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Radiofrequency ablation or stripping of large-diameter incompetent great saphenous varicose veins with C2 or C3 disease

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Objective: **The objectives of this study were to compare the results of radiofrequency ablation (RFA) and stripping for large-diameter varicose target veins for the period of 1 year, based on a composite end point; to analyze the pain severity on a digital rating scale for 7 days after RFA and stripping; and to detect the factors affecting the level of postoperative pain using the cluster analysis.**

Methods: **This was a multicenter retrospective cohort study. Two groups, stripping ≥14 mm and RFA ≥14 mm, of 129 varicose vein disease patients underwent surgical treatment in three specialized clinics. We eliminated symptomatic pathologic reflux with RFA in 64 patients and with stripping in 65 patients. In the postoperative phase, we evaluated the pain level, subcutaneous hemorrhage, and paresthesia. A composite end point with four components was used to analyze the results. These were three clinical adverse effects of the intervention (pain, hemorrhage, and paresthesia) and the technical outcome 1 year after the surgical intervention.**

Results: **The frequency of favorable outcomes was 20 (30.8%) in the stripping ≥14 mm group and 61 (95.3%) in the RFA ≥14 mm group ($P < .0001$). The odds ratio for a favorable outcome between the RFA and the stripping groups was 45.8 (95% confidence interval, 44.5-47.0). The pain clusters that were moderate were created by patients after stripping. These clusters show a link between the pain level on the one hand and an increased body mass index and large vein diameter on the other hand.**

Conclusions: **For large-diameter veins, RFA is superior to stripping in terms of favorable outcomes according to the composite end point chosen. Significant pain after stripping was linked to a large vein diameter and excess weight or adiposis. (J Vasc Surg: Venous and Lym Dis 2016;4:45-50.)**

Radiofrequency ablation (RFA) is one of the main methods to eliminate symptomatic pathologic reflux in incompetent saphenous veins, which makes it an alternative to stripping.[1-5] So far, only one randomized prospective study on the comparison of RFA with ClosureFAST (Covidien, Mansfield, Mass) and stripping has been published.[6] Contemporary studies show only few data about how the diameter of the target vein affects the efficacy of RFA and the postoperative phase. According to the guidelines of the American Venous Forum (2011), saphenous vein diameters >15 mm are a limiting factor for RFA because of an increased risk of incomplete obliteration and target vein phlebitis.[7]

There are, however, no data as to the frequency of complications after RFA for such large vein diameters. So far, only one article has been published giving a comparative study of RFA for veins >12 mm and <12 mm in diameter.[8] Surgical elimination of saphenous reflux may provoke negative complications, such as, most frequently, moderate pain, ecchymoses, hyperpigmentation of the skin, and transient paresthesias during the postoperative phase.[9]

Clinical trials using single-component end points can evaluate only one type of outcomes—either clinical or anatomic. Analyses of secondary end points have been found to be less reliable. Meanwhile, these end points may be no less clinically significant than the primary end point. Therefore, it appears necessary to use composite end points that include several important anatomic and clinical outcomes of RFA and stripping.[10,11]

This trial aimed to gain a comparative assessment of the efficacy of RFA and stripping for large-diameter veins and to evaluate how the great saphenous vein (GSV) diameter affects the postoperative phase. The objective was to compare the results of RFA and stripping for large-diameter varicose target veins for the period of 1 year, based on a composite end point. We hypothesized that the results of RFA are superior to stripping according to the composite end point. The factors affecting the level of postoperative pain were detected by the cluster analysis. Pain severity was analyzed on a digital rating scale for 7 days after RFA and stripping.

METHODS

Design. The trial was based on a multicenter retrospective cohort study. The analysis was based on material of a multicenter prospective nonrandomized trial comparing RFA with ClosureFAST catheter and high ligation and

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stripping.[12] This study analyzes patients who consulted physicians (without referral) in three specialized centers. The advantages and disadvantages of RFA and stripping were explained to the patients in detail, after which they chose their treatment method by themselves.

From 218 patients who participated in the study, we selected all patients with a GSV diameter of 14 to 20 mm. In our practice, we have come to a conditional limitation of 20 mm for RFA. The trial was performed in one state clinic and two private clinics in St. Petersburg, Russia. The study protocol was approved by the regional Ethics Committee of the Federal Science Institute for Experimental Medicine, Russian Academy of Medical Sciences, North-West department. All patients signed an informed consent to participate in the study. The interventions were performed by experienced surgeons.

During the period from August 2009 to August 2010, 129 unselected patients aged 18 years or older were treated for confirmed primary GSV incompetence (classes C2 and C3 in accordance with the Clinical class, Etiology, Anatomy, and Pathophysiology [CEAP] classification) in one leg. In distal compression tests, we set a minimum duration of 0.5 second of reflux along the GSV in an upright position as an ultrasonographic indication for incompetence; 64 RFA and 65 high ligation and stripping procedures were performed.

Inclusion criteria. As inclusion criteria, we used the following parameters: patients aged 18 years or older, GSV diameter of 14 mm to 20 mm, and clinical class C2 or C3 according to the CEAP classification.

Exclusion criteria. Exclusion criteria included current malignant process, history of thrombophlebitis or any previous intervention on the target vein, previous deep venous thrombosis, anticoagulant administration, confirmed thrombophilia, miniphlebectomy on the thigh, GSV duplication, presence of GSV junctional aneurysmal dilation exceeding 2 cm in diameter, extrafascial GSV in the thigh, small saphenous vein incompetence combined with GSV incompetence in one of the legs, chronic arterial disease of the legs, and nonresident patients (to exclude the possibility of patients withdrawing from the study).

The GSV diameter was measured in the standing position 3 cm below the saphenofemoral junction (in line with the international consensus on duplex ultrasound investigation of the veins in chronic venous disease of the lower limbs).[13]

Treatment. RFAs were performed by way of catheter insertion at the distal reflux spot, most often in the proximal third of the lower leg using a 7F angiographic set. The interventions were performed under tumescent anesthesia with 0.05% lidocaine hydrochloride solution in 0.9% sodium chloride. The average quantity was 300 to 400 mL, based on 10 mL per 1 cm of GSV. Anesthesia was performed under ultrasonography control. The tip of the catheter was positioned 2 cm from the saphenofemoral junction, distal to the vena epigastrica superficialis. In accordance with the manufacturer's recommendations in an automatic mode, two cycles were performed, keeping the catheter's working part at a consistent temperature of 120°C during a 20-second cycle in the GSV junction segment. Afterward, in the distal direction, one cycle was performed for each 7-cm-long segment. Stripping procedures included two phases: high ligation and short invaginated stripping. For pain management, we used spinal anesthesia and intravenous anesthesia in rare cases.

We used a hard stripper by Oesch. With all patients, we performed microphlebectomy in varicose subcutaneous tributaries using Oesch hooks. During the postoperative phase, we prescribed ibuprofen 400 mg for the first night. Antibacterial therapy or anticoagulants were not prescribed. After the intervention, we applied a cushioned bandage to the limb for eccentric compression in the projection of the target vein and put class 2 compression hosiery on the patients. We recommended that our patients walk on plain ground for 30 minutes right after the intervention. Compression was sustained throughout the next 24 hours. The patients were instructed to wear the compression hosiery throughout the next 2 weeks during the daytime.

Follow-up and analysis of results. Follow-up included duplex ultrasound examinations after 24 hours, 7 days, 1 month, 3 months, and 1 year. Ultrasound investigation included screening for deep venous thrombosis. Source data and data about the course and the results of the treatment were fixed in questionnaires in line with the international Recommended Reporting Standards for Endovenous Ablation for the Treatment of Venous Insufficiency.[14] In addition, information was collected about pain score (overall pain severity graded on a digital scale from 0 to 10) throughout the first 7 days. On a daily basis, the patients rated their pain level and filled in the questionnaire to hand it in to the physician during the second follow-up examination.

We based our comparison on a composite end point consisting of four criteria. These were three clinical adverse effects of the intervention (pain, hemorrhage, and paresthesia) and the technical outcome. In the RFA group, the technical outcome was determined on the basis of the presence or absence of recanalization at 1 year after the procedure. In the stripping group, it was determined on the basis of the absence of the target vein or presence of residual fragments on the thigh according to the follow-up ultrasound examination 1 year after the intervention.

Recanalization of the target vein and presence of its residual fragments were classified as unfavorable technical outcomes. Favorable outcomes were marked with the variable A, unfavorable outcomes with the variable B, on a nominal scale. Severity of pain in the femoral segment (intervention zone) was scored on a digital rating scale from 0 (no pain) to 10 (extremely severe pain) 1 day after the intervention.

A score of 1 to 3 was defined as mild pain; 4 to 6, moderate pain; and 7 or higher, severe pain. The cutoff point for a pain level to be defined as a favorable outcome was 3 or lower on the scale. The area of subcutaneous hemorrhage in the GSV projection on the thigh was measured in

Table I. Intervention outcomes for grading scales

Variable	*Favorable outcome A*	*Unfavorable outcome B*
Technical outcome	Ablation, obliteration, absence of target vein	Recanalization, presence of residual segment
Pain severity during the first 24 hours	≤3	≥4
Subcutaneous hemorrhage	<20 cm^2	>20 cm^2
Paresthesia	No	Yes

centimeters 24 hours after the procedure using a marked transparent piece of plastic foil (ratio scale). The presence or absence of paresthesia was established on the basis of the patients' complaints about zones of decreased sensitivity on the thigh.

We created grading scales with additional parameters for correct interpretation of the data (Table I). The composite end point encompasses 16 intervention outcomes with different combinations of components: technical outcome, pain, subcutaneous hemorrhage, and paresthesia. With regard to the composite end point, the outcomes were defined as favorable, satisfactory, and dissatisfactory. All the possible outcomes are represented in Table II.

All outcomes with recanalization or residual fragments of the target vein, moderate or severe pain, subcutaneous hemorrhage, or paresthesia were defined as dissatisfactory. All results with a favorable technical outcome, with mild or no pain, but with large subcutaneous hemorrhage or paresthesia were defined as satisfactory. Favorable outcomes meant the results with a favorable technical outcome, with mild or no pain, but with subcutaneous hemorrhage and paresthesia.

In addition, we made a comparative analysis of pain severity throughout the first 7 days after operation in the stripping ≥14 mm group and the RFA ≥14 mm group.

Table II. Possible combinations of components according to the composite end point (possible outcomes of the intervention A or B from Table I)

Composite outcome				
Technical outcome	*Pain level*	*Hemorrhage*	*Paresthesia*	*Result classification*
A	A	A	A	Favorable
A	A	B	A	
A	A	A	B	
A	A	B	B	
A	B	A	A	Satisfactory
A	B	B	A	
A	B	B	B	
A	B	A	B	
B	B	B	B	Dissatisfactory
B	B	A	B	
B	B	A	A	
B	A	A	A	
B	A	B	A	
B	A	B	B	
B	A	A	B	
B	B	B	A	

Both groups included patients with severe, moderate, or no pain in the GSV projection on the femur. When it comes to the analysis of the reasons for different pain levels, applying the Mann-Whitney *U* test is not very informative in comparing median pain levels. Such analysis is possible if groups are divided into clusters.

Statistical analysis. For statistical calculations, we used KNIME (the Konstanz Information Miner) Desktop, version 2.5.4.[15] Sufficiency of the sample size was determined by applying the contingency table for the frequency of outcomes based on the composite end point, using Lehr's equation. The level of statistical significance of the study was 5% with 90% power. We used nonparametric statistics (contingency table based on criterion χ^2). The odds ratio (OR) for a favorable outcome was based on a 95% confidence interval. Cluster analysis was used to establish pain severity. The X-means algorithm and the Xie-Beni index were used to establish the amount of clusters. The pain score was determined in the projection of the GSV on the femur based on a pain severity digital scale ranging from 0 to 10. A decision tree was created for identifying factors that increase pain.

RESULTS

Evaluation of the sample size. The sampling method provides 90% power of the study with a 30% difference between the RFA and stripping groups (5% significance level, 0.6 strictly standardized mean difference).

Characteristics of the trial's participants. We examined all patients participating in the study in all follow-up examinations. None of the patients withdrew from the study. The stripping ≥14 mm group comprised 65 patients; the RFA ≥14 mm group had 64 patients. The characteristics of the patients are shown in Table III. There were no cases of complications resulting in hospitalization or additional procedures or prescriptions in either of the groups.

Comparative analysis of treatment results in the stripping ≥14 mm and RFA ≥14 mm groups. The frequency of favorable, satisfactory, and dissatisfactory outcomes for the stripping ≥14 mm group was 20 (30.8%), 41 (63.1%), and 4 (6.2%), respectively; for the RFA ≥14 mm group, it was 61 (95.3%), 0 (0.0%), and 3 (4.7%), respectively. The frequencies of RFA and stripping outcomes based on the composite end point are shown in Table IV.

We established statistically significant differences between the RFA and stripping groups regarding the

Table III. Characteristics of participants in the stripping ≥14 mm group and radiofrequency ablation (*RFA*) ≥14 mm group

Value	*RFA ≥14 mm*			*Stripping ≥14 mm*			P *value (Mann-Whitney U test)*
	Median	*Upper quartile*	*Lower quartile*	*Median*	*Upper quartile*	*Lower quartile*	
No. of patients	64			65			
CEAP C3	34 (53.1%)			28 (43.1%)			.5
Sex, F	48 (75%)			50 (76.9%)			.92
Age, years	45.5 (46.3 ± 9)	40.75	52.25	49 (48.1 ± 7.9)	42	54	.24
BMI	27 (27.2 ± 1.7)	26.1	28.6	25.9 (26.2 ± .9)	24.5	27.5	<.0001
GSV diameter at junction, mm	15 (15 ± 1)	14	16	15 (15.2 ± 1.2)	14	17	.34
Duration of intervention, minutes	41.5 (41.1 ± 9.3)	34.25	48.25	67 (66 ± 15.7)	52	80	<.0001
VCSS	5 (5.48 ± 1.7)	4	6.25	6 (5.6 ± 1.6)	4	7	.67
CIVIQ2 (integral indicator)	7 (7.9 ± 2.5)	6.2	8.56	7.5 (7.9 ± 2)	6.5	8.75	.4

BMI, Body mass index; *CEAP,* Clinical class, Etiology, Anatomy, and Pathophysiology; *CIVIQ,* Chronic Venous Insufficiency Questionnaire; *GSV,* great saphenous vein; *VCSS,* Venous Clinical Severity Score.
The highlighted rows show parameters with statistical differences between the groups.

frequency of favorable outcomes based on the relevant composite end point. With a type I error level ≤ .05 and a number of degrees of freedom ($df = 2$), the χ^2 value was 41.6 ($P < .001$). The OR for a favorable outcome for RFA and stripping was 45.8 (95% confidence interval, 44.5-47.0).

Ablation/recanalization in the RFA group occurred in 61 (95.3%)/3 (4.7%) patients. In the stripping group, the ratio of no target vein/residual target vein fragments was 61 (93.8%)/4 (6.2%) at 1-year follow-up.

Cluster analysis of pain severity of the stripping ≥14 mm and RFA ≥14 mm groups during 7 days based on a digital rating scale. Patients were divided into four clusters, depending on pain severity, independently from the kind of intervention performed. The first cluster had only cases with mild pain during the first 2 days; from the third to the seventh day, there was no pain. The fourth cluster included mild pain during the first 5 days after the intervention. In the third cluster, there was moderate pain from the first to the fourth day after the intervention and mild pain from the fourth to the sixth day. The second cluster showed moderate pain only during the first 2 days after the intervention and mild pain from the third to the sixth day. On the seventh day, there was no pain in any of the clusters. Pain severity in the clusters during the first 7 days after the intervention is shown in Fig.

The first and the fourth clusters include low pain severity values; the second and the third clusters show high ones. The distribution of patients among the clusters is as follows: first cluster, 32%; second cluster, 17%; third cluster, 18%; fourth cluster, 33%. In the first cluster, the number of patients after RFA was 39 (93%); after stripping, 3 (7%). In the fourth cluster: RFA, 25 (60%); stripping, 17 (40%). The second and the third clusters included only patients after stripping (45 [100%]). We created a decision tree to identify the factors that increased pain severity. For stripping, we established a statistically significant dependence of moderate and severe pain (second and third clusters) on the vein diameter and body mass index (BMI; ≥27.4). With a type I error level ≤ .05, the χ^2 value was 55.1 ($P < .001$).

DISCUSSION

The concept of large-diameter veins does not have a common definition. According to the guidelines of the American Venous Forum published in 2011, the optimal vein diameter for efficient RFA ranges from 2 to 15 mm.[7] The 15-mm limit is defined as a potential relative contraindication to radiofrequency thermal ablation.

So far, only one study has been published that includes a comparative analysis of RFA for veins with diameters smaller and larger than 12 mm.[8] According to that study, for veins >12 mm, RFA is even more effective than for veins <12 mm. However, this study has a number of significant shortcomings; its insufficient power, the short

Table IV. Frequency of radiofrequency ablation (*RFA*) and stripping outcomes based on the composite end point

Category	*RFA, No. (%)*	*Stripping, No. (%)*	*Total, No. (%)*
Favorable	61 (95.3)	20 (30.8)	81 (62.8)
Satisfactory	0 (0)	41 (63.1)	41 (31.8)
Dissatisfactory	3 (4.7)	4 (6.2)	7 (5.4)
Total	64	65	129 (100)

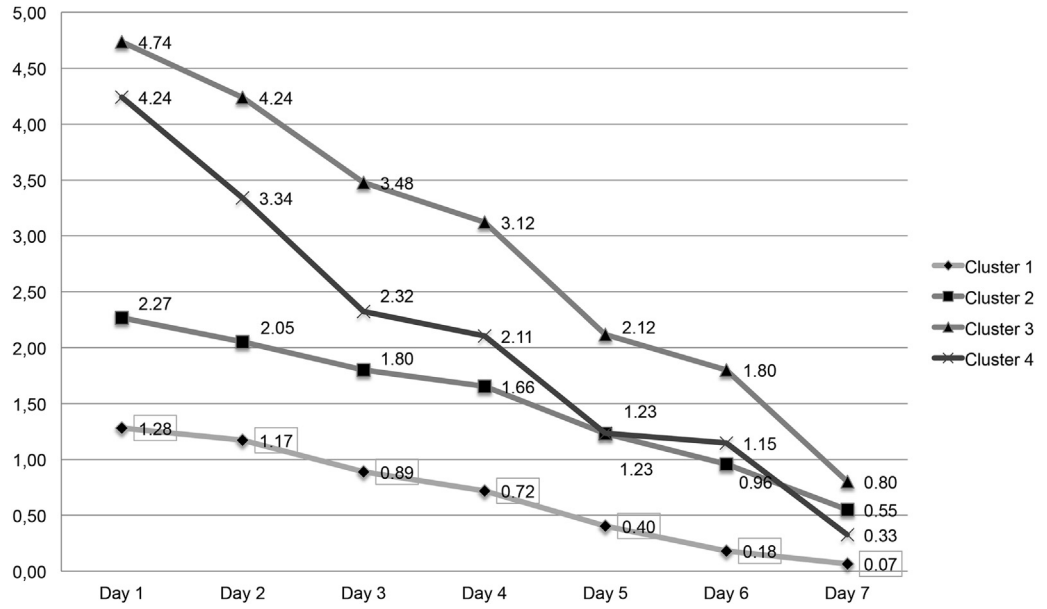

Fig. Pain severity during the first 7 days after the intervention.

duration of its follow-up period, and the absence of randomization significantly impair the credibility of its results. Also, the study does not specify where exactly the vein diameter was measured—in the junction section of the GSV or in its central third.

We analyzed preoperative symptoms and could not discover any contributions of preoperative symptoms to relevant differences in severity on the Venous Clinical Severity Score between the patient groups with different outcomes.

The trial established that RFA is superior to stripping with regard to the number of favorable outcomes it produces on the basis of the composite end point. The contingency table revealed an OR of 45.8 (95% confidence interval, 44.5-47.0). Obviously, the reason for this result is the fact that RFA does not entail hemorrhage as a result of ruptures of GSV tributaries or vein wall perforations. If one considers only pain severity and the technical outcome, again RFA is superior to stripping, as was shown in a randomized controlled study by Rasmussen et al.[6] However, in our study, for the first time a composite end point was applied to evaluate the efficacy and security of modern methods in vein disease treatment. This enabled us to evaluate not only pain severity but also other relevant factors affecting the postoperative phase, such as hemorrhage and paresthesia. In addition, our study shows the limits of RFA in relation to the vein diameter, as opposed to the above-mentioned study.

In cases in which patients had a clinical recanalization after RFA, we performed another thermal obliteration on the recanalized GSV. Target vein remnants after high ligation and stripping were removed using echo-controlled microfoam sclerotherapy or conventional surgery.

We showed that vein diameter and BMI were associated significantly with moderate or severe pain in the stripping group. This result is evident notwithstanding the fact that in the stripping group, the pain level was generally higher than in the RFA group. The median vein diameter in both groups was 15 mm. There were no statistically relevant differences in the vein diameters between the groups; both groups included patients with large-diameter veins, whereas BMI in the RFA group was significantly higher than in the stripping group. If the BMI could impair the pain level to a significant degree in any of the groups, it is the RFA group.

This study has a number of limitations. Notwithstanding this fact, in our trial the number of veins ≥15 mm turned out to be insufficient for a correct analysis. Therefore, as a mark for dividing patients into different groups, we chose the diameter closest to 15 mm that still provides a sufficient sample size for statistical analysis—14 mm. The maximum diameter of the GSV in the junction section was no larger than 2 cm. Our composite end point included not only components that are expected to show effects of similar magnitude and with the same directions, such as pain, ecchymoses, and paresthesias, but also the technical outcome, which essentially differs from them. However, this limitation did not have any impact on the plausibility of the outcomes because any unfavorable technical outcome was classified as dissatisfactory. Results of the treatments were assessed on the basis of the frequency of favorable outcomes. This design was chosen for practical reasons as it allowed us to achieve our goal (the objective of the study). The study is retrospective; however, the character of the analysis is prospective, and it is furnished with all necessary data about the relevant end point.

CONCLUSIONS

For large-diameter veins, RFA is superior to stripping in terms of favorable outcomes based on the relevant composite end point. Significant pain after stripping was linked with a large vein diameter and excess weight or adiposis.

AUTHOR CONTRIBUTIONS

Conception and design: ES, AG
Analysis and interpretation: EI, VB, DR
Data collection: AG, VB, DR
Writing the article: AG, DR
Critical revision of the article: ES, EI, DR
Final approval of the article: ES, AG, EI, VB, DR
Statistical analysis: EI, VB
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REFERENCES

1. Gloviczki P. Handbook of venous disorders: guidelines of the American Venous Forum. 3rd ed. Hodder Arnold: London; 2009. p. 409-17.
2. Edwards AG, Baynham S, Lees T, Mitchel DC. Management of varicose veins: a survey of current practice by members of the Vascular Society of Great Britain and Ireland. Ann R Coll Surg Engl 2009;91:77-80.
3. Saveliev VS, Kirienko AI, Zolotukhin IA, Seliverstov EI. Prospective observational study SPECTRUM: register of patients with chronic diseases of the veins of the lower extremities; [in Russian]. Phlebologiya 2012;6:4-9.
4. Lawson J, Gauw S, van Vlijmen C, Pronk P, Gaastra M, Mooij M, et al. Sapheon: the solution? Phlebology 2013;28:2-9.
5. Greenhalgh T. How to read a paper. The basics of evidence-based medicine. BMJ Books/Blackwell: Malden, Mass; 2006.
6. Rasmussen LH, Lawaetz M, Bjoern L, Vennits B, Blemings A, Eklof B. Randomized clinical trial comparing endovenous laser ablation, radiofrequency ablation, foam sclerotherapy and surgical stripping for great saphenous varicose veins. Br J Surg 2011;98:1079-87.
7. Gloviczki P, Comerota AJ, Dalsing MC, Eklof BG, Gillespie DL, Gloviczki ML, et al. The care of patients with varicose veins and associated chronic venous diseases: clinical practice guidelines of the Society for Vascular Surgery and the American Venous Forum. J Vasc Surg 2011;53(Suppl):2S-48S.
8. Calcagno D, Rossi JA, Ha C. Effect of saphenous vein diameter on closure rate with ClosureFAST radiofrequency catheter. Vasc Endovasc Surg 2009;43:567-70.
9. Subramonia S, Lees T. Randomized clinical trial of radiofrequency ablation or conventional high ligation and stripping for great saphenous varicose veins. Br J Surg 2010;97:328-36.
10. Kleist P. Composite endpoints for clinical trials: current perspectives. Int J Pharm 2007;21:187-98.
11. Yakovlev IC. Combined endpoints in clinical trials: a literature survey; [in Russian]. Kach Klinich Pakt 2010;1:39-53.
12. Shaidakov EV, Petukhov AV, Iliukhin EA, Grigorian AG. Radiofrequency obliteration of veins in surgical treatment of varicose disease; [in Russian]. Angiol Sosud Khir 2013;19:74-82.
13. Coleridge-Smith P, Labropoulos N, Partsch H, Myers K, Nicolaides A, Cavezzi A. Duplex ultrasound investigation of the veins in chronic venous disease of the lower limbs—UIP consensus document. Part I. Basic principles. Eur J Vasc Endovasc Surg 2006;31:83-92.
14. Kundu S, Lurie F, Millward SF, Padberg F, Vedantham S, Elias S, et al. Recommended reporting standards for endovenous ablation for the treatment of venous insufficiency: joint statement of the American Venous Forum and the Society of Interventional Radiology. J Vasc Interv Radiol 2007;18:1073-80.
15. Berthold MR, Nicolas C, Dill F, Gabriel TR, Kötter T, Meinl T, et al. KNIME: the Konstanz information miner. Studies in classification, data analysis, and knowledge organization. Springer: Berlin; 2007. p. 319-26.

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