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ORIGINAL ARTICLE

Comparison of inflammatory parameter levels after sclerotherapy of varicose veins with polidocanol

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ABSTRACT

A**im** To determine changes in inflammatory parameter values after ultrasound-guided foam sclerotherapy (UGFS) of varicose veins. The values of inflammatory parameters taken immediately after treatment and seven days after treatment were compared.

M**ethods** A total of 41 patients with verified varicose vein disease were included. A total of 82 samples were taken from the cubital vein and-C-reactive protein, D-dimer, fibrinogen and leukocytes were analysed.

Results Significant differences were observed in D-dimer values. Significant changes were recorded in D-dimer levels, which showed significant increases 7 days after treatment. D-dimer levels increased from an average of 287.3 ng/mL to 350.9 ng/mL, which is a statistically significant change with a p-value of 0.04. The difference was not statistically significant for other parameters.

Conclusion D-dimers have been shown to be a specific inflammatory parameter in vein sclerotherapy. Increased values of D-dimers did not affect blood hypercoagulability. Sclerosing agents are effective for seven days after treatment, and recovery should be adjusted to this finding. Although an increase in D-dimer values seven days after treatment has been proven, vein sclerotherapy treatment remains a safe, extremely effective and reliable method of treating varicose veins, and will have an increasingly wide usage in the future.

Keywords: C- reactive protein, D-dimer, fibrinogen, UGFS

INTRODUCTION

Varicose veins are as old as Hippocrates (1). The veins of the legs become dilated and of blue colour due to excessive accumulation of blood. This disease and the effort to identify and treat it has a very long history (2).

In the late 1970s, the German pharmaceutical company BASF (Badische Anilin & Sodafabrik), which produced polidocanol, abandoned its use as an anaesthetic because it was found to cause venous thrombosis. And so, by chance, it turned out that this substance could be a good sclerosant. Otto Henschel, who was the scientific director of Kreussler Pharma in Germany at the time, became interested in this substance, and in 1963 Dr. Peter Lunkenheimer was the first to use polidocanol in his patients (3,4).

Polidocanol (Laureth-9 or Lauromacrogol 400) is a synthetic fatty alcohol (alkyl polyglycol ether lauryl alcohol). Chemically, it can be represented as a polymer belonging to the class of alcohols and glycols (5). After intralesional administration, polidocanol induces endothelial cell injury by interfering with calcium signalling and nitric oxide pathways. After endothelial damage, platelets aggregate at the site of injury and attach to the venous wall, resulting in a dense network of platelets, cellular debris, and fibrin that occludes the vessel (6). Polidocanol acts as a detergent, forming aggregations of molecules in the form of micelles. The micelles then interact with the endothelial cell membrane and disrupt the cells by solubilizing essential molecules from the membrane surface. Therefore, when injected intravenously, lauromacrogol 400 (polidocanol) destroys the wall of the blood vessels of the affected varicose veins and thus permanently clogs them (7). Polidocanol induces at first endothelial damage, which causes platelets to aggregate at the site of damage and attach to the vein wall. Then, a dense network of platelets, cellular debris, and fibrin occludes the vessel (8).

The mechanism of sclerotherapy involves the destruction of the venous endothelium of the blood vessel, exposure of the basal layer of collagen to the sclerosing agent, induction of vasospasm and, ultimately, complete fibrosis of the blood vessels. With ultrasound monitoring, sclerosants have been observed to enter the deep venous system via perforators or junctions; but, the clinical incidence of deep vein thrombosis or pulmonary embolism after sclerotherapy is very low (9).

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The use of sclerosing agents as foam has been shown to be more effective and requires lower concentration then the liquid sclerosing agent. The use of foam reduces the amount of agent, maximizes the sclerosing effect by increasing the surface area of contact with the varicose vein walls, and prevents intravascular bleeding (10). Foam sclerotherapy has been reported to have a success rate of 85–95% compared with 35% for liquid in eliminating reflux in large cutaneous veins. Similarly, histological studies have shown similar effects of sclerosing agents at concentrations of 0.5% as a foam and 3% as a liquid (11).
This procedure has been widely used in the last thirty years, while in Bosnia and Herzegovina the procedure expansion started 15 years ago. Our institution has been performing it for the last 15 years and has treated over 3,000 patients (12).
So far, a large number of studies have been conducted measuring laboratory parameters that affect coagulability and inflammation (13,14). However, there are no studies examining sclerotherapy and the selected parameters, such as D-dimers, fibrinogen and thrombocytes.
The aim of this study was to investigate specific inflammatory parameters that may be indicative of inflammatory conditions of the veins and could contribute to future research and clinical practice.

PATIENTS AND METHODS

Patients and study design

The study was designed as a prospective, observational, interventional clinically controlled study. It was conducted at the Cantonal Hospital Zenica and competent laboratories. The study included patients who underwent minimally invasive treatment of varicose veins by ultrasound guided foam sclerotherapy (UGFS) during the period January 2023 to April 2024. A total of 41 patients were included in the study (82 samples in total).
The inclusion criteria were: patients older than 18 and younger than 65 years of age, patients with clinically and ultrasound-verified varicose veins of the lower extremities, disease stage from Ido IV according to the Clinical, Etiological, Anatomical and Pathophysiological (CEAP) classification (4).
The exclusion criteria were patients younger than 18 and older than 65 years, disease stage according to CEAP classification 0, V and VI, previous deep vein thrombosis and pulmonary thromboembolism, chronic diseases: myocardial infarction, degenerative diseases of blood vessels, patients who did not consent to participate in the trial, patients who independently withdrew from research, patients who did not have all the planned parameters taken, peripheral arterial ischemia, pregnancy, disability. Patients with varicose veins stage V and VI were excluded, as the disease is developed and advanced with additional complications such as venous ulcers, which can affect the values of the measured parameters being tested. Also, chronic venous thrombosis and thromboembolic incidents often give false positive laboratory values, and such patients were excluded from the study.
Each patient gave written consent for the study and was informed in detail about all protocols and procedures of this study. Patients under the age of 18 could not give their consent, and according to the pathophysiology of venous diseases, they could not be part of this study. Patients older than 65 are often burdened with additional comorbidities, which could affect the results of the study.
The Ethics Committee of the Cantonal Hospital Zenica gave its approval for this study.

Methods

The study was conducted over a period of fourteen months. During the study, all patients had a minimum of two visits to the doctor, initial and control treatment, and two visits to the laboratory. The first visit was during the procedure and vein treatment itself, then they were referred to the laboratory, and the same procedure was repeated after 7-10 days.
After the physical examination, each patient underwent an ultrasound (Color Doppler) examination of the blood vessels of the lower extremities (Biosound esoate MyLab 25 Xvision probe 5-10Hz, Genoa/ Italy). The examination of the arterial and deep venous system was performed in the supine position, while the superficial venous system was performed in the standing position. Measurements were performed to assess the sufficiency of the saphenofemoral junction and the small saphenous vein.
Immediately before the treatment, patients were administered low-molecular-weight heparin at a dose determined according to body weight (15).
Sclerotherapy was performed with patients in the standing, sitting and lying positions.
After the preparation, the treatment protocol for each patient was standardized. The sclerosant Polidocanol (Aetoksisclerol®, Laboratoires Kreussler, Paris, France) was used.
Sclerosing foam was obtained using a sterile disposable syringe set (20 mL two-piece, three-way stopcock syringe connector). The mixture of sclerosing fluid and room air was 1+4 (one volume of sclerosing agent + four volumes of air; i.e., a ratio of 1/5). Foam preparation and venipuncture were performed according to the Tessari method (16).
Sclerotherapy was guided by ultrasound and performed by direct needle puncture (22 Gauge, length 40 mm, Terumo® Leuven; Belgium), with the patient in the supine and standing positions. The sclerosing agent was applied as a foam. Immediately after the treatment for 10-15 minutes, the patient had blood drawn from the cubital vein by venipuncture for laboratory analysis as follows: complete blood count (CBC) – leukocytes (reference value 4-10x10^9/L) (Sysmex xn-350, Kobe/ Japan), C reactive protein (CRP) (reference value<5 mg/dL) (Olympus AU400, Nagano/Japan), fibrinogen (reference value 1.9-4.3 g/L) (Stago Gennevilliers/France), D-dimer (reference value 50-500 ng/mL) (Afias 1, Gangneung/South Korea).
A follow-up examination and monitoring were performed 7-10 days after the treatment. At that time, a new re-evaluation and examination of the patient were performed. For a more detailed analysis, the patients were statistically processed and divided according to the concentration of the sclerosing agent with which they were treated. The patients were treated with five different concentrations of polidicanol: three patients with 1%, seven with 1.5%, 21 with 2%, six with 2.5% and four patients with 3% polidicanol.

Statistical analysis

Numerical variables were presented as arithmetic means and standard deviations (SD), and as medians, interquartile ranges (IR Q1–Q3), and ranges (min-max), if they did not follow normal distribution. Quantitative variables were tested for normality using the Shapiro-Wilk test and evaluated with QQ-plots and

histograms. Ordinal and categorical variables were described using medians and interquartile ranges, or, as discrete values, presented with frequency distributions. For dependent measurements, a paired t-test was applied if the assumptions for its use were met. The statistical significance level was set at <0.05.
We presented our results in tables and graphs, and stated which p values and which hypothesis test were used. The confidence interval of 95% was used in the results.

RESULTS

Among the 41 patients, 14 (34%) were male and 27 (66%) were female. The mean age of the patients in the total sample was 42±13 years. The median age was 42 years (IR= 32 and 49) years. Analysis of inflammatory markers in the patients treated with polidocanol between the time points immediately after the treatment and seven days after the treatment showed the difference. The most prominent findings were the significant changes in D-dimer level, which showed a significant increase 7 days after treatment. Mean value of D-dimer levels increased from 287.3 ng/mL to 350.9 ng/mL (p=0.04) (Table 1 and figure1). Also, for one patient D-dimer value of 1.278.0 ng/mL was recorded 7 days after the treatment.
We performed a more detailed statistical analysis of different concentrations of polidocanol in order to check whether a particular concentration of polidocanol had a significant effect on the results. The results showed no statistically significant difference in D-dimer values according to different concentrations of sclerosing agents (Figure 2).

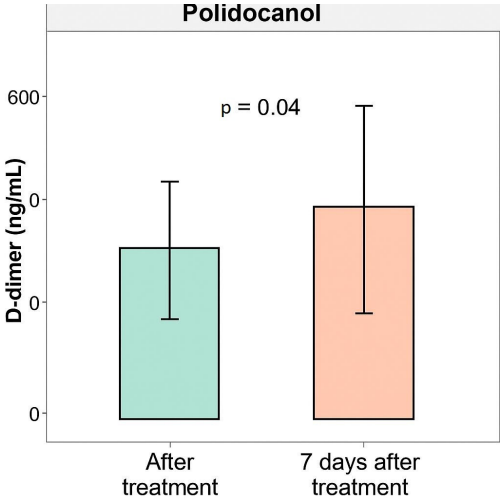

Figure 1. D-dimer values after treatment and 7 days after treatment

Concentration of other markers, including C-reactive protein (CRP), fibrinogen, and leukocytes, did not show statistically significant differences during this post-operative period. CRP level showed a slight decrease from an average of 2.5 mg/dL to 2.0 mg/dL. Similarly, fibrinogen level decreased slightly from an average of 3.7 g/L to 3.6 g/L, leukocytes decreased from 6.4 x 109/L to 6.2 x 109/L (Table 1).

Table 1. Values of laboratory measurements immediately after the treatment and 7 days after the treatment

Variable (reference value)	Sample timing		Difference*	95% CI*,†	P*
	After treatment	7 days after treatment			
C-reactive protein (<5) (mg/dL)			0.51	-0.23; 1.3	0.2
Mean (±SD)	2.5 (±2.7)	2.0 (±1.9)			
Median (Q 1–Q3)	1.5 (0.8–2.4)	1.3 (0.9–2.6)			
Range (Min–Max)	0.4–12.1	0.2–11.0			
D-dimer (50-500) (ng/mL)			-64	-124; -3.2	0.040
Mean (±SD)	287.3 (±129.3)	350.9 (±200.7)			
Median (Q1–Q3)	245.0 (188.0–345.0)	314.0 (243.0–439.0)			
Range (Min–Max)	151.2–722.0	127.0–1.278.0			
Fibrinogen (1.9-4.3) (g/L)			0.12	-0.12; 0.35	0.3
Mean (±SD)	3.7 (±0.7)	3.6 (±0.7)			
Median (Q1–Q3)	3.7 (3.3–4.2)	3.6 (3.2–4.0)			
Range (Min–Max)	2.0–4.8	2.1–5.6			
Leukocytes (4-10) (10^9/L)			0.23	-0.26; 0.71	0.4
Mean (±SD)	6.4 (±1.3)	6.2 (±1.5)			
Median (Q1–Q3)	6.2 (5.6–7.0)	6.3 (5.0–7.0)			
Range (Min–Max)	4.0–9.2	3.6–10.1			

*refers to the Difference, p and 95% CI (Confidence interval) columns;
† indicates the 95% CI that refers to where the two are in the table

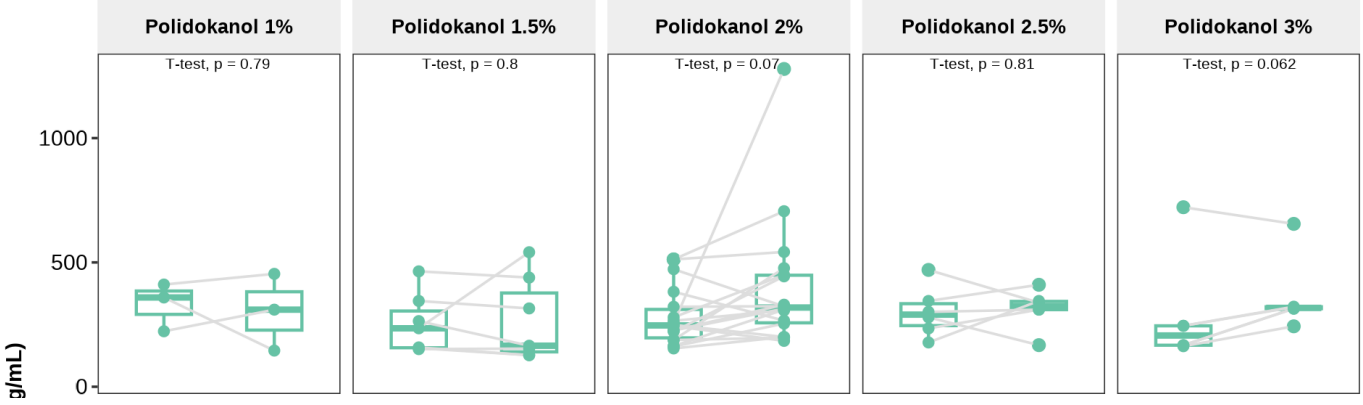

Figure 2. D-dimer values immediately after and 7 days after treatment, according to different concentrations of sclerosing agents

There was no statistically significant difference in CRP values right after the treatment and seven days after the treatment. The mean value decreased by 0.51 (±2.4) mg/dL (Table 1).
No statistically significant difference was found in fibrinogen values after the treatment and 7 days after the treatment. The average value decreased by 0.12 (±0.7) g/L. No statistically significant difference was found in leukocytes values after the treatment and 7 days after the treatment. The average value decreased by 0.23 (±1.5) × 10^9/L (Table 1).

DISCUSSION

Nowadays, there is a large number of non-invasive methods of the varicose vein treatment that have proven to be very effective and reliable (17). Today, detergent-based sclerosing agents have gained the greatest popularity. Polidocanol (lauromacragol) and sodium tetradecyl sulfate are the two sclerosing agents that are most common and most widely used due to their effectiveness, non-toxicity, and affordable price (18).
In our results, among patients treated with polidocanol, biohumoral response showed difference, both immediately after the treatment and at the second measurement seven days after the treatment. The most significant changes were in D-dimer, where measurements after seven days were significantly increased. D-dimer level in patients treated with polidocanol was also increased. Our results are in line with a large number of other studies that have confirmed the elevation of D-dimer levels after sclerotherapy with polidocanol or sodium tetradecyl sulfate (STS) (19,20).
D-dimer values showed a significant difference in measurements immediately after the treatment and seven days after the treatment in patients treated with polidocanol. Previous studies on D-dimers have consistently confirmed that differences between measurements exist, primarily due to procoagulant activity; however, these differences are insufficient to cause harmful effects or disrupt the overall function of the coagulation system during or after venous system treatment (21).
C-reactive protein CRP and fibrinogen are acute phase proteins that increase as nonspecific inflammatory markers. In the literature, elevated values of D-dimer and CRP parameters can be found in patients with varicose veins and some other comorbidities, such as hypertension (22). Since these parameters are nonspecific, it is very difficult to analyse and isolate their response to an exact and specific change occurring in the body. The reason for the increase in values may be a damaged wall and destroyed endothelium, which enhance procoagulant activity in the blood, and thus activate processes that increase the value of the aforementioned parameters (17,23). Recent research shows that CRP values are slightly elevated in patients with varicose veins and in patients who have undergone minimally invasive treatments. Changes are minimal and negligible in medical practice (23).
C-reactive protein did not show a statistically significant difference between measurements taken immediately after treatment and seven days later. It is interesting that the average value after 7 days was lower. Reportedly, no significant difference in CRP levels immediately and 7 days after polidocanol treatment was found (24,25).
Fibrinogen levels were slightly changed but without statistically significant difference after treatment and seven days later. Fibrinogen is one of the main parameters in the procoagulant activity of blood and its values can be changed under the influence of various parameters. Even varicose veins themselves can cause an elevation of blood fibrinogen level (27). Changes in fibrinogen level in our study were minimal. A large number of studies also showed minimal non-significant differences in fibrinogen levels (26,27).
The results of the analysis of formed blood elements were without significant difference in values. Most similar studies state that sclerosing agents do not have a significant effect on formed blood elements (28,29).
A limitation of this study is the relatively small number of patients and samples, although it was sufficient to achieve moderate statistical power; additionally, the study was conducted at a single centre. Also, data obtained after the first follow up were insufficient for some patients. The majority of patients had one-month and three-month follow-up. We did not show all clinical outcomes and stratification of patients because they did not have an impact on the results.
Polidocanol is a safe sclerosant and does not cause severe complications such as thromboembolic effects nor does it provide a biohumoral response related to the onset of thrombotic incidents. It is important to choose an adequate sclerosant depending on the diameter of the vein. For total endothelial dysfunction, a minimum concentration of sclerosant of 0.5% is required. Sclerosant agents are effective for 7 days after treatment, so recovery should be adjusted to this knowledge (compression therapy, repeated treatment, etc.). For optimal outcomes, it is important that the patient is adequately prepared, the appropriate vein is selected, the correct concentration is used, and the patient is properly monitored with diagnostic and laboratory tests.
Sclerotherapy is an extremely effective and reliable method for treating varicose veins and is expected to see increasingly widespread use.

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TRANSPARENCY DECLARATION

Competing interests: None to declare.

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