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DIAGNOSIS AND TREATMENT OF VARICOSE VEINS COMPLICATED WITH ACUTE SUPERFICIAL VEIN THROMBOSIS

321.13 – SURGERY

Summary of Ph.D. Thesis in Medical Sciences

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CONTENT

CONCEPTUAL LANDMARKS OF THE RESEARCH

The actuality of the topic. The thrombosis in the superficial veins of the lower extremities is defined as superficial venous thrombosis (SVT). It usually occurs spontaneously, often in persons with pre-existing varicose veins; for those cases the term acute varicothrombophlebitis (VTPh) being also used [1]. The rate of SVT reaches 3-11% in the general population [2, 3], but the exact annual incidence of the disease seems to be significantly higher [4]. For instance, in the United States alone it is estimated to be about 125,000 cases per year. It is supposed that the prevalence of SVT may be approximately two times higher that of deep vein thrombosis (DVT) and pulmonary thromboembolism [5]. Even previously SVT was considered a clinical entity with a benign, self-limiting evolution, actually SVT is seen as a pathology with an unpredictable clinical course. Moreover, recent publications in the field highlight a surprisingly high rate of associated thromboembolic events in this category of patients [6, 7, 8].

Apparently, the diagnosis of VTPh in patients with varicose veins of the lower limbs does not present difficulties. It is based on objective assessment and anamnestic data collection – identification the signs of local inflammation, pain, presence of edema, hyperemia and induration at the level of varicose vein. However, clear data on the diagnostic accuracy of clinical evaluation in patients with VTPh are lacking in the scientific literature. In addition, the local clinical modifications do not reveal the real extension of the thrombotic process [3, 9]. In this context, Duplex ultrasound (DUS) is currently considered as an instrumental examination of choice for confirmation / exclusion of SVT; however, dynamic imaging evaluation, especially in the cohort of patients undergoing surgical treatment, is not a common practice yet [10, 11]. The results of such an examination, performed in all patients in order to monitor the entire venous system of the extremities with the identification of possible changes at different intervals of time from the beginning of the treatment, would be very useful in assessing the dynamics of the pathological process, comparing the efficacy and safety of different curative strategies.

The practical significance of the changes identified in laboratory analysis in patients with acute VTPh is not specified, and the role of routine testing and biomarkers derived from common lab tests remains to be studied supplementary. The diagnostic and prognostic value of other paraclinical examination, such as the determination of blood viscosity or the assessment of indices of thromboelastography has not been studied in practice in these patients so far.

Therapeutic strategy in acute VTPh remain controversial till now. On the one hand, many of the Eastern "schools of surgery" continue to advocate an aggressive approach in the acute phase of the process – emergent surgery, allowing to achieve two objectives at the same time: (1) the evacuation of thrombotic masses and, potentially, the prevention of thrombus extension to the deep veins and (2) the treatment of primary chronic venous disease. On the other hand, most guidelines

and recommendations regarding the management of SVT, including acute VTPh, established recently by various Western medical societies recommend conservative treatment as a curative option of choice [12, 13]. Taking into consideration the above mentioned, both the current role of emergent surgery and the adequate surgical volume in such conditions need to be specified.

With regard to anticoagulant medication, it is necessary to identify those curative regimens (prophylactic *vs*. intermediate *vs*. therapeutic doses) that are associated with the best clinical outcomes, both short-term and long-term clinical outcomes, associated with highest degree of patients' satisfaction. The optimal duration of conservative treatment according to the currently available recommendations differs significantly from actual medical practice, without taking into account the type of acute VTPh (with or without involvement of the trunk of great saphenous vein), as well as the individual thrombotic risk of the patient [12, 13, 14]. The significance of those factors in the selection of different therapeutic approaches should to be clarified.

The aim of study. Improvement of the results of treatment of acute varicothrombophlebitis (VTPh) of lower limbs basing on identification of risk factors associated with venous thromboembolism and determination of the criteria for selection of optimal curative approach.

Objectives of the study.

1. Study of current patterns in the management of patients with acute VTPh in Republic of Moldova and its comparison to international practice.

2. Analysis of correlations between clinical manifestations, imaging data and results of laboratory tests in patients with various types of acute VTPh.

3. Assessment of efficacy and safety of various protocols of medical treatment used in patients with acute VTPh and determination of factors with an impact upon the results of conservative treatment.

4. Evaluation of the risks associated with surgical treatment of VTPh in acute phase and determination of possibilities for reduction of the rate of postoperative complications.

5. Comparison of the results of surgical and medical treatment of acute VTPh basing on clinical and patient reported outcomes.

Scientific research methodology. The present study is non-randomized retro-prospective observational research with two independent groups of patients: the surgical group - including patients undergoing surgery of the superficial venous system during the acute phase of VTPh and the conservative group - patients who received pharmacological treatment. According to the research protocol, the duration of active surveillance of patients was 6 months from the time of diagnosis and treatment initiation, and included 4 control examinations performed at: 7-14 days (clinical and imaging), one month (clinical and imaging), 3 months (clinical), and 6 months (clinical). The primary treatment endpoint while assessing its efficacy included evaluation of superficial venous thrombosis

extension or recurrence; development of deep vein thrombosis and / or symptomatic pulmonary embolism during the follow-up period. The obtained data were statistically analyzed, and the obtained results allowed to draw the study conclusions. The research protocol was approved by the Research Ethics Committee of Nicolae Testemitanu State University of Medicine and Pharmacy of the Republic of Moldova (no. 38, 12.02.2018).

The novelty and scientific originality of the obtained results. For the first time, by application of an electronic questionnaire a cross-sectional descriptive cohort study on acute VTPh management at the national level was conducted, and it demonstrated the major differences between the applied treatment options, as well as the differences between current international practices and recommendations of current clinical guidelines.

It has been shown that the selection of a specific therapeutic approach by the surgeon in case of acute VTPh is currently empirical, and the factors with a real impact on the decision-making process have been identified by application of multivariate analysis.

For the first time, the predictive value of the local clinical signs of VTPh (area of skin hyperemia and perivenous inflammatory infiltrate) has been established in the initial differentiation of forms with and without the involvement of the saphenous trunk.

Based on DUS data and quantitative analysis of thrombotic mass echogenicity, the centripetal evolution (from the level of varicose tributary veins towards the trunk) of superficial venous thrombosis with secondary involvement of the saphenous trunk associated with accelerated thrombus growth was confirmed.

For the first time, the importance of markers of systemic inflammation in patients with acute VTPh was studied and the association between C-reactive protein level (CRP) level and platelet / lymphocyte ratio (PLR) with the thrombosis extension and the probability of the proximal saphenous trunk involvement was demonstrated.

It has been established that in patients with acute VTPh and a positive D-dimer test, the length, volume and rate of progression of superficial venous thrombosis are significantly higher in comparison with the same parameters in patients with a negative test.

For the first time, by thromboelastography, the haemostatic balance disorder with a tendency towards structural hypercoagulability (intensification of blood cells aggregation, amplification of the fibrin polymerization process and increased density of fibrin-thrombocyte thrombus) was demonstrated in patients with acute VTPh, significantly expressed in patients with involvement of the saphenofemoral junction.

For the first time, a significant difference in the estimated values of blood viscosity was established in patients diagnosed with acute VTPh during the hottest time of the year *vs* the coldest period of the year, which may explain the seasonal variations in the incidence of this disease.

The low risk of postoperative venous thromboembolism associated with emergent surgical treatment of non-truncal forms of VTPh and forms with limited involvement of the saphenous trunk has been demonstrated, and risk factors for surgical wound complications have been identified.

For the first time, using the Cox regression statistical model, the true impact of the individual's risk for thromboembolic complications (estimated by the Caprini score) on the results of anticoagulant treatment in acute VTPh was demonstrated.

No statistically significant difference was identified between the rates of venous thromboembolic events after surgical and conservative treatment of acute VTPh during the 6-month follow-up period, and the superiority of the results reported by the patients in the group treated with anticoagulants was determined.

Scientific-applied problem solved. The scientific-applied problem solved in the thesis consists in identification of the risk factors associated with the negative outcomes of the surgical and conservative treatment of acute VTPh, allowing modification of the management paradigm of this pathology by scientifically based selection of the optimal curative approach in each individual case.

Theoretical significance. The implementation of the retro-prospective observational study comparing the results of the surgical and conservative treatment in acute VTPh allowed to fill the existing research gaps, mentioned in meta-analysis and international systematic review. The current studies in the field demonstrated the greatest variability of available therapeutic options currently used for the treatment of superficial venous thrombosis and the empirical nature of clinical decision making. The analysis of the interrelationships between clinical data, imaging data and laboratory test results demonstrated the association of extensive forms with saphenofemoral junction involvement with haemostatic balance disorders and systemic inflammatory reaction, indicating the necessity for anticoagulant treatment. The comparable efficacy of the surgical and conservative approach in the treatment of acute VTPh demonstrated in the study and the identification of risk factors for treatment failure will serve as a basis for optimization of curative approach. New directions for further studies in this area have been identified.

The applicative value of the research. Taking into consideration the study results, the diagnostic value of the local clinical signs of acute VTPh was specified, and the importance of USD examination and laboratory tests (PLR, CRP, and D-dimers) in the elaboration of the treatment plan was demonstrated. The obtained results scientifically proved the necessity for modification of the current therapeutic approach by preferential use of anticoagulant treatment in case of extensive superficial venous thrombosis (with involvement of saphenofemoral junction) and application of surgical treatment in the acute phase of the disease exclusively for patients with non-truncal or limited distal involvement of the saphenous trunk. The identification of risk factors associated with

postoperative complications or failure of anticoagulant treatment of acute VTPh will allow the implementation of appropriate corrective measures.

Implementation of research results. Taking into consideration the results the present research, new diagnosis and treatment methods for patients with acute VTPh were implemented in the Surgery Departments of two medical institutions, namely the PHI Municipal Clinical Hospital "Gheorghe Paladi" and the Institute of Emergency Medicine, Chisinau. Likewise, the results of the scientific study (interpretation of clinical data with prognosis the type of acute VTPh depending on the location of thrombotic masses, development of new concepts related to curative tactics) were applied in the teaching process at the Department of General Surgery - Semiology no. 3, *Nicolae Testemitanu* State University of Medicine and Pharmacy of the Republic of Moldova.

Approval of the scientific results. The results of the research were presented and discussed within the following scientific forums: "Another Phlebology-2017" Congress (Budapest, Hungary, 2017), Международный молодежный медицинский конгресс (Санкт-Петербург, Россия, 2017), Annual scientific conference of young specialists from PHI Institute of Emergency Medicine "Performances and perspectives in medical and surgical emergencies" (Chisinau, Moldova, 2017), Interdisciplinary Conference with international participation "Medical Days of Severin and Timoc", 9th edition, (Drobeta-Turnu Severin, Romania, 2018), 19th Meeting of the European Venous Forum (Athens, Greece, 2018), National Phlebology Conference with International Participation "New Trends in Phlebology" (Timișoara, Romania, 2018), the 7th International Medical Congress for Students and Young Doctors – MedEspera (Chisinau, Moldova, 2018), Annual scientific conference of young specialists from PHI Institute of Emergency Medicine "Performances and perspectives in medical and surgical emergencies" (Chisinau, Moldova, 2018), the 13th Congress of the Association of Surgeons " Nicolae Anestiadi "and the 3rd Congress of the "Society of Endoscopy, Minimally Invasive Surgery and Ultrasonography "V.M.Guțu" from the Republic of Moldova (Chisinau, Moldova, 2019), the Congress of *Nicolae Testemitanu* State University of Medicine and Pharmacy of the Republic of Moldova dedicated to the 75th Anniversary (Chisinau , Moldova, 2020), the 8th International Medical Congress for Students and Young Doctors – MedEspera (Chisinau, 2020), Leading Innovative Vascular Education (LIVE) 2020 Symposium - (Larissa, Greece, 2020), Leipzig Interventional Course *LINC* (Leipzig, Germany, 2021), meeting of the Association of Surgeons "Nicolae Anestiadi" (Chisinau, 2021).

The results of the study reflected in this thesis were discussed and approved at the meeting of the Department of General Surgery - Semiology no. 3 of *Nicolae Testemitanu* State University of Medicine and Pharmacy of the Republic Moldova (minutes no. 12 from 22.04.2022), and Scientific Profile Seminar "Surgery" (321.13), "Pediatric surgery" (321.14), "Urology and andrology" (321.22) (minutes no.2 from 25.05.2022).

Publications on the thesis topic. 20 scientific papers were published on the topic of the thesis, including: articles in international journals indexed in SCOPUS / PubMed - 3, articles in reviewed international journals - 1, articles in journals from the National Register of profile journals - 3, materials / abstracts at international conferences (abroad) - 8, materials / abstracts at national conferences (organized in the Republic of Moldova) - 5.

Summary of the thesis' chapters. The thesis includes annotations in Romanian, Russian and English, list of abbreviations, introduction, 5 chapters, general conclusions, and practical recommendations. The list of bibliographic sources includes 241 sources, annexes, the statement on the assumption of responsibility, the author's CV. The introduction part of the paper reflects the actuality and scientific-applied importance of the problem studied in the thesis, the purpose, objectives, scientific novelty, theoretical importance, applicative value of the paper, and the approval of the study results.

Keywords: superficial venous thrombosis, acute varicothrombophlebitis, venous thromboembolism, duplex ultrasound, conservative treatment, surgical treatment.

THESIS CONTENT

1. ACUTE VARICOTROMBOPHLEBITIS: CURENT ASPECTS OF DIAGNOSIS AND TREATMENT

In this chapter contemporary views on the etiopathogenesis and classification of superficial venous thrombosis in patients with varicose veins are reflected. The controversies and unresolved issues related to the clinical, laboratory and instrumental diagnosis of acute VTPh, as well as the treatment option in the respective pathology are presented.

2. CLINICAL DATA AND RESEARCH METHODS

2.1. Study design and general characteristics of the research group

The study is based on evaluation the data of 190 patients diagnosed with acute VTTh of the lower limbs, examined and treated in the clinical sections of the Department of General Surgery - Semiology no. 3 of the *Nicolae Testemitanu* State University of Medicine and Pharmacy of the Republic of Moldova (Department of Vascular Surgery from the Institute of Emergency Medicine and Surgical Departments from the PHI Municipal Clinical Hospital "Gheorghe Paladi", Chisinau). The clinical data were accumulated over a period of four years: 2016 – 2020. According to the inclusion criteria, the following patients were enrolled: (1) age ≥ 18 years; (2) the first episode of acute lower limb VTPh, confirmed by clinical examination and DUS; (3) the duration of clinical manifestations ≥ 14 days; (4) the signed informed consent for participation in the study. The following exclusion criteria were applied: (1) the presence of the ipsi- or contralateral DVT, confirmed by DUS;

(2) the presence of superficial venous thrombosis in absence of varicose veins; (3) thrombosis developed following the application of some therapeutic methods as laser ablation or sclerotherapy; (4) administration of anticoagulant therapy for other medical indications (e.g., atrial fibrillation, heart valve prostheses); (5) VTPh complicated with infection of soft tissue.

The presented study was observational and included two groups of patients: **the surgical group** - patients undergoing surgery on the superficial venous system during the acute period of VTPh and **the conservative group** - patients treated by the administration of pharmacological treatment. The selection of the therapeutic approach for each patient was made taking into consideration the surgeon's opinion or the opinion of the medical council and the patient's preferences. The patient's assignment to any of the study groups was performed *post factum* and was not influenced by the research protocol. At the end of the enrolment procedure, 190 patients were included in the study: 105 - in the conservative group and 85 - in the surgical group. It should be noted that in 5 (4.7%) patients in the conservative group acute VTPh was diagnosed simultaneously in the both lower limbs.

The duration of active surveillance of patients was 6 months and included 4 control examinations: at 7-14 days (clinical and imaging), one month (clinical and imaging), 3 months (clinical) and 6 months (clinical). At 3 to 6 months, DUS was performed selectively - in case of clinical condition worsened. At the end of the *follow-up period*, the participants were informed about the necessity to contact investigators in case of appearance of the symptoms suggestive for VTPh recurrence. In this way, the total duration period of patients' surveillance ranged from 6 to 54 months, with a mean value of 31 (25-75% IQR 18-43) months.

In the general group, the rate of female patients was 127/190 (66.8%), being higher in extreme age groups: 83.3% - patients up to 30 years and 75% - patients over 70 years. The patients' age ranged from 21 to 82 years, mean value – 60 (25-75% IQR 49-66) years. According to the CEAP classification of chronic venous diseases 76 (38.9%) lower limbs were assigned to the clinical level C2; 107 (54.8%) - clinical level C3 and 12 (6.1%) - level C4. Obesity was diagnosed in 74 (38.9%) patients, and the mean BMI was 28.6 (25-75% IQR 25.4-31.3). The current study included 11 (5.7%) patients with acute VTPh diagnosed during pregnancy and 4 (2.1%) - in the postpartum period.

2.2. Diagnostic and therapeutic methods applied in the study

The diagnosis of VTPh was established based on clinical manifestations and confirmed by DUS. The presence of a hypo- or hyperechoic area incompressible with the transducer, circular in the transverse and rectangular in the longitudinal plane, served as the ultrasonographic confirmation criteria of the VTPh. The distribution of the thrombotic process in the superficial venous system was described according to anatomical principle (involvement of the great saphenous vein or the small saphenous vein) and according to the Verrel-Steckmeier classification: type I - thrombosis in the

safenian trunk with no extension to saphenofemoral or saphenopopliteal junction; type II - thrombosis of the safenian trunk up to the level of saphenofemoral or saphenopopliteal junction; type III - thrombosis of the saphenous trunk with prolapse of thrombotic masses through the saphenofemoral or saphenopopliteal junction in the common femoral or popliteal vein respectively. Types II and III were defined as "periosteal VTPh", and cases of isolated thrombosis of varicose tributary veins – "non-truncal VTPh". On DUS the total length and the total volume of the thrombus was estimated; also the growth rate in correlation to the days from the onset of VTPh were recorded. For the quantitative evaluation of the degree of echogenicity of the thrombotic masses, the analysis of digital ultrasound images was performed with the determination of the "GSM" values (*gray scale median*).

Laboratory tests included: complete blood count, liver tests, urea and creatinine levels, blood sugar, serum protein, basic coagulation parameters, ABO typing and Rhesus factor. A number of indices were derived from the test results: neutrophil-lymphocyte ratio (NLR), platelet-lymphocyte ratio (PLR), lymphocyte-monocyte ratio (LMR), blood viscosity in high-velocity conditions (VS_{HSR}) and low-velocity conditions (VS_{LSR}) of shearing. The value of C-reactive protein (CRP), the D-dimer test, and the parameters of piezothromboelastography (pTEG) were determined in a number of patients.

Surgical treatment included classical surgical techniques applied in 76 patients, and 9 (10.5%) patients underwent laser ablation of the safenian trunk. Anticoagulation therapy were administered to 105 patients in the conservative group. The selection of a specific antithrombotic agent, as well as its dose and duration of administration, were not specified by the research protocol and based on the drug's availability, the clinical decision of the physician, and patient compliance. The dose of the anticoagulant was defined as "prophylactic" or "curative" according to the manufacturer's recommendations, and the "intermediate" dose was defined as 50-70% of the "curative". Concomitant medication in patients in the conservative group included: non-steroidal anti-inflammatory drugs – in 65 (61.9%) patients and antibacterial preparations – in 7 (6.6%) cases.

2.3. Used definitions, methods of scientific research and statistical analysis

The composite rate of cases of extension or recurrence of TVPh was established as the *primary endpoint* in evaluating the effectiveness of the treatment; development of DVT (symptomatic or asymptomatic) and / or PE (symptomatic) during treatment and *follow-up period*. The extension of thrombosis has been defined as an increase in the length of thrombotic masses by at least 4 cm. Cases associated with *de novo* development of thrombosis in any part of the superficial venous system of the lower limbs or the reappearance of thrombotic masses after the complete initial recanalization of the thrombotic vein associated with characteristic clinical signs were considered as VTPh recurrence. The following parameters were used as *secondary endpoints* in estimation the effectiveness of the treatment: (1) regression of clinical signs of VTPh; (2) modifications of the clinical severity of chronic

venous insufficiency (CEAP clinical level, VCSS score); (3) the patient's quality of life modifications (ABC-V questionnaire); (4) the degree of patient satisfaction with the results of applied treatment (VAS, Likert scale). The rate of surgical wound complications was considered as final point in assessment the treatment safety in patients treated surgically, and in those treated conservatively - the rate of bleeding complications.

The data obtained in the study were subjected to statistical analysis. The independent samples t test or the Mann-Whitney U test were used to compare the quantitative data. The ANOVA or Kruskal-Wallis test were used to assess the difference between mean values from 3 or more groups. The categorical variables were compared using the Fischer's exact test or the $\chi 2$ test. The results were considered statistically significant if $p < 0.05$.

For measurement of the association between a binary variable and a predictive continuous or binary variable, the odds ratio (OR) and / or relative risk (RR) were calculated. The degree of correlation was determined by the Pearson or Spearman coefficient. The evaluation of the impact of several independent variables on a dichotomous result was performed in two stages: (1) by univariate analysis (simple logistic regression) the variables with potential impact were determined ($p < 0.2$); (2) these factors were tested by multiple logistic regression model.

The Kaplan-Meier curves were used for analysis of the incidence of primary outcome of the treatment efficacy during follow-up period, and the *log-rank* (Mantel-Cox) test was used for groups comparison. In order to evaluate the impact of one or more variables on the curves, Cox proportional hazard regression model was used, the results being presented as hazard ratio (HR - *hazard ratio*) with a 95% confidence interval.

The diagnostic importance of the clinical and paraclinical criteria (clinical signs, lab tests, imaging methods) was evaluated by calculating the sensitivity, specificity, positive and negative predictive values using standard formulas. The comparison of the diagnostic value of several criteria was performed by construction of the ROC curves (*receiver operating characteristic*) and determining the AUC (*area under curve*).

3. ANALYSIS OF THE CURRENT NATIONAL TRENDS IN THE MANAGEMENT OF PATIENTS WITH ACUTE VARICOTROMBOPHLEPHITIS

3.1. The results of the survey conducted among the members of the Association of Surgeons "Nicolae Anestiadi" from the Republic of Moldova

In order to highlight the current trends in the diagnosis and treatment of acute VTPh at the national level, a survey of the members of the Association of Surgeons "Nicolae Anestiadi" was conducted. The questionnaire included 15 questions and a description of 4 clinical cases of VTPh,

accompanied by photographic images of the affected limb and the DUS result presented graphically. Complete responses were recorded from 102 (31.1%) of participants.

In 76 (74.5%) cases, local surgeons reported that they perform mandatory DUS in all patients with acute VTPh. Only 8 (7.8%) participants indicated that they never use ultrasonography in the management of this pathology. Almost half of the participants – 52 (50.9%) confirmed that they use just one type of treatment of VTPh in their daily practice, the most common - prescribing anticoagulation therapy. Two curative approaches are used by 37 (36.2%) participants, and 13 (12.7%) physicians reported application of all three available options (Figure 1). It is important to mention that almost 1/3 of surgeons – 30 (29.41%), do not use anticoagulation therapy at all in the treatment of VTPh. On the other hand, the surgical treatment is used as curative care by more than half of the doctors - 61 (59.8%).

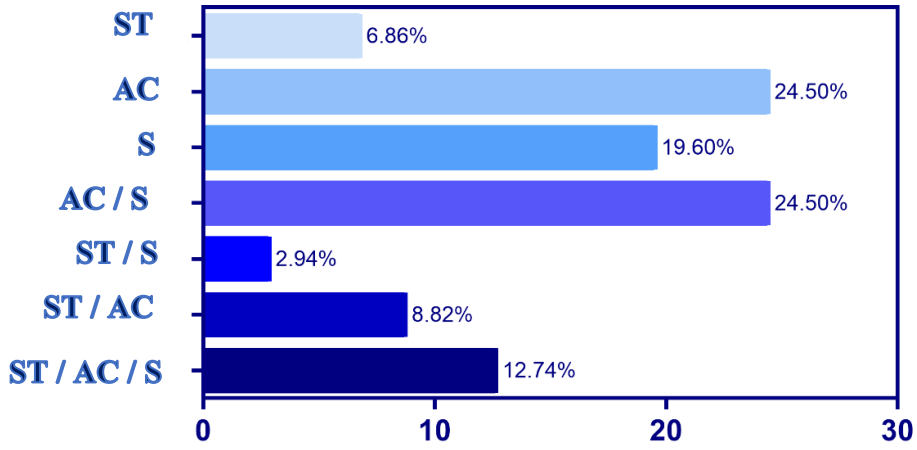

Figure 1. Structure of curative options for acute VTPh, used by local surgeons in practice (ST - symptomatic treatment, AC - anticoagulant treatment, S - surgery)

According to the questionnaires' results, heparin sodium is used in most cases - 91 (89.2%), followed by fractionated heparin – 77 (75.4%) and rivaroxaban – 43 (42.1%). Regarding the indicated dose of anticoagulants used for the treatment of acute VTPh, 57 (55.8%) participants mentioned they prescribe curative doses, 19 (18.6%) – intermediate doses, and 14 (13.7%) – prophylactic doses (12 participants omitted the question). The number of surgeons who indicated anticoagulant treatment for a period of up to a month and those who recommended administration of these medicines for a month or more was the same – 45 (44.1%) practitioners, respectively. Among doctors who prefer a short term treatment 13 (12.7%) recommend anticoagulants for one week, 17 (16.6%) – for 2 weeks and 15 (14.7%) – for 3 weeks. The response rate with the indication for prescribing anticoagulants for one month or more was similar: 23.52% and 20.58%, respectively.

Of particular interest is highlighting the preferred therapeutic approach selected by survey participants according to type of VTPh (Table 1).

Table 1. Therapeutic approaches preferred by participants in the survey of the four clinical vignettes of superficial vein thrombosis (n = 102)

Preferred therapeutic approach	Case 1 Thrombosis of GSV tributaries	Case 2 Thrombosis of GSV trunk at the knee level	Case 3 Thrombosis of GSV trunk up to SFJ	Case 4 Thrombosis of SSV trunk and SPJ
Surgery in acute phase	44 (43,1%)	61 (59,8%)	74 (72,5%)†	58 (56,8%)
Anticoagulation for <1 month	20 (19,6%)	26 (25,4%)	17 (16,6%)	6 (5,8%)
Anticoagulation for ≥1 month	10 (9,8%)	7 (6,8%)	9 (8,8%)	33 (32,3%)*
Symptomatic treatment	28 (27,4%)**	8 (7,8%)	2 (1,9%)	5 (4,9%)
* - $p < 0,001$ *vs* all other cases. † - $p < 0,05$ *vs* Case 1 and Case 4				

According to the data from the table, the surgery was considered the most appropriate option in all the cases presented by the respondents. The number of specialists who advocated for surgical treatment was significantly higher in acute VTPh type II *vs* isolated thrombosis of tributary varicose veins and VTPh type I, III. It reflects the traditional surgical concept regarding the necessity for mechanical disconnection of the SFJ / SPJ in the case when the thrombus apex reaches deep veins. Respectively, in case of non-axial VTPh the rate of physicians who prefer symptomatic treatment without the administration of anticoagulants was significantly higher.

3.2. Determinants of decision-making regarding treatment approach in acute varicothrombophlebitis

The patients included in the study were treated by 16 surgeons, health professionals in the medical institutions where the research was conducted. Fifty percent of physicians at the time of completion of the study had 10 years or more of practical experience. The total number of VTPh cases treated over the four-year period per one specialist ranged from 1 to 52, with an average of 5 (25-75% IQR 2-14) patients. Personal experience of treating ten or more cases of acute VTPh had 6 (37.5%) surgeons. It was observed the surgical treatment in the acute phase of thrombosis was significantly more frequently applied by doctors with a higher professional experience: 69 (55.6%) *vs* 16 (24.2%) cases of VTPh treated surgically by surgeons with experience in the field up to 10 years ($p <0.001$). No statistically significant difference was established in the selection of surgical treatment based on the number of cases treated overall during the study.

Assessing the impact of demographic factors on the decision regarding the curative approach included the patient's gender and age, BMI, and the presence of associated diseases. The female patients constituted the majority in both groups: 52/85 (61.1%) in the surgical group and 75/105 (71.4%) in the conservative group, the difference being statistically insignificant. Both the mean age of the patients and the rate of people older than 60 years were similar in both groups: 60 (25-75% IQR 45.5-68) years and 52 (49.5%) in the conservative group *vs* 59 (25-75% IQR 50.5-64.5) years

and 34 (40%) in the surgical group. Patients who underwent surgery had BMI significantly higher than those treated conservatively: 29.9 (25-75% IQR 27-32.6) *vs* 27.6 (25-75% IQR 24, 8-30.4), respectively (p <0.01). The rate of patients with grade I-III obesity was also higher among operated patients – 42 (49.41%) compared to the value recorded in the conservative group - 32 (30.47%), (p <0,05). The average number of concomitant illnesses per patient and the severity of comorbidities expressed by the Charlson index did not differ statistically between the conservative and surgical groups. Thus, we can conclude that except for the nutritional status, the demographic factors did not influence the therapeutic approach, and the studied groups are comparable according to the basic characteristics.

Theoretically, the most important role in clinical decision-making on the patient's treatment option could be the "VTPh-specific" factors: the severity of the clinical signs and symptoms of SVT and the DUS results regarding the extension of the thrombotic process. When evaluating the expression of the typical local signs of VTPh, exclusively pain syndrome showed a statistically significant difference between the conservative and surgical group, the mean value of VAS being 7 (25-75% IQR 5-8) and 7 (25-75% IQR 6-8), respectively (P = 0.04). Both the surface area of the hyperemia and the area of the inflammatory infiltrate did not differ statistically: 69 (25-75% IQR 34.1-125.5) cm^2 and 33.4 (25-75% IQR 17.5-66, 7) cm^2 - in the conservative group *vs* 80.6 (25-75% IQR 38.7-116.8) cm^2 and 31.9 (25-75% IQR 14.9-49.9) cm^2 - in the surgical group (p > 0,05). The duration of thrombotic event to hospital admission was similar: 6.5 (25-75% IQR 5-8) days and 7 (25-75% IQR 5-8) days, respectively (p > 0.05). The comparison of the DUS results performed before the initiation of treatment is presented in Table 2.

Table 2. Duplex ultrasound characteristics of thrombotic process in patients with conservative group and surgical group

Index	Conservative group (n = 110)	Surgical group (n = 85)	p values
VTPh bilateral, n (%)	5 (4,76%)	0 (0%)	NS
Involvement of GSV system, n (%)	84 (76,3%)	66 (77,64%)	NS
Involvement of SSV system, n (%)	12 (10,9%)	6 (7,05%)	NS
Non-truncal VTPh, n (%)	68 (61,81%)	44 (51,76%)	NS
VTPh type I Verrel-Steckmeier, n (%)	15 (13,63%)	26 (30,58%)	< 0,01
VTPh type II Verrel-Steckmeier, n (%)	19 (17,27%)	10 (11,76%)	NS
VTPh type III Verrel-Steckmeier, n (%)	7 (6,36%)	4 (4,7%)	NS
Thrombus length (cm)	30 (IQR 20-50)	30 (IQR 15-50)	NS
Thrombus to JSF/JSP distance (cm)	30 (IQR 10-45)	25 (IQR 15-60)	NS
Thrombus protrusion through JSF/JSP (mm)	10 (IQR 6-25)	15 (IQR 7-33,5)	NS

According to the presented data, the anatomical localization of the thrombotic process in the superficial venous system did not differ statistically. Cases with simultaneous involvement of both lower limbs were treated exclusively conservatively, but due to the small number of observations the

difference was not statistically significant. Only a truly higher rate of cases of thrombosis of the thrombosis remotely from JSF / JSP in the group of patients undergoing urgent or delayed surgery was determined. Therefore, the univariate analysis demonstrated only the following factors have statistically significant impact: years of professional experience, the patient's nutritional status, the severity of the VTPh-induced pain syndrome and the thrombus localization in the safenian trunk. Three of these four factors proved their statistical significance under a binary logistic regression model (Table 3).

Table 3. Factors impacting the clinical decision in favour of surgical treatment of acute VTPh (multivariate analysis)

The analysed factor	Regression coefficient (B)	p values	Probability rate (OR)
Surgical experience ≥ 10 years	1,272	< 0,0001	3,56 (95% CI 1,77-7,17)
Obesity gr. I-III	0,805	< 0,05	2,23 (95% CI 1,16-4,27)
Severity of pain according to VAS	0,146	= 0,097	1,15 (95% CI 0,97-1,37)
VTPh type I Verrel-Steckmeier	0,838	< 0,05	2,31 (95% CI 1,05-5,04)

The obtained data confirm that the strongest influence on the doctor's decision to operate a patient with acute VTPh has the "doctor-specific" factor – the duration of professional activity that indirectly reflects the personal experience of the surgeon. Experience of more than 10 years increases the probability of surgical treatment during the acute phase of thrombosis by 3.5 times. In order to reduce the degree of subjectivity of clinical decisions and to optimize the treatment of acute VTPh, development and implementation in daily practice of the scientifically argued national standards for the management of patients with SVT are necessary.

4. IMPORTANCE OF CLINICAL, IMAGING AND LABORATORY EXAMINATION IN PATIENTS WITH ACUTE VARICOTHROMBOPHLEPHITIS

4.1. Analysis of the clinical manifestations particularities of acute varicothrombophlebitis

In the cohort of patients with acute VTPh, the constant clinical symptom was local pain, manifested by all patients during primary examination. The severity of the pain, assessed using the VAS scale at the time of including the patient in the study, ranged from 2 to 10, with a median value of 7 (25-75% IQR 5-8) points. The pain syndrome was more severe during the first days after the onset of VTPh with a tendency to subsequent spontaneous diminution. The median value of the VAS scale recorded in the first week of the disease was significantly higher compared to that value at day 7-10: 8 (25-75% IQR 7-8) *vs* 4 (25-75% IQR 3-6), respectively (p <0.0001). Correlation analysis

demonstrated a strong inverse association between VTPh duration and pain severity according to VAS: r_s = -0.62 (95% CI -0.7 - -0.52), p <0.0001.

Skin hyperemia above the thrombosed superficial veins was present in 155/195 (79.4%) lower limbs with acute VTPh. In 31 (15.8%) cases the area of cutaneous hyperemia was localized or extended to the thigh, that according to the common opinion indicates the development of thrombosis in the proximal segment of GSV. Comparing these data with the DUS results it was demonstrated in most of cases - 24/31 (77.41%) thrombi were localized in the anterior accessory saphenous vein of the thigh (5 cases), at the level of other tributaries of the GSV on the thigh (9 cases) or in the tributaries on the thigh and in the saphenous trunk below the knee joint (10 cases). Thus, the presence of skin hyperemia at the thigh is not associated with a high probability of thrombosis type II - III Verrel-Steckmeier. Even more important is that the hyperemia of the thigh skin was observed during the primary examination only in 6 (20.6%) from total 29 cases of thrombosis of the proximal trunk of the GSV. Therefore, the presence of skin hyperemia on the thigh in the patient with acute VTPh can neither confirm nor infirm the involvement of the proximal saphenous trunk.

The surface area of skin hyperemia determined by the analysis of digital images of the affected limb varied from 8.2 to 364.6 cm^2, the median value 72.8 (25-75% IQR 36.5-123.9) cm^2. In patients with thrombosis of the saphenous trunk with any median length of the surface of hyperemia exceeded the respective value determined in patients with non-truncal VTPh was - 104.9 (25-75% IQR 60.45-158.5) cm^2 *vs* 65.01 (25 -75% IQR 29.2-97.3) cm^2, p = 0.001. The rate of truncal VTPh cases was significantly higher in the subgroup of patients with hyperemia area ≥ 100 cm^2 - 18/30 (60%) in comparison to 18/59 (30.5%) in patients with less extensive hyperemia (P = 0,01). Thus, the determination during the clinical examination of patients with VTPh of areas of cutaneous hyperemia greater than 100 cm^2 is associated with an almost double risk of involvement of the GSV trunk (RR – 1.96 [95% CI 1.21-3.18] , p <0.01). Opposite to the severity of the pain syndrome, a moderate and even strong positive correlation was established between the hyperemia surface and the length and, correspondingly, the volume of the thrombus in the superficial venous system evaluated by ultrasonography: r_s = 0.45 (95% CI 0.26-0, 61) and r_s = 0.56 (95% CI 0.39-0.69), respectively (p <0.0001 in both cases).

Soft tissue induration at the level of thrombosed vein was an almost constant sign, being discovered in 187 (95.8%) cases. The surface area of the skin induration varied from 2.9 to 208.4 cm2, on average 33.1 (25-75% IQR 16.75-61.95) cm^2. As in the case of hyperemia, the area of soft tissue induration was significantly bigger in the patients with thrombosis of the GSV trunk in comparison with patients with non-truncal forms of VTPh: 45.6 (25-75% IQR 30.35-75, 3) cm^2 vs. 27.4 (25-75% IQR 13.3-48.5) cm^2, p <0.001.

4.2. Ultrasound characteristics of superficial venous thrombosis and clinical-imaging correlations

The anatomical distribution of acute VTPh cases according to DUS data was as follows: isolated impairment of the GSV system – 163 (83.5%), including thrombosis at the level of anterior accessory saphenous veins - 13 lower limbs; isolated involvement of the SSV – 18 (9.2%); simultaneous involvement of the GSV and SSV – 3 (1.5%) and non- saphenous veins involvement – 11 (5.6%) cases. In the general group of patients, the number of cases of non-trunk VTPh was higher, 114 cases from 195 observations (58.4%). According to DUS data from 81 lower limbs with saphenous trunk thrombosis type I VTPh was diagnosed in 41 (21.02%) cases, type II – in 29 (14.87%), and type III – in 11 (5.64 %). Thus, thrombotic masses at the level or near the anatomical junctions with deep veins were discovered in one-fifth of all clinical observations.

The total length of the thrombus varied from 2.5 to 90 cm, and the volume of thrombosis – from 0.44 cm^3 to 220.6 cm^3, the median values of the respective parameters being 30 (25-75% IQR 20-50) cm and, corresponding, 16.29 (25-75% IQR 7.63-31.42) cm^3. In patients with thrombosis in the saphenous trunk without the involvement of SFJ / SPJ, the distance between the thrombotic apex and the junction ranged from 6 to 80 cm, the mean value being 33.5 ± 22.7 (95% CI 30-37) cm. Out of these 29 cases classified as type II in 12 (41.3%) patients the thrombosis' limit was localized exactly at the border with deep veins. In the other 17 observations, the average distance between the thrombus and the junction was 2 (25-75% IQR 1-3.5) cm. In patients with acute VTPh type III, the length of the thrombus' apex protrusion in the lumen of the femoral or popliteal vein was on average 1 (25-75% IQR 0.6-2.5) cm, the maximum recorded extension – 3.8 cm.

There is a commonly accepted empirical view regarding the development of SVT in dilated varicose tributaries where there are local conditions that promote thrombogenesis: venous stasis and alteration of vascular endothelium. In current research, the rate of non-truncal VTPh was almost 60%. Moreover, cases of isolated thrombosis of the saphenous trunk (without thrombosis at the level of varicose veins) were detected extremely rarely - only in 3 (1.53%) observations. The determination of the rate of thrombotic masses growth, calculated as the ratio between the days from the onset of the disease and the total volume of the thrombus, highlighted the association of this criterion with the type of VTPh. The rate of thrombus formation increased progressively from 3.7 ± 5.95 (95% CI 2.59-4.81) cm^3 / day in cases of non-trunk thrombosis to 6.47 ± 7.79 (95%). CI 3.98-8.96) cm^3 / day in patients with VTPh type I and reached the maximum value of 8.75 ± 8.86 (95% CI 5.87-11.62) cm^3 / day in patients with periosteal thrombosis. Differences in thrombogenesis rate showed statistical significance for truncated and non-truncated forms of thrombosis ($p < 0.001$, ANOVA). Thus, we can observe that the involvement of the saphenous trunk in thrombosis and its progression in the proximal direction is associated with accelerated thrombogenesis. Performing the analysis of DUS images, it

was demonstrated that the thrombotic masses in varicose tributaries have a significantly higher degree of echogenicity in comparison to the thrombus in the saphenous trunk - 69.28 ± 17.2 (95% CI 64.39-74.17) *vs* 46.4 ± 14.84 (95% CI 42.18-50.62) GSM units, respectively (p <0.0001). GSM values determined at the level of varicose veins showed a strong positive correlation (r_s = 0.79 [95% CI 0.65-0.87], p <0.0001) with the time from the onset of thrombosis, while the echogenicity of the thrombus in the saphenous trunk showed a moderate correlation with this variable (r_s = 0.42 [95% CI 0.16-0.63], p <0.01). Respectively, in the linear regression model used to evaluate the dynamics of the modification of the echogenicity median depending on the duration of VTPh, the determination coefficient R^2 was three times higher for the "tributaries" curve: 0.54 *vs* 0.18 - for the "trunk" curve. The elaborated statistical models confirmed the progressive increase of thrombus echogenicity in the superficial veins day to day from the beginning of the disease: by +3.43 ± 0.45 GSM units in tributaries (p <0.0001) and by +1.75 ± 0, 52 GSM units in the trunk (p <0.01), (figure 2).

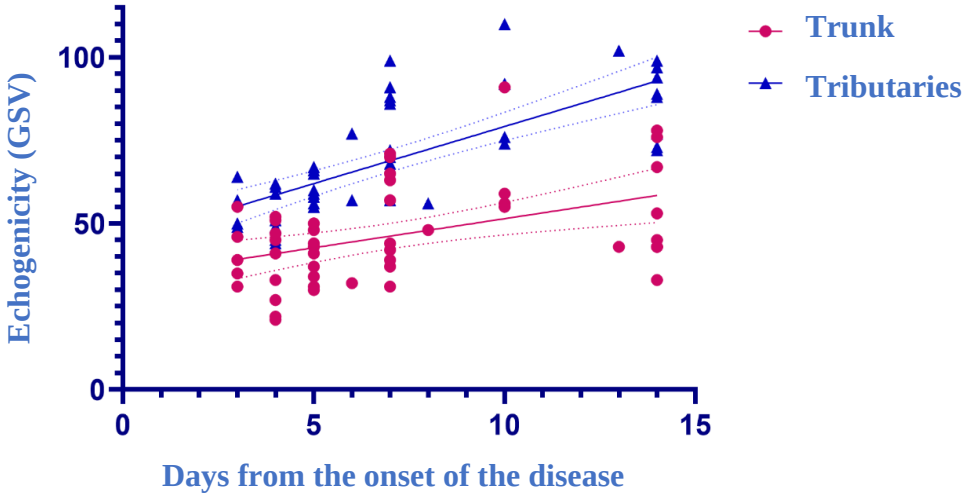

Figure 2. Linear regression lines (95% CI) showing increased echogenicity of thrombotic masses in varicose tributaries and saphenous trunk as a function of duration disease

From clinical point of view, the obtained data can be interpreted as evidence of the initial formation of thrombotic masses in the varicose veins with their eventual extension and secondary involvement of the saphenous trunk. Weaker correlation of GSM values for the saphenous trunk with the days after the disease onset indicates that after the development of the thrombus in varicose veins, the subsequent progression of the thrombotic process has individual variability. In other words, both the risk of truncal form of VTPh development and the time required for the thrombus to pass from the tributary vein level to the trunk with its extension along the saphenous axis differ from one patient to another, being influenced by factors that should be determined as follows.

4.3. The role of laboratory tests in assessing inflammatory response and blood clotting disorders in acute varicothrombophlebitis

The level of CRP was determined at the moment of patient inclusion in the study in 45 cases. The determined values ranged from 0 mg/L (detection limit) to 165 mg/L, the median value being 7 (25-75% IQR 3-30) mg/L. Values > 5 mg/L of CRP were recorded in 28 (62.2%) patients, and values higher than 10 mg/L - in 20 (44.4%). Comparative analysis showed a gradual increase in CRP values in subgroups of patients with different types of VTPh: from 5.5 (25-75% IQR 2-16) mg/L in non-trunk thrombosis to 7 (25-75% IQR 4-38) mg/L in type I Verrel-Steckmeier; 26.5 (25-75% IQR 12.75-97.25) mg/L in type II and up to 28 (25-75% IQR 8-48) mg/L in type III. The median CRP level for type II-III VTPh was significantly higher in comparison to type I VTPh and non-trunk form – 26.5 (25-75% IQR 11-65.25) *vs* 6 (25-75 % IQR 3-18.7) mg/L, $p < 0.05$. In patients with CRP within the normal range, the rate of VTPh type II-III was only 4% in comparison with 25% in patients with CRP ≥ 10 mg/L, and the rate of thrombus growth was 2 times lower – 2.33 (25-75% IQR 0.74-8.18) cm^3/day and 5.74 (25-75% IQR 1.82-15.02) cm^3/day, respectively.

It is important to mention that the CRP level showed almost no correlation with the time interval from the disease onset (r_s = -0.06 [95% CI -0.35 - 0.24], p> 0.05), and the values of this inflammatory marker determined repeatedly over 14 days did not show a significant decrease – 6.5 (25-75% IQR 4.75-33.25) mg/L *vs* initial value of 7 (25-75% IQR 3-30) mg/L, ($p > 0.05$). In this regard, we can observe the systemic inflammatory reaction in case of VTPh does not tend to decrease in the acute phase of thrombosis and is present for a long time.

The values of the inflammation markers derived from the routine complete blood count have not been evaluated in the cohort of patients with VTPh so far. Within the research the correlation between the parameters that characterize the extension of superficial thrombosis (thrombus length in the GSV trunk, total volume of thrombotic masses) and the values of CRP, NLR, PLR and SII was evaluated (Table 4).

Table 4. Correlation between the extent of superficial venous thrombosis and the level of markers of systemic inflammation

Inflammatory markers	The degree of thrombosis extension	
	The length of thrombus in GSV trunk (mm)	The total volume of thrombus (cm^3)
CRP (mg/L)	r_s = 0,30, p > 0,5 (95% CI -0,2-0,68)	r_s = 0,48, p < 0,001 (95% CI 0,2-0,68)
NLR*	r_s = 0,22, p > 0,5 (95% CI -0,11-0,51)	r_s = 0,05, p > 0,5 (95% CI -0,14-0,24)
PLR*	r_s = 0,44, p < 0,01 (95% CI 0,13-0,66)	r_s = 0,001, p > 0,5 (95% CI -0,19-0,19)
* – from the analysis were excluded patients with associated diseases that according to the literature influence the value of the studied markers (oncological diseases, acute infections, chronic liver disease, pregnancy and lactation)		

According to the table data, only the PCR level demonstrated a moderate positive correlation with the total volume of thrombosis in the superficial venous system, and only the PLR value had a moderate positive correlation, statistically significant, with thrombus length in the GSV trunk. It was found that in patients with PLR ≤ 160 the rate of periosteal venous thrombosis is significantly lower in comparison with the rate in patients with increased PLR - 11/86 (12.7%) *vs* 13/39 (33.3%), P = 0.01When the PLR values are high, the probability of involvement of the saphenous trunk in thrombosis is almost threefold: RR = 2.6 (95% CI 1.28-5.29), p < 0.01. The evaluation of the discriminatory power of the PLR index > 160 in the diagnosis of periosteal forms of SVT revealed an AUC value equal to 0.68 (95% CI 0.54-0.82), p < 0.01.

In current research, the level of D-dimers at the time of patient inclusion in the study was determined in 42 cases. The test results ranged from 69-2866 ng / mL, and the median was 535 (25-75% IQR 268.5-917) ng/mL. Of interest is the subgroup of patients with D-dimer values greater than 500 ng/mL - *cut-off* limit for the positive diagnosis of DVT. The data presented in figure 3 demonstrate that the median value of thrombus length is 2 times, and thrombosis' volume 4 times higher in patients with D-dimer level ≥ 500 ng / mL in comparison with the patients with negative test. The thrombus growth' rate was also significantly higher when the D-dimer test is positive – 6.76 (25-75% IQR 2.03-8.98) cm^3/day *vs* only 1.72 (25-75% IQR 0.56-3.84) cm^3/day in patients with negative test (p < 0.05).

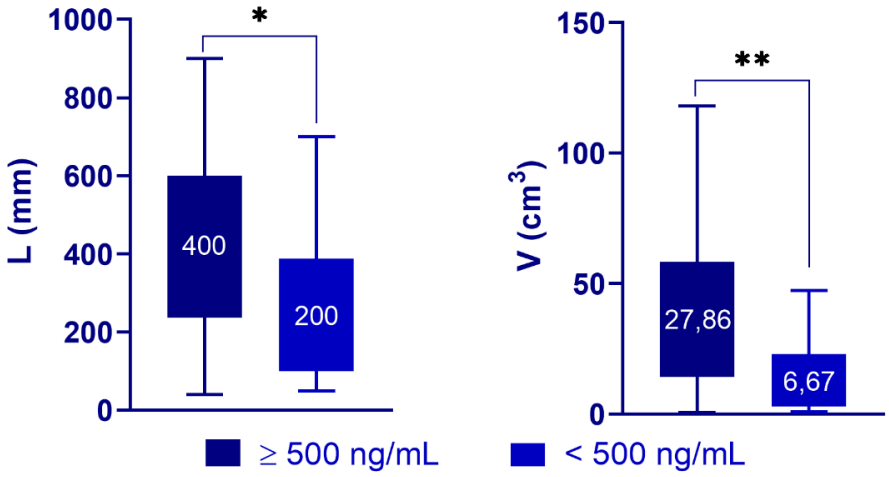

Figure 3. Comparison of the length and total volume of thrombotic masses in patients with acute VTPh and positive or negative D-dimer test (L - length, V - volume, * - p <0.05, ** - p <0.01)

The median value of D-dimers level was significantly higher in patients with saphenous trunk involvement in comparison to the cases of non-trunk VTPh: 804 (25-75% IQR 365.8-1815) ng/mL *vs* 355 (25-75% IQR 202-662.8) ng/mL, respectively (p < 0.01). Similarly, the level of D-dimers in patients with periosteal VTPh exceeded the respective index in cases of type I VTPh and the isolated impairment of varicose tributaries: 876 (25-75% IQR 611-1637) ng/mL *vs* 395 (25-75% IQR 216-

710) ng/mL, respectively (p <0.05). Corresponding, D-dimer values showed a moderate positive correlation with thrombus length (r_s = 0.41 [95% CI 0.12-0.64], p < 0.01) and volume (r_s = 0.45 [95 % CI 0.16-0.67], p < 0.01).

Evaluation of pTEG parameters showed a tendency towards global amplification of the haemostatic potential, reflected by the value of the TCI index (total coagulation intensity) significantly higher in comparison with the reference values - 24.04 ± 9.15 (95% CI 21.26-26, 82). It was established that in the general group of patients with VTPh the mean value of parameter A5 (maximum amplitude of the pTEG curve) was also higher than the upper limit of the normal value – 650.4 ± 131.9 (95% CI 610.3 -690.5) and demonstrated a true positive correlation with ultrasound characteristics of VTPh: r_s = 0.55 with thrombus length; r_s = 0.46 with thrombus volume and r_s = 0.44 with rate of thrombus volume increase (p < 0.01).

The indices CCI (contact coagulation intensity) and CPI (clot polymerization intensity) demonstrated a true positive correlation with the degree of thrombotic masses expansion (r_s = 0.39 and r_s = 0.53, respectively). Thus, the tendency for hypercoagulability in patients with VTPh is manifested by intensified aggregation of major blood elements (↑ CCI), amplification of the fibrin polymerization process (↑ CPI) and as a result – increased density of fibrin-thrombocyte thrombus (↑ A5). By evaluating the results of the correlational analysis, the values of CCI, CPI and A5 were estimated comparatively in patients with periosteal thrombosis and those with non-trunk VTPh or type I VTPh (figure 4).

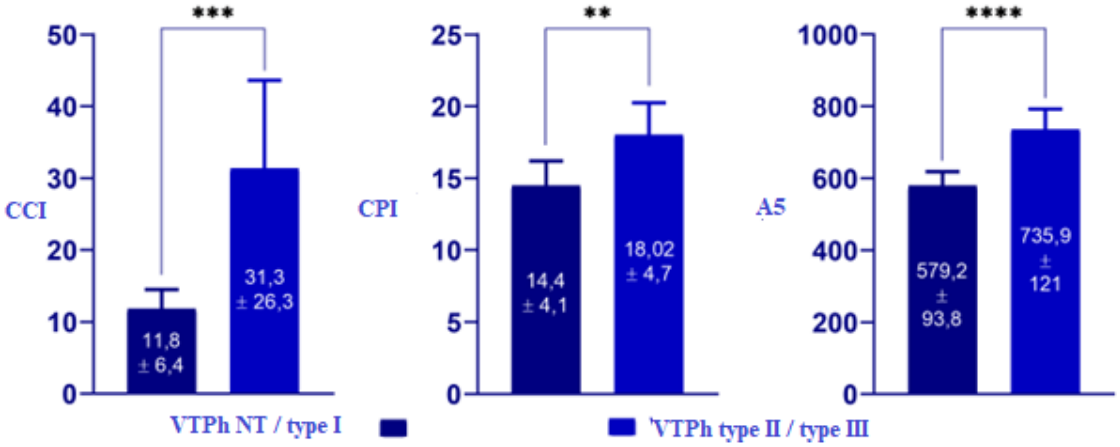

Figure 4. Comparison of CCI, CPI and A5 index of pTEG in patients with non-trunk acute VTPh (NT) and type I vs VTPh type II-III (** - p <0.01, *** - p <0.001 , **** - p <0.0001)

The presented graphics demonstrate the existence of significant differences between the mean values of the indices CCI, CPI and A5 in the subgroup of patients with isolated thrombosis of the tributaries or involvement of the distal saphenous trunk in comparison with the patients with periostial VTPh. It is possible to affirm the pTEG results demonstrated the pro-thrombotic status of patients

with acute VTPh. The tendency towards hypercoagulation in patients with type II-III VTPh can also be observed and by visual analysis of pTEG curves in which the deviation of the curve to the left and upwards is discovered (figure 5).

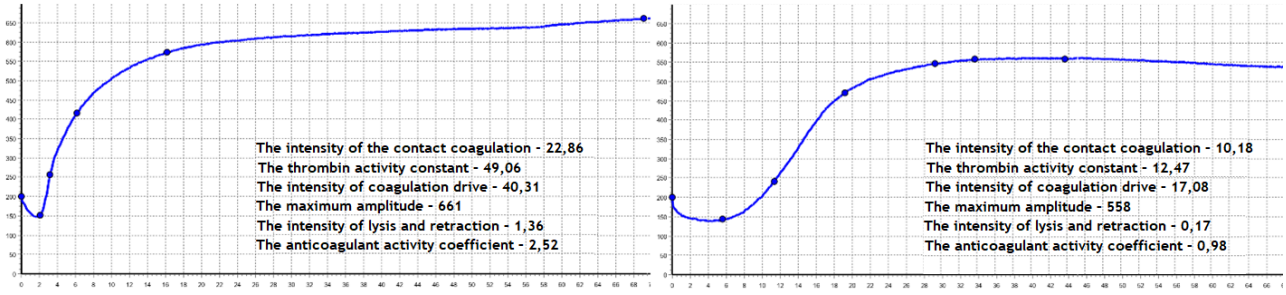

Figure 5. pTEG curves recorded patients with Verrel-Steckmeier type II VTPh (left) and isolated thrombosis of varicose tributaries (right)

In the current study, the true influence of seasonal factor on blood viscosity values was observed. In patients with acute VTPh hospitalized between October and March, the values of VS_{HSR} and VS_{LSR} were significantly higher than in patients hospitalized during the warm season of the year: 16.62 ± 1.11 (95% CI 16.29-16.95) cP *vs* 15.89 ± 0.99 (95% CI 15.46-16.32) cP and 49.39 ± 22.86 (95% CI 42.6-56.18) cP *vs* 34.45 ± 22, 03 (95% CI 24.92-43.98) cP, respectively ($p < 0.05$ in both cases). The inverse correlation of viscosity with ambient temperature may explain seasonal variations in the addressability of patients with VTPh.

5. RESULTS OF DIFFERENT THERAPEUTIC APPROACHES APPLIED FOR ACUTE VARICOTROMBOPHLEBITIS

5.1. Evaluation of the surgical treatment results and determination the risk factors for postoperative complications

Surgical treatment in the acute period of VTPh was performed in 85 patients. Most patients – 54 (63.5%) were operated during the first 24 hours after hospitalization, the median time being 24 (25-75% IQR 24-48) hours. At the time of surgery, the median time period from the onset of thrombosis was 7 (25-75% IQR 5-11) days, and 44 (51.7%) patients were operated during the first week of the disease. Perioperative administration of anticoagulants was used in all patients with a median duration of 4 (25-75% IQR 3-6) days. Fractioned heparins were used: prophylactic doses – 62 (72.9%) and intermediate – 23 (27%) patients. Antibiotic prophylaxis was performed in 72 (84.7%) patients.

In the majority of cases – 75 (88.2%) patients, surgery was performed with spinal anesthesia; local infiltration anesthesia was used in 10 (11.7%) patients. The classic interventions (crossectomy

+ saphenous *stripping* + phlebectomy) were performed in 69.4% (59/85) of the observations. The detailed information regarding the performed interventions is presented in figure 6.

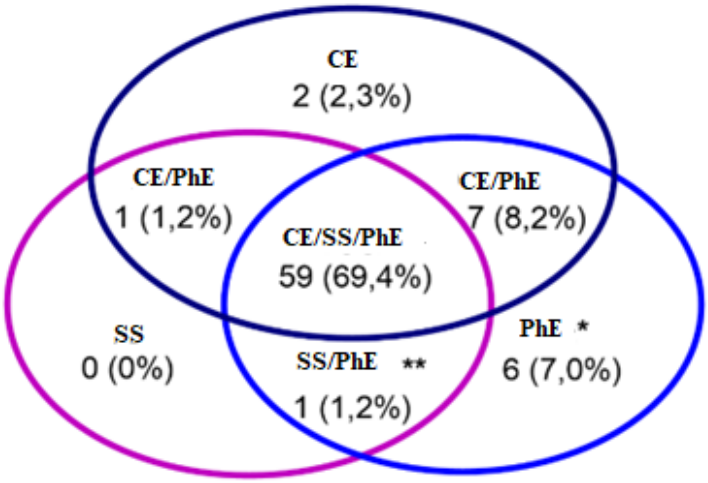

Figure 6. Structure of open surgeries performed in patients with acute VTPh (CE - crossectomy, SS - saphenous stripping, PhE - phlebectomy; * - in 2 cases PhE was associated with AASV disconnection and in one case - with disconnection of the incompetent perforator on thigh, ** - thrombosis of the remaining Saphenous trunk in patients with recurrent varicose veins)

Thrombectomy at the level of SFJ during crossectomy was required in 5 (5.8%) cases. The Muller procedure was the preferred technique for phlebectomy of varicose tributaries, performed in 69 (81.1%) operated patients and was preceded by phlebocentesis for evacuation of the intraluminal thrombus. Only in 10 (11.7%) patients the thrombosed varicose veins were removed by separate incisions after Narrath or removed *en-bloc*. Laser intravenous ablation was performed in 9 (10.5%) patients. In 7 (8.2%) cases the intravenous intervention was anticipated by the SFJ/SPJ disconnection by open approach. The length of the saphenous segment subjected to ablation varied from 7 cm to 30 cm (mean value: 19.7 ± 7.6 cm), and the median value of the thermal energy density was 88.5 (25-75% IQR 59.05 -95.3) J/cm, being similar with that used in patients with uncomplicated varicose veins.

During the follow-up period, 9 (10.58%) cases of postoperative DVT were diagnosed. In 8 (9.41%) cases, thrombosis was asymptomatic, being detected on control DUS performed at 1-2 weeks after the surgery. In all cases DVT was distal (tibial, gastrocnemian, soleal veins). In one at 3 months after the intervention, characteristic clinical signs of DVT appeared, and during DUS popliteal vein thrombosis was confirmed. During follow-up period, the symptomatic PE rate was zero. Of particular practical importance is the identification of factors associated with thromboembolic venous complications after surgical treatment of acute VTPh. Initially by univariate analysis, the clinical,

instrumental, laboratory data and therapeutic particularities were compared (table 5). The case of DVT development in 3 months after the intervention was excluded from the analysis

Table 5. Determination of factors associated with postoperative DVT in patients with acute VTPh (surgical group)

Index*	DVT p/o (+) (n = 8)	DVT p/o (-) (n = 76)	p-values
Age (years)	63 (56,5-67,5)	59 (50,25-63)	NS
Male, n (%)	4 (50%)	27 (35,5%)	NS
BMI (kg/m^2)	30,41 (23,46-31,39)	29,77 (26,92-32,86)	NS
Charlson index	2 (1-2)	2 (0-2)	NS
Caprini score	6 (5-6)	5,5 (5-6)	NS
Truncal VTPh, n (%)	8 (100%)	32 (42,1%)	< 0,01
Total thrombus length (cm)	62,5 (51,2-70,0)	28,0 (15,0-40,0)	< 0,0001
Total thrombus volume (cm^3)	62,64 (26,33-163,7)	14,53 (7,73-28,87)	< 0,001
Thrombus growth rate (cm^3/zi)	8,08 (6,1-14,52)	2,52 (0,92-6,43)	< 0,01
PLR index	105 (66,48-169,8)	127,9 (105,3-168,3)	NS
CCI parameter of pTEG	39,81 ± 42,71	12,87 ± 10,49	= 0,05
A5 parameter of pTEG	774,2 ± 130,1	601,3 ± 128,8	< 0,05
Thromboprophylaxis duration (days)	5 (3,25-8)	4 (3-5,75)	NS
Prophylactic doses of heparin	6 (75%)	55 (72,3%)	NS
„Classic" intervention	7 (87,5%)	55 (72,3%)	NS
* – media ± SD or median with (25-75% IQR) are presented			

The data presented in the table demonstrate the existence of a true association between the development of postoperative DVT and the hypercoagulation status of the patient, indirectly reflected by the expansion, volume and growth rate of thrombotic masses significantly higher, and directly by increase of the main parameters of pTEG. Whole blood viscosity (adjusted to plasma fibrinogen concentration) was also higher in the subgroup with postoperative thrombosis: VS_{HSR} = 17.74 ± 1.96 and VS_{LSH} = 71.25 ± 41.83 *vs* VS_{HSR} = 17.07 ± 1.02 and VS_{LSH} = 60.14 ± 21.63 – in patients without DVT, but due to the limited number of observations in the first group the difference was not statistically significant. The clinical and demographic characteristics of the patients, the particularities of the performed treatment (dose and duration of heparin administration), as well as the type or volume of surgery did not influence the risk of postoperative DVT.

According to multiple logistic regression, thrombosis length proved to be a true and independent risk factor for development of postoperative DVT – P = 0.002, OR = 1.01 (95% CI 1.0-1.02). Using the coordinates of the ROC curve, the *cut-off* value of the thrombosis length with the best discriminatory power was determined being < 45 cm and provided very good predictive performance: AUC – 0.9 (95% CI 0.83-0.98); sensitivity – 100% (95% CI 63-100); specificity – 76.3% (95% CI 64.9 - 85.6); negative predictive value – 100%. From practical point of view, this would mean that in patients with acute VTPh in whom the total length of thrombosis is less than 45

cm, the risk of postoperative DVT is minimal – the probability being lower with 98% than in patients with more extensive thrombosis (OR = 0.02 [95% Cl 0.001-0.33], P = 0.007).

Another possible complication of VTPh surgical treatment is the disorder of the surgical wound regeneration process. In the current study, wound complications were diagnosed in 6 (7.05%) patients, and the multiple logistic regression model identified three risk factors with a significant influence on the complication rate (Table 6).

Table 6. Impact of surgical treatment features on the risk of wound complications in patients with acute VTPh (multiple logistic regression)

Risk Factors	OR	95% CI	p - values
Interval "VTPh onset - surgery"	1,31	1,0-1,72	= 0,045
Refuse from antibacterial prophylaxis	11,49	1,1-120,26	= 0,041
Phlebectomy by non-Muller technique*	11,24	1,1-115,23	= 0,042
* – Narrath technique or *en-bloc* excision of thrombosed varicose veins			

Thus, performing the intervention during the first week after the disease onset, the use of antibiotic prophylaxis and the usage of mini-phlebectomy techniques can help reduce the rate of wound complications in patients operated for acute VTPh.

5.2. The effectiveness of the conservative approach and the determination of optimal anticoagulant treatment regimens

In the study, antithrombotic medication was used as the basic method for the treatment of VTPh in 105 (55.2%) patients (110 lower limbs). Most patients – 65 (61.9%) received only one type of anticoagulant preparations during the entire course of treatment: rivaroxaban in 34 (32.3%) cases or fractioned heparin in 31 (29.5%) cases. The detailed characteristic of the used medications is shown in figure 7.

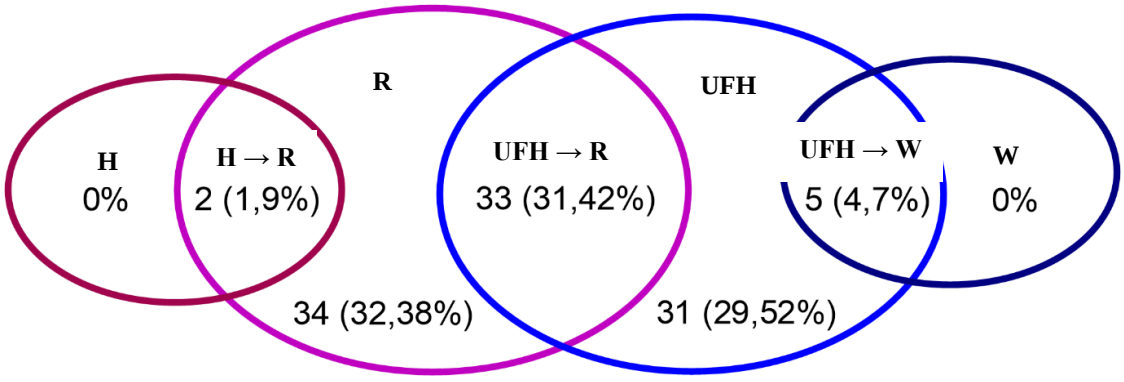

Figure 7. Anticoagulant preparations used for the conservative treatment of acute VTPh (H - heparin, UFH - unfractionated heparin, R - rivaroxaban, W - warfarin)

Prophylactic doses of anticoagulant drugs were administered in 13 (12.3%) cases; intermediate in 87 (82.8%), and therapeutic only in 5 (4.7%) patients. The duration of anticoagulant treatment was 28 (25-75% IQR 20.7-35.2) days. During 6 months of follow-up the rate of primary treatment efficacy endpoint was 5.4% (6/110 cases): extension of VTPh – 3 patients (at 2 weeks – one case and at one month – 2 cases); symptomatic recurrence of VTPh – 2 patients (at 4 and 5 months, respectively) and development of DVT at the level of the popliteal vein in one patient (at one month). No symptomatic cases of PE were reported. During the follow-up period the volume of thrombotic masses decreased from 16.3 (25-75% IQR 7.1-29.5) cm^3 at the time of inclusion in the study to 11.9 (25-75% IQR 6.3-21, 8) cm^3 at the first control examination and to 4.4 (25-75% IQR 1.7-7.6) cm^3 at one month. The reduction of thrombus volume after 2 weeks was on average equal to 4.3 cm^3 (by 26.5%) statistically insignificant and conversely, by the end of the first month the volume decreased approximately 3 times (by 72.7%) in comparison to previous values ($p < 0.0001$). Thus, it is observed that in 2 weeks the anticoagulation treatment prevents the extension of SVT, but by this term the process of resolution the thrombotic masses have an insignificant degree.

The duration of anticoagulation therapy influenced on the results of conservative treatment of acute VTPh. In all 6 cases of the primary endpoint ("treatment failure") anticoagulants were used for a period < 6 weeks, and in 3 of these cases for < 3 weeks. The reduction in both the length and volume of thrombotic masses evaluated at 30 days was higher when using anticoagulants for > 2 weeks in comparison to shorter period of anticoagulation therapy: 20% (25-75% IQR 10-38.3) *vs* 38.7% (25-75% IQR 23.5-52.9) and 45.9% (25-75% IQR 34.7-67.1) *vs* 79.5% (25-75% IQR 61-87.4), respectively ($p < 0.05$).

The dose of anticoagulant had a lesser impact on the evolution of thrombosis. The reduction in the length and volume of thrombotic masses in patients treated with prophylactic doses for ≥ 6 weeks was not lower to that recorded in patients treated with intermediate doses: 40% (25-75% IQR 40-75) and 73.3% (25 -75% IQR 60.2-93.8) *vs* 22.2% (25-75% IQR 16.7-50) and 73.4% (25-75% IQR 58.5-88.6), respectively ($p > 0.05$). Thus, when the treatment duration is equal to 6 weeks, the reduction of the anticoagulant dose from the intermediate to the prophylactic one does not negatively influence the resolution of the thrombotic process.

The type of anticoagulant drug did not show an association with the treatment results. In patients treated with fractionated heparin the rate of treatment failure was 2 (6.4%) cases, in patients treated with rivaroxaban – 2 (5.8%) and in the case of consecutive use of different medicines – 2 (5%), ($p > 0.05$). In the regression model the risk rate of treatment failure was HR = 0.78 (95% CI 0.14-4.26) for fractionated heparins; HR = 0.88 (95% CI 0.12-6.29) for rivaroxaban and HR = 1.2 (95% CI 0.17-8.54) for combinations of medicines.

It is very important to mention that the conservative treatment demonstrated sufficient efficacy in the subgroup of 26 patients with thrombosis at the level of SFJ/SPJ or with thrombus protrusion in the deep veins. At 1-2 weeks and one month from the beginning of the treatment, the retraction of the thrombus apex was found to be 18.1 ± 5.1 mm and 37.8 ± 19.5 mm, respectively. Thus, in 23 (88.4%) patients with periosteal thrombosis by the end of the surveillance period, the presence of thrombotic masses in the deep veins or close by SFJ/SPJ was not recorded. In order to determine the risk factors for conservative treatment failure in the multiple regression model factors with a potential impact on the results were included (Table 7).

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Table 7. Risk factors for failure of conservative treatment of VTPh during 6-month surveillance (Cox proportional hazard model)

Risk Factors	HR	95% CI	p-values
Duration of anticoagulant administration (days)	0,91	0,83-0,99	= 0,039
Caprini score	1,86	1,1-3,14	= 0,019
Non-truncal form of VTPh*	0,24	0,04-1,35	= 0,1
* – *vs* VTPh with involvement of the saphenous trunk			

Extension the duration of anticoagulant treatment was associated with a 9% reduction of the risk of VTE per day of treatment and vice versa - increasing the Caprini score with one point doubles the probability of treatment failure. Using the ROC curves the *cut-off* value of the score was established – 4 points, below this value the probability rate of VTE after the treatment end is almost zero.

During the monitoring period, haemorrhagic complications were registered in 6 (5.7%) patients in the form of gingival haemorrhages (3 cases), epistaxis (1 case) or macrohematuria (2 cases). The intensity of anticoagulation treatment and the type of drug administered did not truly influence the rate of bleeding complications. The median value of the haemorrhagic risk score VTE-BLEED was significantly higher in patients with haemorrhagic complications – 2.75 (25-75% IQR 1.75-3.75) points *vs* 1.0 (25 -75% IQR 0-1.5) points in those without haemorrhage ($p < 0.001$).

5.3. Comparison of the efficacy, safety and patient-reported outcomes of surgical and conservative treatment

In the present study, the cumulative indices of venous thromboembolism recorded during 6 months was 10.5% (9 from 85 lower limbs) in the surgical group and 5.4% (6 from 110 lower limbs) in the conservative group. Analysis of Kaplan-Meier curves did not show a statistically significant difference between the compared groups, and the value of risk rate of treatment failure was 0.48 (95% CI 0.17-1.34) for the conservative group *vs* the surgical group (P = 0,16), (figure 8)

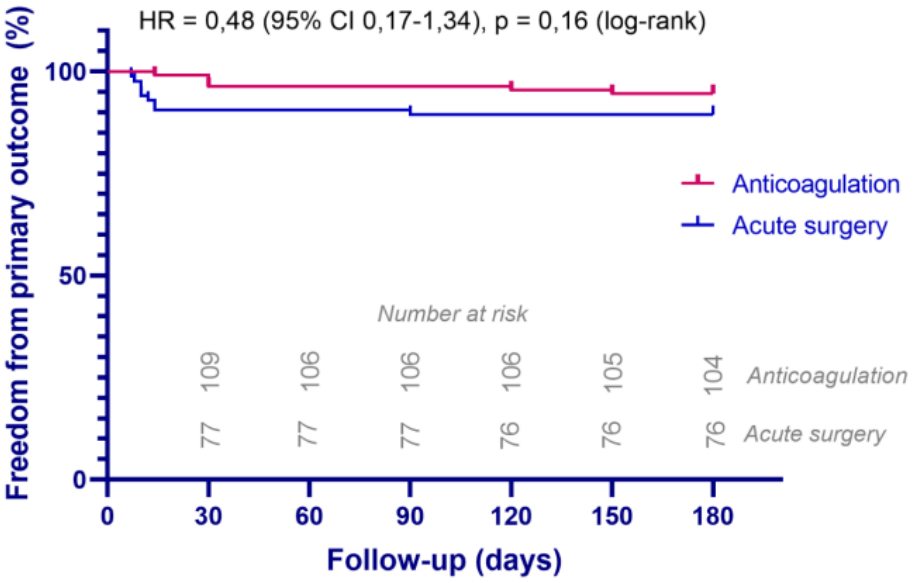

Figure 8. Kaplan-Meier curves for the cumulative incidence of VTE over 6 months in the groups of conservatively treated (n = 110) and surgically treated (n = 85) VTPh patients

In order to identify the factors associated with the risk of treatment failure in the general cohort of patients with acute VTPh, a multivariate Cox regression analysis was performed. According to the results obtained in the current research and taking into account the data presented in similar studies in the statistical model 5 potential risk factors were included (Table 8).

Table 8. Risk factors for failure of VTPh treatment during 6-month surveillance in the general cohort of patients (Cox proportional hazard model)

Risk Factors	HR	95% CI	p-values
Surgical treatment (*vs* conservative)	0,59	0,18-1,92	= 0,38
Total length of thrombosis (cm)	1,02	1,0-1,05	= 0,02
Caprini score	1,42	0,95-2,12	= 0,08
Patient age (years)	1,02	0,97-1,07	= 0,4
Male (*vs* female)	0,68	0,23-1,98	= 0,47

It has been demonstrated that performing surgery is not an independent risk factor for VTE. Identically, demographic characteristics did not have a true influence on treatment outcomes. The unique independent risk factor is the extension of VTPh, the probability of treatment failure (regardless of its type) being higher by 2% for every centimetre of length of the thrombosed venous segment.

In the general cohort of patients, the mean value of VCSS score decreased from 3.6 ± 1.2 (95% CI 3.4-3.8) points initially to 1.7 ± 1.4 (95% CI 1.4-.9) points in the control evaluation ($p < 0.0001$). The decrease of the score was significant in both groups: from 3.6 ± 1.2 (95% CI 3.45-3.82)

to 0.6 ± 0.7 (95% CI 0.5-0.83) points in the surgical group and from 3.7 ± 1.2 (95% CI 3.4-4) to 2.9 ± 1 (95% CI 2.6-3.1) points in the conservative group (p < 0,0001). The decrease in VCSS was greater in operated patients – on average by 2.8 ± 0.8 (95% CI 2.6-3) points *vs* only 0.8 ± 0.8 (95% CI 0.6-1) after conservative treatment (p < 0.001). At the end of the surveillance, the clinical class C0-C1 was registered in 73 (85.8%) patients from the surgical group and in none of the patients from the conservative group. The assessment of the treatment results of acute VTPh by the patients is reflected in table 9.

Table 9. Assessment of acute VTPh treatment results by patients in the surgical and conservative group ("patient reported outcomes")

Index	Surgical group (n = 85)	Conservative group (n = 105)	p-values
Initial ABC-V score (points)	40,2 ± 7,81 (95% CI 36,74-43,67)	37,25 ± 9,28 (95% CI 33,65-40,85)	NS
ABC-V score after 3 months (points)	23,1 ± 8,39 (95% CI 19,17-27,03)	18,01 ± 5,83 (95% CI 15,65-20,37)	< 0,05
Likert score (points)	18,73 ± 1,31 (95% CI 18,45-19,01)	19,2 ± 1,41 (95% CI 18,93-19,47)	< 0,05
VAS for patient satisfaction	8 (8-9)	9 (8-9)	< 0,0001

It is observed that the values of the ABC-V score, recorded at an interval of 3 months of surveillance indicate the significantly higher level of life quality in patients in the conservative group in comparison with those operated in the acute phase of VTPh. Likewise, comparing the mean values of the Likert score and the VAS scale demonstrates a higher degree of patient satisfaction after conservative treatment, but in both groups an acceptable level of satisfaction was recorded.

GENERAL CONCLUSIONS

1. National trends in management of acute VTPh are characterized by the major variability of the used curative options, especially with reference to anticoagulation treatment regimes. The selection of a certain method of treatment by the surgeon is empirical and is significantly influenced by the personal experience of the specialist, the presence of periosteal thrombosis of the saphenous trunk, obesity and the number of comorbidities.

2. According to DUS in more than ¾ of cases of the superficial vein thrombosis the varicose tributaries (58.4%) or the distal saphenous trunk (21%) are exclusively involved. The rapid progression of thrombosis with involvement of the proximal saphenous trunk and development of periosteal forms of VTPh is associated with systemic inflammatory reaction and reflects the disbalance of the hemostatic system of the patient with a tendency towards the hypercoagulation.

3. Conservative treatment demonstrates 94.5% efficacy in preventing the extension/recurrence of superficial vein thrombosis, development of deep vein thrombosis and pulmonary embolism in patients with acute VTPh, including the periosteal forms, and the independent factors associated with the risk of treatment failure are: duration of anticoagulation therapy (HR – 0.91 / day) and individual thrombotic risk assessed according to the Caprini score (HR – 1.86 / point).

4. In patients with isolated thrombosis of varicose tributaries or with a total length of the thrombosed venous segment less than 45 cm according to DUS, urgent surgical treatment is associated with minimal risk of postoperative deep vein thrombosis and allows to reduce significantly of both VTPh symptoms and severity of clinical manifestations of varicose disease.

5. During the 6-month follow-up, the rate of venous thromboembolic events in patients with acute VTPh is 7.6% in the general group; and the initial degree of thrombosis extension is, regardless of the applied treatment type, the only true risk factor for treatment failure, its probability being higher by 2% for every centimetre of length of the affected venous segment.

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PRACTICAL RECOMMENDATIONS

1. The surface area of cutaneous hyperemia > 150 cm^2 and the area of soft tissue induration adjacent to the thrombosed superficial veins < 17 cm^2 can be used as a positive clinical criterion (predictive value - 92.3%) and negative (predictive value - 89.5%) for forecasting the risk of the GSV trunk involvement in patients with VTPh and selecting the initial treatment until imaging investigations are performed.

2. Imaging examination by DUS in case of acute VTPh should include examination of both superficial and deep venous system (preferably in the contralateral limb) with mandatory measurement of total thrombosis length and distance between thrombus apex and junctions with deep veins. The rate of thrombus growth determined as the ratio between its volume (length) and the interval from the onset of the disease can be used as an indirect criterion that reflects the degree of activation of the blood coagulation system.

3. The PLR index ≥ 160, derived from the complete blood count and the level of D-dimers ≥ 611 ng / mL are associated with a significant likelihood of extensive thrombosis of the saphenous trunk and periosteal form of VTPh and should be considered in elaboration of diagnostic-curative strategy.

4. In patients with non-truncal VTPh or Verrel-Steckmeier type I and chronic venous insufficiency, it is rational to perform surgery in the acute phase of thrombosis, the volume of the intervention being determined according to the principles of varicose disease treatment. Surgical treatment should be accompanied by standard pharmacological thromboprophylaxis.

5. Patients with extensive VTPh (periosteal forms or the total length of the thrombosed venous segment greater than 45 cm) undergoing surgery in the acute phase require control DUS at 7-14 days postoperatively in order to exclude asymptomatic deep vein thrombosis.

6. Reduction of the rate of wound complications after surgical treatment of acute VTPh can be achieved by performing preoperative antibiotic prophylaxis, using the Muller technique for thrombus/phlebectomy at the level of varicose veins and performing interventions during the first week after the onset of the disease. Intravenous thermal ablation seems to be a perspective option.

7. The duration of anticoagulation therapy in case of acute VTPh should be longer than 3 weeks (optimal 6 weeks), with the use of intermediate doses of fractionated heparin or direct oral anticoagulants. The individual correction of the anticoagulant regimen is based on: total thrombosis length, SFJ/SPJ involvement, the Caprini thrombotic score and the VTE-BLEED hemorrhagic score. The intensification of the anticoagulant treatment is obtained by extension of its duration over 6 weeks and / or switching to therapeutic doses, and reducing the intensity - by switching to prophylactic doses without shortening the duration of treatment.

8. Concomitant administration of anticoagulants and non-steroidal anti-inflammatory drugs does not improve treatment outcomes and can be used only for symptomatic treatment (reduction in the severity of acute pain).

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ADNOTARE

Bzovîi Florin **„Diagnosticul și tratamentul maladiei varicoase complicate cu tromboză venoasă acută superficială”**. Teză de doctor în științe medicale, Chișinău, 2022.

Structura tezei. Teza este expusă pe 142 pagini de text de bază: introducere, 5 capitole, concluzii generale și recomandări practice, 22 figuri și 23 tabele. Bibliografia include 241 surse. Rezultatele principale ale studiului au fost publicate în 20 lucrări științifice.

Cuvinte-cheie: tromboza venoasă superficială, varicotromboflebita acută, trombembolismul venos, ultrasonografia duplex, tratament anticoagulant, tratament chirurgical.

Scopul lucrării. Ameliorarea rezultatelor tratamentului varicotromboflebitei (VTF) acute a membrelor inferioare în baza identificării factorilor de risc asociați cu evenimente venoase tromboembolice și precizarea criteriilor de selectare a abordului curativ optim.

Obiectivele cercetării. Studierea tendințelor actuale în managementul bolnavilor cu VTF acută în Republica Moldova și compararea acestora cu practicile internaționale. Analiza corelațiilor între manifestările clinice, datele imagistice și rezultatele testelor de laborator la bolnavii cu diferite forme de VTF acută. Aprecierea eficacității și siguranței diferitor scheme farmacoterapeutice utilizate la bolnavii cu VTF acută și determinarea factorilor cu impact asupra rezultatelor tratamentului conservator. Evaluarea riscurilor asociate cu tratamentul chirurgical al VTF în faza acută și determinarea posibilităților de micșorare a ratei complicațiilor postoperatorii. Compararea rezultatelor tratamentului chirurgical și conservativ al VTF acute în baza criteriilor clinice și scorurilor raportate de către pacienți.

Noutatea și originalitatea științifică. Cu ajutorul unui chestionar online a fost demonstrată variabilitatea semnificativă în managementul autohton al VTF acute. S-a stabilit valoarea predictivă a semnelor clinice locale ale VTF în diferențierea prealabilă a formelor cu și fără implicarea trunchiului safenian. A fost studiată valoarea markerilor inflamației sistemice la bolnavii cu VTF acută. A fost evidențiată dereglarea echilibrului hemostatic cu tendință spre hipercoagulabilitate la bolnavii cu VTF acută, în special la cei cu forma periostială a trombozei. A fost stabilită diferența semnificativă a valorilor estimate de viscozitate sangvină la pacienții diagnosticați cu VTF acută în perioada caldă și rece a anului, fapt ce poate explica variațiile sezoniere în incidența acestei maladii. A fost demonstrat riscul scăzut al evenimentelor venoase tromboembolice postoperatorii la pacienții cu forma non-trunculară a trombozei și identificați factorii de risc ai complicațiilor de plagă operatorie. Cu ajutorul modelului statistic de regresie Cox a fost demonstrat impactul veridic al gradului individual de risc al complicațiilor tromboembolice a pacientului (estimat în baza scorului Caprini) asupra rezultatelor tratamentului anticoagulant al VTF acute.

Problema științifică soluționată în teză constă în identificarea factorilor de risc asociați cu rezultatele negative ale tratamentului VTF acute, fapt ce va permite modificarea paradigmei de management al patologiei respective prin selectarea științific argumentată a abordului curativ optim în fiecare caz individual.

Semnificația teoretică și valoarea aplicativă a lucrării. Prezentul studiu a demonstrat asocierea formelor extinse, periostiale ale trombozei cu dereglări ale echilibrului hemostatic și reacție inflamatorie sistemică, argumentând necesitatea tratamentului anticoagulant. Eficacitatea comparabilă a abordului chirurgical și conservator în tratamentul VTF acute demonstrată în cadrul studiului și determinarea factorilor de risc ai eșecului tratamentului vor servi ca bază pentru optimizarea conduitei curative. În baza studiului a fost precizată valoarea diagnostică a semnelor clinice locale ale VTF acute și demonstrată importanța examenului duplex și a testelor de laborator (rata trombocite-limfocite, proteina C reactivă și D-dimerii) în elaborarea planului de tratament.

Implementarea rezultatelor științifice. Rezultatele obținute au fost implementate în activitatea secțiilor de chirurgie ale IMSP Spitalului Clinic Municipal „Gheorghe Paladi”, Institutului de Medicină Urgentă, Chișinău, precum și în procesul didactic la Catedra chirurgie generală – semiologie nr.3 a USMF „Nicolae Testemițanu”. S-au obținut 4 acte de implementare a inovațiilor.

РЕЗЮМЕ

Бзовый Флорин **„Диагностика и лечение варикозной болезни, осложнённой острым тромбозом поверхностных вен”**. Диссертация на соискание учёной степени кандидата медицинских наук, Кишинэу, 2022.

Структура диссертации. Основной текст диссертации изложен на 142 листах и включает: введение, 5 глав, выводы и практические рекомендации, 22 рисунка и 23 таблицы. Библиография включает 241 источник. По теме опубликовано 20 научных работ.

Ключевые слова: тромбоз поверхностных вен, острый варикотромбофлебит, венозный тромбоэмболизм, дуплексное сканирование, антикоагулянты, хирургическое лечение.

Цель работы. Улучшение результатов лечения острого варикотромбофлебита (ВТФ) нижних конечностей, идентификации факторов риска венозных тромбэмболических осложнений и определении критериев выбора оптимального лечебного подхода.

Задачи исследования. Изучение характерных особенностей медицинских подходов при остром ВТФ в Республике Молдова и сравнение их с международной практикой. Анализ корреляции клинических, ультразвуковых данных и результатов лабораторных тестов у больных с различными формами острого ВТФ. Оценка эффективности и безопасности различных схем фармакотерапии, применяемых при остром ВТФ и выявление факторов, влияющих на результаты консервативного лечения. Изучение рисков, связанных с хирургическим лечением острого ВТФ и определение возможностей для снижения доли послеоперационных осложнений. Сравнительный анализ хирургического и консервативного подходов при остром ВТФ, основанный на клинических и сообщаемых пациентом результатах лечения.

Научная новизна. Проведено исследование, показавшее значительную вариабельность подходов при остром ВТФ. Установлена диагностическая значимость местных симптомов ВТФ в клинической дифференцировке форм с поражением притоков или ствола магистральных подкожных вен. Изучена прогностическая роль лабораторных маркеров системного воспаления. Доказано нарушение гемостаза с тенденцией к гиперкоагуляции при остром ВТФ, в особенности при приустьевых формах тромбоза. Выявлено различие расчётной вязкости крови у больных острым ВТФ в тёплое и холодное время года, что может объяснить сезонную динамику заболеваемости. Установлен низкий риск послеоперационных тромбоэмболических осложнений у больных с не-стволовыми формами ВТФ и определены факторы риска раневых осложнений. Методом регрессионного анализа доказано достоверное влияние индивидуального тромботического риска пациента с ВТФ (по шкале Каприни) на результаты лечения антикоагулянтами.

Научная задача, решённая в диссертации, состоит в идентификации факторов риска негативного исхода лечения острого ВТФ, что позволяет оптимизировать существующие подходы и научно обосновать выбор индивидуального метода лечения.

Теоретическая и практическая значимость. Результаты исследования показали наличие гиперкоагуляции и системной воспалительной реакции при распространённых, приустьевых формах ВТФ, что обосновывает необходимость антикоагуляции. Сходная эффективность хирургического и консервативного подходов и определение факторов риска негативного исхода заболевания позволяет оптимизировать лечение больных ВТФ. Установленная в исследовании значимость клинических симптомов, результатов дуплексного сканирования и лабораторных тестов (индекс тромбоциты-лимфоциты, С-реактивный белок, Д-димеры) способствует обоснованию выбора метода лечения ВТФ.

Внедрение результатов исследования. Научные результаты были внедрены в клиническую работу отделений хирургии Муниципальной Клинической больницы „Gheorghe Paladi”, Кишинэу; Института Ургентной Медицины Республики Молдова и в учебный процесс кафедры общей хирургии – семиологии №3 ГУМФ им. Н.А. Тестемицану. Зарегистрировано 4 акта внедрения результатов исследования.

SUMMARY

Bzovii Florin **„Diagnosis and treatment of varicose veins complicated with acute superficial vein thrombosis”**. The thesis for the degree of Doctor of Medical Science, Chisinau, 2022.

Structure of the thesis. The thesis includes 142 pages of the main text: introduction, five chapters, general conclusions and practical recommendations, 22 figures and 23 tables. The bibliography includes 241 references. The principal results of the study were published in 20 scientific papers.

Key words: superficial vein thrombosis, acute varicothrombophlebitis, venous thromboembolism, duplex ultrasound, anticoagulation, surgical treatment.

The aim of study. Improvement of the results of treatment of acute varicothrombophlebitis (VTPh) of lower limbs basing on identification of risk factors associated with venous thromboembolism and determination of the criteria for selection of optimal curative approach.

Objectives of the study. Study of current patterns in the management of patients with acute VTPh in Republic of Moldova and its comparison to international practice. Analysis of correlations between clinical manifestations, imaging data and results of laboratory tests in patients with various types of acute VTPh. Assessment of efficacy and safety of various protocols of medical treatment used in patients with acute VTPh and determination of factors with an impact upon the results of conservative treatment. Evaluation of the risks associated with surgical treatment of VTPh in acute phase and determination of possibilities for reduction of the rate of postoperative complications. Comparison of the results of surgical and medical treatment of acute VTPh basing on clinical and patient reported outcomes.

Scientific originality and novelty. Significant variability of local patterns in the management of acute VTPh was demonstrated using an online questionnaire. The predictive value of local clinical signs of VTPh in initial differentiation of the forms with and without involvement of the saphenous trunk was established. The value of the markers of systemic inflammation in patients with acute VTPh was studied. The disbalance of hemostasis with a tendency towards hypercoagulability was demonstrated in patients with acute VTPh, especially in those with periosteal form of thrombosis. A significant difference in estimated values of blood viscosity during the hot and cold period of the year was found in patients with acute VTPh, which may explain the seasonal variations in the incidence of disease. The low risk of postoperative venous thromboembolic events in patients with non-truncal VTPh was demonstrated and risk factors for complications of surgical wound were identified. Using Cox regression statistical model, the significant impact of individual level of the risk of thromboembolic complications (estimated basing on the Caprini score) upon the outcomes of anticoagulant treatment of acute VTPh was demonstrated.

The scientific problem solved in the thesis consist in identification of risk factors associated with negative outcomes of treatment of acute VTPh, allowing modification of treatment paradigm and scientifically argued selection of the optimal curative approach in each individual case.

Theoretical significance and applicative value. The present study demonstrated the association of extensive, periosteal forms of thrombosis with disequilibrium of hemostatic balance and systemic inflammatory reaction, arguing the need for anticoagulant treatment. The comparable efficacy of surgical and conservative approach in the treatment of acute VTPh demonstrated in the study and determination of risk factors associated with treatment failure serve as a basis for optimization of curative approach. Basing on the results of study, the diagnostic value of local clinical signs of acute VTPh was determined and the importance of duplex ultrasound examination and laboratory tests (platelet-lymphocyte ratio, C-reactive protein and D-dimers) in the elaboration of treatment strategy was demonstrated.

Implementation of scientific results. The results of study were implemented in the clinical activity of the departments of surgery at Municipal Clinical Hospital „Gheorghe Paladi” from Chisinau, Institute of Emergency Medicine from Republic of Moldova and Department of general surgery – semiotics nr.3 at the State University of Medicine and Pharmacy „Nicolae Testemițanu”. Four acts of implementation of the results were registered.

ABBREVIATIONS

APTT – activated partial thromboplastin time

AUC– area under curve

BMI – body mass index

CEAP – classification clinical, etiological, anatomical and pathophysiological on chronic venous disorders

cP – centipoise

CRP – C-reactive protein

DUS – duplex ultrasound

DVT – deep vein thrombosis

GSV – great saphenous vein

LMR – lymphocyte to monocyte ratio

NLR – neutrophil to lymphocyte ratio

PLR – platelet to lymphocyte ratio

pTEG – piezothromboelastography

ROC – receiver operating characteristic

SFJ – saphenofemoral junction

SPJ – saphenopopliteal junction

SSV – small saphenous vein

SVT – superficial venous thrombosis

VAS – visual analogue scale

VCSS – venous clinical severity score

VS_{HSR} – high shear rate

VS_{LSR} – low shear rate

VTPh – varicothrombophlebitis