 25  | 13.08    | 5.14                |
| **Extent of the area involved** | 25   | 43.30    | 16.65               |
| **The diameter of the vein involved RF** | 10 | 21.12    | 6.52                |
| **The length of the vein involved RF** | 10 | 12.71    | 6.52                |
| **D-dimer 24 hours before operation** | 35 | 219.71   | 111.76              |
| **D-dimer one week after surgery** | 35 | 914.2    | 1239.41             |
| **D-dimer two weeks after surgery** | 35 | 913.41   | 823.45              |

**Study site**
This cross-sectional study was performed on 35 patients with lower extremity venous insufficiency who were referred to the specialized vascular surgery clinic of Razi Hospital in Rasht, during the second half of 2019.

**Baseline assessment**
Each patient had the following baseline information collected: The complete history of the patients was obtained and they were clinically examined by a vascular surgeon. Patients were then referred to a single radiology center for duplex ultrasonography to assess the insufficiency of the superficial and deep venous systems of the lower extremities.

**Blood collection and analysis**
Systemic blood samples were taken from antecubital veins, 24 hours before surgery, and one week after. Also, two weeks after controlled ultrasound in patients undergoing RF to assess the obstructive condition of the vein, the third systemic blood sample was taken to check the D-
Table 2. Gender frequency, side involved in two groups

| Treatment method | RF   | Sclerotherapy |
|------------------|------|---------------|
| Gender           | No.  | percent       | No.  | percent       |
| Man              | 5    | 50            | 20   | 80            |
| Female           | 5    | 50            | 5    | 20            |
| Side involved    |      |               |      |               |
| Right            | 4    | 40            | 6    | 24            |
| Left             | 6    | 60            | 19   | 76            |

dimer level. It should be noted that all blood samples were sent to a single laboratory.

Follow up Patients
The D-dimer level was routinely assessed and was entered 24 hours before surgery, one and two weeks after the surgery, and postoperative complications in the preparation checklist.

D-dimer quantitation
The kit used for the D-dimer test was from Diasorin, USA, and the Liaison device, D-dimer quantitation were also performed by a commercial ELISA technique with a normal value of less than 442 ng/ml and a lower limit of detection of 5 ng/ml. Technicians performing the assays were blinded to patients’ identity and timing of the samples.

Statistical analysis
Statistical analyses were performed using SPSS 22 software. Frequency indices of mean and standard deviation were used to describe the parameters, and the repeated test measures were used to compare the means in the two treatment methods. P values <0.05 associated with the time variable were considered statistically significant.

Results
35 patients who underwent varicose veins of the lower extremity treated with radiofrequency ablation and foam sclerotherapy under ultrasound guidance were enrolled including 25 men and 10 women. The mean age was 44 years (range 19-60). Among these, 35 patients had RF and foam sclerotherapy on a single leg (n=25 left and n=10 right). 25 patients were treated by the method sclerotherapy and RF 10 cases by sclerotherapy. No complications have been reported in patients. The mean BMI was 27.65±2/68 ml. The mean area involved in sclerotherapy was 43/30±16/65 cm2. The mean venous vein diameter and length in RF were 21.12 ±19.23 mm and 12/71 ± 6/52 cm, respectively. The mean D-dimer was obtained 24 hours before surgery, one and two weeks after surgery, respectively, 219.71 ± 111.76, 914.20±1239.41, and 913.41±823.45, respectively. Demographic information is given in Table 1. Gender and position involved in the two treatment groups did not show a statistically significant difference (P = 0.423). Table 2There was no significant difference in the level of dimer D-dimer in the three treatment groups by sex (P = 0.926). There was no significant difference between the dimer levels in the three measurement times in the two treatment groups by side involved (P = 0.315). There was no significant difference between the dimer levels in the three treatment groups in terms of BMI (P = 0.631, Table3). The mean age and BMI in the three different measurement times by the two treatment groups of age and BMI after the operation are abnormally distributed Table4.

Discussion
Varicose veins are the most common manifestation of chronic venous insufficiency[5]. Varicose veins can be associated with great discomfort, and they bear a significant impact on productivity and quality of life, which can improve by surgery [6, 7]. Adequate surgery is essential to prevent unnecessary recurrence and avoidable complications [8]. To our knowledge, in our study, the level of D-dimer, 24 hours before the surgery was not significantly different between the two treatment methods, but one and two weeks after the surgery, the level of D-dimer was significantly higher in patients receiving sclerotherapy or RFA, although they showed no side effects. After a thrombogenic stimulus, thrombin reaches its maximum point within minutes [17]. Similar studies have shown that normalization occurs due to excessive fusion and ineffective sclerosis to undetectable values below the injection area [18, 19]. Here our goal is to detect a similar anticoagulant effect on body tissue, whereas other studies concentrated...
on postoperative complications or pain. In our study, it was shown that factors such as age, sex, 

| Table3: D-dimer in two treatment groups by gender, segregation of the side involved and BMI |
|---------------------------------------------------------------|
| **D-dimer 24 hours before operation** | treatment method | mean | Standard deviation |
| **Man** | RF& Sclerotherapy | 226/1 | 121/6 |
| | Sclerotherapy | 230/82 | 120/95 |
| **RF& Sclerotherapy** | 203 | 101/95 |
| **Female** | Sclerotherapy | 145/6 | 32/78 |
| | RF& Sclerotherapy | 424/4 | 190/96 |
| **Sclerotherapy** | 1161/2 | 1544/32 |
| **D-dimer one week after surgery** | RF& Sclerotherapy | 406/6 | 145 |
| **Man** | Sclerotherapy | 923/4 | 862/83 |
| **Female** | RF& Sclerotherapy | 385 | 163/46 |
| | Sclerotherapy | 887 | 1007/33 |
| **Sclerotherapy** | 319/2 | 83/28 |
| **D-dimer two weeks after surgery** | RF& Sclerotherapy | 757/4 | 320/26 |
| **Man** | Sclerotherapy | 145 | 32/78 |
| **Female** | RF& Sclerotherapy | 1463/2 | 1544/32 |
| **Sclerotherapy** | 923/4 | 862/83 |
| **D-dimer 24 hours before operation** | RF& Sclerotherapy | 253/91 | 105/80 |
| **BMI** | Sclerotherapy | 205/5 | 127/44 |
| **Left** | RF& Sclerotherapy | 268 | 115/31 |
| **Sclerotherapy** | 205/5 | 127/44 |
| **Right** | RF& Sclerotherapy | 526 | 1261/2 |
| **Sclerotherapy** | 980/84 | 1009/05 |
| **BMI** | **Above 30** | **RF& Sclerotherapy** | **268** | **115/31** |
| **Sclerotherapy** | **197/4** | **118/28** |
| **BMI** | **25-30** | **RF& Sclerotherapy** | **261/07** | **113/34** |
| | **Sclerotherapy** | **220/55** | **123/38** |
| **Above 30** | **RF& Sclerotherapy** | **125** | **56/56** |
| | **Sclerotherapy** | **202/66** | **68** |
| **BMI** | **19-25** | **RF& Sclerotherapy** | **526** | **1261/2** |
| | **Sclerotherapy** | **195/22** | **608/35** |
| **Above 30** | **RF& Sclerotherapy** | **436/71** | **171/86** |
| | **Sclerotherapy** | **1099** | **168/42** |
| **BMI** | **268/5** | **70** |
| **Above 30** | **RF& Sclerotherapy** | **950/66** | **785/25** |
| | **Sclerotherapy** | **605/6** | **239/49** |
| **BMI** | **19-25** | **RF& Sclerotherapy** | **366/71** | **141/38** |
| | **Sclerotherapy** | **870/92** | **1072/09** |
| **Above 30** | **RF& Sclerotherapy** | **259/5** | **21/12** |
| | **Sclerotherapy** | **1235** | **441/76** |
Table 4: Mean age and BMI in three different measurement times by two treatment groups

| Treatment Method          | Member | Min | Max | Average |
|---------------------------|--------|-----|-----|---------|
| Sclerotherapy             | 10     | 19  | 60  | 42/58   |
| RF & Sclerotherapy        | 25     | 19  | 60  | 42/58   |
| BMI                       | 10     | 19  | 34  | 26/45   |
| RF & Sclerotherapy        | 25     | 20  | 36  | 28/85   |

BMI, involved side and involved vein did not make a significant difference in the mean D-dimer in the two groups. More recently, Hamel-Desnos and a total of 20 patients in each group were evaluated, 90% of whom were female with a mean age of 58 years old. On the day 28th, the rate of venous occlusion in both groups was 100%. In all samples, no biological changes were observed, regardless of the average increase in D-dimer levels during days 1 to 14. The results of this study showed that foam sclerotherapy seems to have minor effects on peripheral blood vessels in terms of inflammation and coagulation [20]. Finally, our trial indicates a gradual and distance-dependent decrease in an active concentration of sclerosis in the target veins. In addition, it can be concluded that the injection and dispersion of a foam-formed sclerosing, only in one injection area can lead to increased activity in the foam inlet, it means where the fusion reaches its maximum. Our important finding is that elevated D-dimer levels occurred shortly after surgery (sclerotherapy or RFA), and this can occur in the absence of concomitant deep vein thrombosis (DVT) or deep occlusive occlusion [21]. In the future, it is suggested that a similar study with larger sample size and longer duration of D-dimer and long-term side effects of sclerotherapy and RFA be evaluated. Due to the very high prevalence of varicose veins and new procedures such as RF and scrotherapy, the effect of these treatments at the D-dimer level is valuable to us because in case of symptoms of venous thromboembolism, this sensitive test has its diagnostic value in this The group loses disease, as in this study it was found that the level of D-dimer in patients undergoing radiofrequency therapy and sclerotherapy or sclerotherapy alone increases significantly and remains high for two weeks. Of the patients we examined, the D-dimer level did not remain within the normal range. However, in our complementary studies, there was no evidence of venous thromboembolism.

In conclusion, the results show that the level of D-dimer, 24 hours before the surgery was not significantly different between the two treatment methods, but one and two weeks after the surgery, the level of the D-dimer was significantly higher in patients receiving sclerotherapy and RFA. This increase was not associated with complications in these patients, so it can be said that the increase in D-dimer level after RF treatment or sclerotherapy was normal in patients with varicose veins due to the absence of abnormal clinical symptoms after the surgery, furthermore, it can be concluded that there should not be any concerns about dangerous complications such as DVT and pulmonary thromboembolism just because the level of post-operative D-dimer is high in patients, therefore, they can be reassured about the patient’s health and avoid spending extra time and money on laboratory tests and more radiological imaging to prove the patient’s health.

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Author contribution

H. H. Conceptualization and Supervision, N. K. Data gathering, M. F. Data gathering, Writing—original draft, H. E.K. Data analysis, Z. J. Review and editing, A. N. Data gathering, M. T. Data gathering, S. Y. Data gathering

Conflict of interest statement

The authors declare they have no conflict of interest.
**Ethical approval**

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