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SUMMARY

Introduction/Objective Assessment of the effect of graduated elastic compression stockings on clinical findings, complications and inflammatory and thrombotic markers in patients with superficial vein thrombophlebitis.

Methods This prospective study was conducted between January and July 2017, in the Clinic for Vascular and Endovascular Surgery of Clinical Centre of Serbia. All the patients were clinically examined, and color duplex ultrasonography of the superficial and deep venous systems was performed. In all cases we follow clinical finding, inflammatory and thrombotic markers and complication superfitial vein thrombosis (SVT).

Results SVT was detected in 60 patients (36 women, aged from 23 to 75 and 24 men, aged from 18 to 76. Most patients were with unilateral, subacute, above knee located SVT. Regarding the typical clinical symptoms of SVT, patients were divided in four groups. Majority of our patients (group D) had all symptoms associated. Regarding the severity of SVT and risk factors, patients were divided into a greater risk group (Group I) and a lesser risk group (Group II), and treated with low-molecular-weight heparin (LMWH) aspirin (ASA)and two classes of GECS regarding the level of SVT. Laboratory testing of inflammatory and thrombotic markers in patients with SVT was performed at the beginning and at the end of therapy

Conclusions In treatment of superficial venous thrombosis higher class of graduated compression therapy has stronger influence in decrement of inflammatory and thrombotic factors
and prompt and adequately chosen therapy of superficial venous thrombosis allows stoppage and regression of thrombotic process.

Keywords: graduated elastic compression stockings; inflammatory and thrombotic markers; superficial vein thrombophlebitis

САЖЕТАК

Увод/Циљ Циљ рада је процена утицаја градуисаних еластичних компресивних чарапа на клинички налаз, компликације као и на маркере инфламације и тромбозе код пацијената са површним тромбофлебитисом.

Методе Студија је дизајнирана као проспективна и обављена је од јануара до јула 2017. године на Клиници за васкуларну и ендоваскуларну хирургију Клиничког центра Србије. Сви пацијенти су подвргнути клиничком прегледу а након тога је учињена и колор-дуплекс ултрасонографија површног и дубоког венског система. Код свих пацијента праћен је клинички налаз, маркери инфламације и тромбозе као и компликације површног венског тромбофлебитиса (ПВТ).

Резултати ПВТ је дијагностикован код 60 пацијента (36 жена старости од 23 до 75 година као и 24 мушкарца старости од 18 до 76 година). Већина пацијента је имала унилатерални, субакутни ПВТ локализован изнад колена. Имајући у виду клиничке симптоме пацијенти су били подељени у четири групе. Већина пацијената у нашој студији (група Д) имала је све удружене симптоме ПВТ. Узимајући у обзир степен ПВТ као и факторе ризика пацијенти су били подељени у групу са повишеним ризиком (Група II) и у групу са мањим ризиком (Група I) и третирани су применом хепарина мале молекулске масе, аспирином као и са две класе градуисане компресивне терапије узимајући у обзир ниво ПВТ. Лабораторијско испитивање инфламаторних и тромботских маркера код пацијената са ПВТ обављено је пре започињања и по завршетку терапије.

Закључак У третману ПВТ виши степен градуисане компресивне терапије има значајнији утицај на смањење вредности маркера инфламације и тромбозе те да брза и адекватно одабрана терапија ПВТ омогућава заустављање и регресију тромбортског процеса.

Кључне речи: градуисане еластичне компресивне чарапе; маркери инфламације и тромбозе; површни венски тромбофлебитис

INTRODUCTION

Acute superficial thrombophlebitis of the lower extremities is one of the most common vascular diseases affecting the population. Although it is generally considered a benign disease, it can be extended to the deep venous system and cause pulmonary embolism.

Superficial vein thrombophlebitis (SVT) frequently occurs in varicose veins. It can be caused by trauma, such as catheter insertion or direct intimal injury. It is believed that hidden infection in varicose veins is a potential factor for development of thrombophlebitis, which might be exacerbated after operations, injection treatments, trauma, or exposure to radiation therapy. While considering factors leading to SVT, the clinician must remember all the components constituting Virchow's triad – namely: intimal injury, stasis, and changes in blood coagulation [1, 2]. SVT manifests as a local pain, itching, tenderness, reddening of the skin, and hardening of the surrounding tissue [3].

The color duplex ultrasonography of superficial and deep veins is a highly reliable diagnostic method and has an important role in deciding among a conservative or surgical treatment or follow-up of the operated patients [4].

Conservative treatment of SVT depends on its etiology and extent as well as the severity of symptoms. It usually implies platelet antiaggregation and anticoagulation therapy, combined with graduated elastic compression stockings (GECS) [5, 6].

This study was performed in order to estimate the effect of the graduated elastic compression stockings on the clinical finding, complication and inflammatory and thrombotic markers in patients with superficial vein thrombophlebitis.

METHODS

This study was designed as a prospective study. It was conducted between January and July 2011, in the Clinic for Vascular and Endovascular Surgery of Clinical Centre of Serbia.

This study was approved by the institutional ethics committee, and written consent was obtained from all the patients for the publication of the paper and any accompanying images.

The criterion for inclusion in this study was the presence of acute or subacute SVT, located below-knee or distally above knee, but without propagation in deep or perforating veins. All the patients were clinically examined, and after that color duplex ultrasonography of the superficial and deep venous systems was performed. All the cases were treated as outpatients.

Coagulation profile has been examined in 10 patients. That included: protein C activity level, protein S activity level, activated protein C resistance, antithrombin III level and activity, and lupus anticoagulant antibodies.

Classification of patients into groups was made based on estimation of the potential risk for spreading of thrombosis and affecting deep or perforating veins. The main criterions were level of SVT, proximity of perforating veins, as well as obesity, immobility and physical inactivity. According to this, the patients were classified in group with greater risk (group I) or lesser risk (group II).

Patients in the first group were treated with low-molecular-weight heparin (LMWH) and in the second group with aspirin (ASA). Patients in both groups have also been treated with graduated elastic compression stockings (GECS), class I (18–21 mmHg) or class II (23–32 mmHg) depending on the CEAP classification. Patients with C0 and C1 stage were treated with class I, while patients with C2-C6 were treated with class II GECS.

The effect on the biochemical parameters, inflammatory and thrombotic markers (leukocyte number, D-dimmer, fibrinogen, C-reactive protein, alkaline phosphatase, creatine kinase, lactate dehydrogenase, gamma glutamyl transferase, alanine transaminase and aspartate transaminase) was estimated 14 days after the initial examination.

All cases in which rapid propagation or propagation toward sapheno-femoral venous junction was detected, were excluded from the study. Those patents usually were treated surgically (by performing ligation or crossectomy).

Data analysis was assessed using statistical evaluation in addition to various descriptive and analytic statistical methods (measures of central tendency, T-test, F-test and others).

RESULTS

SVT was detected in 60 patients: 36 women (aged from 23 to 75) and 24 men (aged from 18 to 76). Group I consisted of 28 and group II of 32 patients. No patient had a history of malignancy or was peripartum. No patient reported a history of trauma to the lower extremities. Patients` demographic characteristics are presented in Table 1.

Most patients were with unilateral, subacute, above knee located SVT. Table 2 presents clinical characteristics of SVT.

Regarding the typical clinical symptoms of SVT, patients were divided in four groups (Table 3). Patients in groups A, B and C had isolated erythema, pain or swelling. Majority of our patients (group D) had all symptoms associated.

Regarding the severity of SVT and risk factors, patients were divided into a greater risk group (Group I) and a lesser risk group (Group II). Patients in Group I were treated with low-molecular-weight heparin (LMWH), while patients in Group II were treated with aspirin (ASA). Patients were treated with two classes of GECS regarding the level of SVT. Patients with below knee SVT were treated with class I compression, whereas the patients with above knee SVT were treated with class II compression (Table 4).

Laboratory testing of inflammatory and thrombotic markers in patients with SVT was performed at the beginning and at the end of therapy (mean values are presented in Figure 1). All our patients with SVT had D-dimer value elevated over the baseline. Also, in all patients, increase in the values of inflammatory parameters, CRP and fibrinogen was observed.

After two-week therapy we have noticed that in most patients, 57 of them (95.5%), there was a subjective improvement, with stoppage of thrombosis progression.

In two patients treated with ASA and class I GECS there was thrombus propagation into Cockett perforating veins. Afterwards they were treated with LMWH, and eventually with oral anticoagulants.

One patient treated with LMWH and class II GECS has suffered proximal propagation of SVT through sapheno-femoral junction into common femoral vein. Two months later, that patient had a malignant process in the lungs established.

None of our patients has suffered pulmonary embolism.

DISCUSSION

Pharmacological and mechanical methods are used in the prevention and therapy of superficial and deep vein thrombosis. Pharmacological methods alter the blood coagulation, while mechanical methods include pneumatic compression and, specially, graduated elastic compression stockings. The exact mechanism how GECS function remains partially unknown. It is assumed that graded circumferential pressure, combined with activity of muscles, causes propulsion of blood from superficial to deep venous system through perforating veins [5–8].

SVT is characterized by formation of thrombi inside superficial veins, with involvement or occlusion of the lumen and inflammatory reaction along the venous path [9]. Inflammation and thrombosis are closely connected. Several clinical studies have examined the relation between levels of inflammatory markers and venous thrombosis. The common conclusion for all of them is that the risk of development of venous thrombosis is associated with elevations in plasma levels of CRP, interleukin 6 and IL-8, monocyte chemotactic protein 1, tumor necrosis factor alpha, and other. In the acute phase of SVT a majority of inflammatory markers were increased, particularly hsCRP, IL-6 and TNF-α. This finding was expected, since inflammation represents one of the basic pathogenetic mechanisms of SVT and is not limited only to the vessel wall, but usually affects the surrounding tissue as well [10].

One of the recent studies has shown that CRP is elevated in patients with acute DVT compared to controls, and that levels decline during the first few days of DVT treatment. Similar conclusions were made for IL-8 levels, leading to the conclusion that the thrombotic process produces a systemic inflammation. It is also believed that the decrement in levels of inflammatory factors is partly caused by heparin treatment (because of its anti-inflammatory effects) [11].

The fragments of the disintegrating fibrin in the clot are fibrin degradation products and one of them is D-dimer, which consists of variously sized pieces of cross-linked fibrin. Almost all patients with acute superficial or deep venous thrombosis have an elevated D-dimer level. An elevated D-dimer is associated with many illnesses, and therefore, is not specific for venous thromboembolism. D-dimer tests can have a high sensitivity which is useful because a normal test excludes the diagnosis of venous thromboembolism. D-dimer testing is most appropriate in the assessment of outpatients because the prevalence of disease and the likelihood of comorbidity are lower than in inpatient population, making a test of exclusion particularly valuable. Therefore, it is often used in conjunction with clinical probability scoring or color duplex ultrasonography to reduce the need for further imaging [11, 12].

In the literature there are not many papers that study the biochemical parameters of inflammation with the treatment of SVT. One of the earliest and most cited papers is a study in which DeTakats speculated that dormant infection in varicose veins was a factor in the development of thrombophlebitis. The paper mentions the experience with the treatment of 1,500 patients with resting infection using parenteral therapy [13].

All examined biochemical markers of inflammation (leukocyte number, CRP, and fibrinogen) were significantly reduced in group I with ASA therapy probably due to larger decrease in markers of inflammation with aspirin therapy, probably because of anti-inflammatory effects of aspirin.

The paper by Harenberg et al. has shown a decrease of D-dimer during UFH and LMWH treatment of deep vein thrombosis. Also, in patients with acute VTE, D-dimer was elevated and it decreased after three days of treatment with unfractionated heparin (UH) or with LMWH, but remained above the normal levels for the first week of treatment [14]. The

role of the pretest clinical probability score and/or the D-dimer concentration in the diagnostic management of thrombophlebitis and/or deep vein thrombosis (DVT) has been the objective of many studies and D-dimer testing is most appropriate in the assessment of outpatients because the prevalence of disease and the likelihood of comorbidity are lower than in inpatient populations, making a test of exclusion particularly valuable [15]. We found that no significant decrease of D-dimer was noted in both groups, but all values remained above the cut-off value.

Uncu et al. have evaluated the efficacy of LMWH compared to combined therapy of LMWH with non-steroidal anti-inflammatory drugs in treatment of SVT. They have found that significant improvements were achieved for both groups after the treatment in terms of all SVT symptoms. The results of their study suggest that the combined therapy of LMWH with an anti-inflammatory agent is more effective than LMWH, and that it might be an important option in the standard treatment of SVT [16].

Yasim et al. have evaluated serum concentrations of procoagulant, endothelial and oxidative stress markers in early primary varicose veins compared to healthy volunteers. They have investigated vascular endothelial marker levels and the effect of endothelial damage on coagulation parameters and vasodilator substances to determine metabolic markers of oxidative stress in patients with varicose veins and vascular endothelial damage caused by oxidative stress.

They have not found statistically significant difference between the study group and the control group. Their conclusion was that systemic increased oxidative stress seems not to be related to the early stages of chronic venous insufficiency [17].

Poredos has noted that inflammation has been accepted as a possible mechanism through which different factors cause formation of thrombus. They suggest that inflammation of the vein wall initiates thrombus formation, and that inflammation and coagulation systems are coupled by a common activation pathway. Therefore, the key event in the initiation of venous thrombus formation is most probably vein wall inflammation, but expected relationship between inflammatory markers as indicators of inflammatory process and clinical venous thromboembolism (VTE) has not been recognized yet. In their opinion C-reactive protein does not appear to be useful in predicting future venous thrombosis or to be

useful in the diagnosis of VTE [17]. In patients with SVT, levels of inflammatory markers are increased in the acute phase of the disease and most of the markers significantly decrease after 12 weeks. Also, levels of circulating inflammatory markers are negatively related to the recanalization rate of thrombosed superficial veins, which indicates that inflammation inhibits the resolution of thrombus and the recanalization of occluded veins [18].

According to the results of the present trial, which are supported by coherent data from the literature, it is not justified to recommend compression stockings in addition to LMWH and NSAIDs for prolonged time periods, but they might have beneficial effects early in the disease process [19].

Graduated elastic compression stockings provide the graded compression to the leg, highest at the level of ankle. They assist the calf muscle pump and reduce elevated venous tension and valvular reflux. The final effect is reduction of edema, improvement of tissue microcirculation and prevention of development of skin lesions. The same effect is documented with using knee-length and thigh-length compression stockings, however knee-length stockings are easier to apply and wear. Existing studies investigating the effect of GECS in patients with chronic venous disease have been graded as having low quality, while a Cochrane review concluded that there is insufficient, high quality evidence to determine whether or not compression stockings are effective as the sole and initial treatment of varicose veins [20].

Some studies also confirm that compression stocking therapy in the varicose vein wall may change the levels of biomarkers associated with vein insufficiency [21]. A higher level of class II GECS in our study led to a significant reduction of symptoms, equivalent to a greater effect on venous hypertension.

CONCLUSION

1. D-dimer is a successful diagnostic test in the initial phase and recovery phase.

2. In treatment of superficial venous thrombosis higher class of graduated compression therapy has stronger influence in decrement of inflammatory and thrombotic factors.

3. The prompt and adequately chosen therapy of superficial venous thrombosis allows stoppage and regression of thrombotic process.

4. Elastic bandage combined with a anticoagulant therapy with anti-inflammatory drugs is the method of choice.

Conflicts of interest: None declared.

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Table 1. Demographic characteristics

Characteristic		Group I	Group II
Sex	Men	11	13
	Women	17	19
Mean Age		48.29	51.69

Table 2. Superficial vein thrombophlebitis (SVT) characteristics

Characteristics		Group I	Group II
Topographic map	Above knee	9	23
	Below knee	19	9
Type	Acute SVT	10	18
	Subacute SVT	18	14

Table 3. Clinical presentation of superficial vein thrombophlebitis

Group	Symptoms	n (%)
A	Erythema or inflammation	7 (11.7)
B	Pain, induration and tenderness	9 (15)
C	Swelling and tissue warmth	18 (30)
D	Symptoms associated	26 (43.3)
Total		60 (100)

Table 4. Patients' groups regarding therapy and class of graduated elastic compression

Group	Therapy, compression	n (%)
Group I	LMWH + class I	14 (23.3)
	LMWH + class II	14 (23.3)
Group II	ASA + class I	16 (26.7)
	ASA + class II	16 (26.7)
Total		60 (100)

ASA – acetylsalicylic acid; LMWH – low-molecular-weight heparin

Figure 1. The graduated elastic compression stockings compression effects on inflammatory and thrombotic markers