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Mid-Term Results of Cyanoacrylate Embolization of Saphenous Veins

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ABSTRACT

Objective. To evaluate the results of cyanoacrylate embolization (CAE) of great (GSV) and small (SSV) saphenous veins in patients with varicose veins (VVs) of the lower limbs.

Material and methods. This is an ongoing prospective observational study including patients with VVs who underwent CAE of GSV or SSV. The outcomes are assessed in a week, 1, 3, 6 and 12 months after surgery, and then every year. Efficacy criteria are technical success, no vein recanalization, absence of residual reflux along the vein and within sapheno-femoral junction, GSV stump length, vein involution, no need for additional treatment for varicose tributaries after 3 months, no need for redo intervention on the treated vein, absence of varicose vein recurrence, reduction of CEAP class and VCSS score. Safety criterion is the absence of adverse reactions (ARs) associated with CAE.

Results. CAE was performed on 142 limbs in 115 patients with VVs. GSV trunk was embolized in 82% of cases, SSV trunk — in 18%. Technical success was achieved in all cases. GSV stump length varied from 0 to 45 mm (mean 16.7±9.0 mm). Sclerotherapy for varicose tributaries within 3 months was performed on 80 (56%) legs. Follow-up period was 1-24 months. Additional sclerotherapy of tributaries was required for 38 (27%) limbs. GSV involution was observed in 3 (2%) cases within 12-24 months. Trunk recanalization within 3-12 months after intervention was found on 13 out of 142 (9%) limbs with reflux at the junction and on 3 out of 117 (2%) limbs after GSV obliteration. VV recurrence occurred on 8 (6%) limbs, as reported by the investigator, and on 3 (2%) limbs, as reported by the patient. AEs included phlebitis of the trunk (*n*=16; 11%) and thrombophlebitis of residual tributaries (*n*=8; 6%), cord sensation (*n*=8; 6%), glue propagation out of the junction (*n*=3; 2%), skin sensitivity disturbance (*n*=5; 4%), subcutaneous granuloma (*n*=1; 1%), subcutaneous hematoma (*n*=2; 1%), deep vein thrombosis (*n*=1; 1%), and allergy (5 out of 115 patients; 4%).

Conclusion. CAE is a reliable method for saphenous vein ablation.

Keywords: *chronic venous disease, varicose veins, cyanoacrylate embolization, endovenous obliteration.*

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Introduction

Chronic venous disease (CVD) is associated with a significant social and economic burden [1]. Superficial reflux deteriorates symptoms and signs of CVD and affects the quality of life [2—5]. This is the reason for eliminating venous reflux with open (high ligation and stripping) or endovascular surgery [6—8]. The endovascular venous interventions may be divided into thermal tumescent (laser, radiofrequency, steam, microwave ablation) and non-thermal non-tumescent (sclerotherapy, mechano-chemical ablation, cyanoacrylate embolization). The non-thermal technologies, particularly cyanoacrylate embolization (CAE) and mechano-chemical ablation (MOCA), provide reliable technical success with the advantages of no tumescent anesthesia, reduced procedure time, increased comfort of the patient, and no risk of nerve injury [9].

Cyanoacrylate embolization for superficial veins was introduced more than 25 years ago [10]. It became popular recently with the development of the modern adhesive formulation and devices for glue delivery. CAE doen't need tumescent anesthesia. It also guarantees low level of intra- and postoperative pain, minimal skin bruising, high rate of venous occlusion that is comparable with radiofrequency ablation at 5 years follow-up, no need for compression after the intervention, and a high rate of spontaneous regression of varicose tributaries [11—14]. All these lead to fast rehabilitation, return to the work and high satisfaction rate of the patients. The main limitations and disadvantages of the technology are a high rate of inflammatory reactions as well as a lack of glue resorption.

The aim of this study — was to evaluate the results of cyanoacrylate embolization of the great (GSV) and small

(SSV) saphenous trunks in patients with varicose veins (VVs) of the lower limbs.

Material and methods

This ongoing prospective observational study was started in 2017 at the «Neftyanik» hospital (Tyumen, Russia). The inclusion criteria were as follows: age over 18; varicose veins of lower limbs of C2 and > according to CEAP; GSV or SSV reflux of 0.5 sec or more at duplex ultrasound (DUS); signed informed consent. The exclusion criteria were technical incompatibility of CAE; pregnancy and breastfeeding; known allergy to cyanoacrylate adhesives or multiple allergy; history of venous thromboembolism; anticipated low compliance; rejection for participating in the study.

The cyanoacrylate embolization was performed in compliance with well-established descriptions [11, 12, 15]. After local infiltration anesthesia of the skin, the vein was canulated closely to the distal point of reflux with a 16G-needle under ultrasound navigation followed by the introduction of J-wire up to the junction. Over the wire, the 7F-introducer was inserted into the vein and was positioned at 5 cm below the junction. The syringe with 3 ml of adhesive was connected to the dispenser and catheter. After filling the catheter with the glue up to the distal notch, it was inserted through the introducer up to the proximal notch. Catheter was positioned at 5 cm below the junction. The extraction of introducer by 5 cm allows to lock it with the catheter and dispenser and achieve the final ready status of the delivery system. Before starting the glue delivery, the position of the catheter tip was checked by DUS. At 2 cm below the junction, the vein was compressed by the ultrasound probe. 0.1 ml of glue was delivered two times with an interval of 1 cm. After that, the catheter was pulled 3 cm distally, and the treated segment was manually compressed with junction compression by an ultrasound probe for 3 minutes. After that, 0,1 ml of adhesive was delivered for every venous segment of 3 cm length with compression by ultrasound probe for 30 sec afterward.

Treatment of varicose tributaries can be done simultaneously with CAE or in a few months after it. Decision is based on the patient's symptoms and concerns. Delayed treatment is usually used in the absence of spontaneous regression of varicose veins in a few months and/or persistence of venous symptoms. Ultrasound-guided foam sclerotherapy (UGFS) is the common method [16].

Class II above-knee stockings were prescribed for 3—6 weeks only after UGFS or in cases of venous symptoms. The isolated CAE in patients without severe symptoms does not require elastic compression [12].

Patients were followed clinically and by DUS at the 1 week, 1, 3, 6, and 12 months and then every year after the procedure or if they have any complaints. Clinical assessment included assessement of CEAP clinical class [17] and CVD severity by the VCSS score [18] at the baseline, 6, 12 months, and then every year. Adverse events (AEs) were also recorded.

Duplex ultrasound was performed for the post-interventional screening [19]. Reflux duration of 0.5 sec and more was considered as pathological [20]. The total duration of follow-up is not limited.

Efficacy outcomes were as follows: (1) technical success of CAE; (2) absence of the vein recanalization; (3) absence of residual reflux along the treated vein; (4) absence of SFJ reflux after GSV embolization; (5) length of the stump after GSV embolization; (6) involution of the treated vein; (7) no need for additional treatment for varicose tributaries after 3 months; (8) no need for repeated intervention on the treated vein; (9) absence of varicose veins recurrence as reported by the investigator; (10) absence of varicose veins recurrence as reported by the patient (symptomatic recurrence); (10) decrease of CEAP clinical class at 6, 12 months, and annually; (11) decrease of VCSS score at 6, 12 months, and annually.

The technical success was defined as no need for another intervention on the treated vein at one week after embolization. The recanalization was defined as vein compressibility and/or presence of blood flow at the length of 5 and > cm at DUS. The residual reflux along the treated vein or at the SFJ of duration 5 and > sec was considered relevant. The length of GSV stump was measured from the proximal part of the adhesive masses to the common femoral vein (CFV). Involution of the treated vein was defined as absence of any anatomical structure in the typical anatomical points. Varicose veins recurrence was defined as appearance of new or residual varicose tributaries after their full clinical disappearance, as recognized by the investigator or reported by the patient as a complaint (symptomatic recurrence). The decrease of CEAP clinical class was defined as transitioning of any higher class to the lower one.

An adverse event was defined as any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease associated with the CAE. The serious adverse event (SAE) was defined as death, or life-threatening, or required hospitalization or prolongation of hospital admission, or leading to persistent or significant disability or incapacity, or associated with a congenital anomaly or birth defect; or considered as significant by the investigator. Three experienced surgeons assessed the relationship of any reported AE to the implanted cyanoacrylate adhesive.

All outcomes were reported as for the last visit unless otherwise specified.

The study protocol was approved by the Institutional Review Board of the Tyumen State Medical University.

Statistical analysis. The limb is the primary unit for analysis unless otherwise specified. The absolute values are presented as mean with standard deviation (SD) or median with interquartile range (IQR). The relative values are presented as percents with 95% confidential interval (CI) calculated by Wilson. The chi-squared test was

used to compare the relative values and a paired t-test — to compare absolute values. The time to event is presented as a Kaplan—Meier curve. $p<0.05$ is suggested as significant. The analysis was performed with IBM SPSS Statistics v.26.

Results

Since December 2017 to February 2020 the CAE was performed in 142 limbs of 115 patients: 56 women and 59 men aged from 28 to 82 years (mean age of 45.9±10.8 years) with the maximal CEAP clinical of C2 (n=72; 50%), C3 (n=47; 33%), C4 (n=22; 16%), and C5 (n=1; 1%). The VCSS score ranged between 2 and 13, with the mean value of 5.9±2.1.

The GSV trunk with the maximal diameter of 4.5—18.0 mm (mean of 8.7±2.6 mm) measured at the mid-thigh in the upright position, was treated in 117 (82%) legs. The SSV trunk with the maximal diameter of 3.7—13.0 mm (mean of 6.9±2.2 mm) in the upright position was treated in 25 (18%) limbs. The GSV was canulated at the lower-calf in 21 (18%), mid-calf in 5 (4%), upper-calf — 65 (56%), and lower-thigh — 26 (22%) legs with the total length of embolization between 15—80 cm (mean of 50±14 cm). The SSV was canulated in lower-calf in 6 (24%) and mid-calf in 19 (76%) legs with the total length of embolization between 12—35 cm (mean of 24±6 cm). Sclerotherapy for varicose tributaries immediately after the CAE was performed in 70 (49%) limbs. In total, 80 (56%) legs underwent UGFS within 3 months. Elastic compression was prescribed for 92 (65%) limbs: for 3 weeks in 38 (27%) and for 6 weeks in 54 (38%) cases.

Patients were followed for between 1 and 24 months (median of 6 months with the IQR of 1—12 months): at 1 week and 1 month were followed 142 (100%) limbs, at 3 months — 101 (71%) at 6 months — 72 (51%), at 12 months — 49 (35%) limbs.

The efficacy outcomes are represented in **Table 1**. Technical success was achieved in all limbs. The lengths of the GSV stump varied from 0 to 48 mm (mean of 19.1±**9**.7 mm) at 1 week after embolization and significantly reduced to 0-45 mm (mean of 16.7±9.0 mm) at the last visit ($p<0.01$). Trunk recanalization in parallel with reflux appearance along the treated vein was found in 13 of 142 (9.2%) limbs at 3—12 months after the intervention. The time to event is represented in **Figure**. Totally 10 of 117 (8.5%) GSV trunks and 3 of 22 (12.0%) SSV trunks were recanalized without significant difference (p=0.70). The reflux at the SFJ in association with total GSV recanalization was found in 3 of 117 (2.6%) legs. Due to the deterioration of venous symptoms and/or varicose veins recurrence, it was decided to perform a second intervention. The second CAE (n=2), UGFS (n=7), laser ablation (n=1) were applied for segmental recanalization, and radiofrequency obliteration (n=3) — for total recanalization of the target vein. All of the secondary procedures had a technical success.

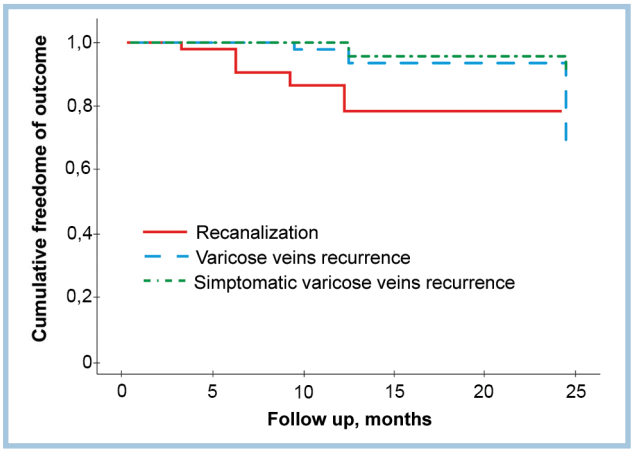
Vein involution was observed in 3 of 142 (2.1%) limbs. No signs of vein wall structures or remnant adhesive masses in its lumen were detected at 12—24 months after GSV embolization. The initial diameter of these veins was 6.0, 8.2, and 9.8 mm that corresponded with the standard deviation of 6.1 —11.3 mm in the whole sample.

Additional sclerotherapy beyond 3 months after the intervention was required in 38 (26.8%) limbs. It was a primary treatment for varicose tributaries in 16 legs and a repeated treatment in other 22. In total, 22 of 142 (15.5%) limbs required second session, 46 (32.4%) limbs never needed it.

Varicose veins recurrence was observed in 8 (5.6%) limbs by investigators and in 3 (2.1%) limbs by patients. In total, 3 of 8 confirmed recurrences were symptomatic. The time to event is represented in **Figure**. Of 8 limbs, the association with target vein recanalization was found in 3 cases. So the new varicose veins occurred in 5 of 129 (3.9%) limbs without and in 3 of 13 (37.5%) legs with the recanalization ($p<0.05$).

At 6 months CEAP clinical class decreased in 53 of 72 (73.6%; $p<0.01$) followed limbs and at 12 months — in 27 of 49 (55.1%; $p<0.01$). No changes were observed in C4 and C5 CEAP clinical classes. VCSS score decreased from 6.2±2.1 at baseline to 1.6±1.5 at 6 months ($p<0.01$) being calculated for 72 limbs and from 6.4±1.8 at baseline to 1.8±1.5 at 12 months ($p<0.01$) being calculated for 49 limbs.

In total, an adverse event with a certain or probable relationship with CAE was registered in 33 of 115 (23.2%) patients with the mean number of 1.5±0.7 per subject (**Table 2**). Multiple AEs were observed in 14 (9.9%) patients. The most common was the phlebitic reaction of the ablated trunk (predominantly GSV) that occurred in 16 of 142 (11.3%) limbs at 5—34 days after the intervention (**Table 3**). In most cases, the duration of symptoms was limited to 5—10 days and required only treatment with systemic or topical non-steroidal anti-inflammatory drugs (NSAID) and/or antihistamines (AH). In one patient



Kaplan-Meier curves for the efficacy of cyanoacrylate embolization of saphenous veins.

Table 1. **Efficacy of cyanoacrylate embolization of saphenous veins**

Outcome	Results
Technical success of CAE, no./no total limbs (%, 95% CI)	142/142 (100,0; 97,4—100,0)
Absence of recanalization, no./no total limbs (%, 95% CI))	129/142 (90,8; 84,9—94,5)
Absence of residual reflux, no./no total limbs (%, 95% CI)	129/142 (90,8; 84,9—94,5)
Absence of reflux at the SFJ, no./no total limbs (%, 95% CI)	114/117 (97,4; 93,3—99,0)
Length of the GSV stump, mean ± SD (mm)	16,7±9,0
Involution of the treated vein, no./no total limbs (%, 95% CI))	3/142 (2,1; 0,7—6,0)
No need for additional treatment for varicose tributaries, no./no total limbs (%, 95% CI)	104/142 (73,2; 65,4—79,8)
No need for repeated intervention on the treated vein, no./no total limbs (%, 95% CI)	129/142 (90,8; 84,9—94,5)
Absence of varicose vein recurrence as reported by the investigator, no./no total limbs (%, 95% CI)	134/142 (94,4; 89,3—97,1)
Absence of varicose vein recurrence as reported by the patient (symptomatic), no./no total limbs (%, 95% CI)	139/142 (97,9; 94,0—99,3)
Improvement in CEAP clinical class at 6 months, no./no total limbs (%, 95% CI)	53/72 (73,6; 62,4—82,4)
improvement in CEAP clinical class at 12 months, no./no total limbs (%, 95% CI)	27/49 (55,1; 41,3—68,2)
Improvement in VCSS score at 6 months, mean difference ± SD	–4,6±2,0
Improvement in VCSS score at 12 months, mean difference ± SD	–4,6±2,1

Note. CAE — cyanoacrylate embolization; CI — confidence interval; GSV — great saphenous vein; SD — standard deviation; SFJ — sapheno-femoral junction.

Table 2. **Adverse events associated with cyanoacrylate embolization of saphenous veins**

Characteristic of adverse event	Results
Serious adverse event, no,/no. of total pts. (%; 95% CI)	0/115 (0,0; 0,0—3,2)
Adverse event, no,/no. of total pts. (%; 95% CI)	33/115 (23,2; 16,4—31,7)
Multiple adverse event, no,/no. of total pts. (%; 95% CI)	14/115 (9,9; 5,7—16,7)
Number of adverse events per subject, mean ± SD	1,5±0,7
Phlebitis of the trunk, no,/no. of total limbs (%; 95% CI)	16/142 (11,3; 7,1—17,6)
Phlebitis with thrombosis of untreated tributaries, no,/no. of total limbs (%; 95% CI)	8/142 (5,6; 2,9—10,7)
Cord sensation, no,/no. of total limbs (%; 95% CI)	8/142 (5,6; 2,9—10,7)
Glue propagation out of the junction, no,/no. of total limbs (%; 95% CI)	3/142 (2,1; 0,7—6,0)
Hyper- or paresthesia, no,/no. of total limbs (%; 95% CI)	4/142 (2,8; 1,1—7,0)
Hypo- or anesthesia, no,/no. of total limbs (%; 95% CI)	1/142 (0,7; 0,1—3,9)
Subcutaneous granuloma, no,/no. of total limbs (%; 95% CI)	1/142 (0,7; 0,1—3,9)
Subcutaneous hematoma, no,/no. of total limbs (%; 95% CI)	2/142 (1,4; 0,4—5,0)
Deep vein thrombosis, no,/no. of total limbs (%; 95% CI)	1/142 (0,7; 0,1—3,9)
Allergy, no,/no. of total patients (%; 95% CI)	5/115 (4,3; 1,8—9,7)

Note. CI — confidence interval; SD — standard deviation.

Table 3. **Individual characteristics of adverse events after cyanoacrylate embolization of saphenous veins**

Patient, age (y.o.)	CEAP clinical class	Type of AE	Treated vein	Time onset	Time relief	Treatment
Female, 42	C3	Phlebitis of the trunk	GSV	14 d	14 d	Systemic NSAID
Female, 53	C3	Phlebitis of the trunk	GSV	13 d	7 d	Systemic NSAID
Female, 42	C3	Phlebitis of the trunk	GSV	5 d	3 d	Systemic NSAID
Female, 31	C2	Phlebitis of the trunk	GSV	6 d	4 d	Systemic NSAID
Male, 44	C4	Phlebitis of the trunk	GSVx2	24 m	5 d	Rivaroxaban 10 mg once daily + systemic NSAID
Male, 32	C2	Phlebitis of the trunk	GSV	14 d	7 d	Systemic NSAID
Male, 39	C2	Phlebitis of the trunk	SSV	14 d	5 d	Systemic NSAID
Male, 36	C2	Phlebitis of the trunk	GSV	6 d	8 d	Systemic NSAID
Male, 46	C3	Phlebitis of the trunk	GSV	4 d	6 d	Systemic NSAID
Male, 28	C4	Phlebitis of the trunk	GSV	7 d	7 d	Systemic NSAID
Male, 43	C4	Phlebitis of the trunk	GSV	11 d	6 d	Systemic NSAID
Female, 58	C2	Phlebitis of the trunk	GSV	10 d	4 d	Topical NSAID
Female, 48	C2	Phlebitis of the trunk	GSV	13 d	5 d	Systemic NSAID
Female, 48	C3	Phlebitis of the trunk	GSV	21 d	6 d	AH + topical NSAID
Female, 37	C2	Phlebitis of the trunk	GSV	17 d	5 d	AH + topical NSAID
Female, 37	C2	Phlebitis of the trunk	GSV	34 d	7 d	AH + topical NSAID
Female, 69	C4	Phlebitis with thrombosis of tributaries	GSV	10 d	5 d	Systemic NSAID
Female, 47	C3	Phlebitis with thrombosis of tributaries	GSV	7 d	3 d	Systemic NSAID
Female, 40	C4	Phlebitis with thrombosis of tributaries	GSV	10 d	5 d	Systemic NSAID
Female, 31	C2	Phlebitis with thrombosis of tributaries	GSV	7 d	7 d	Topical NSAID
Female, 46	C3	Phlebitis with thrombosis of tributaries	GSV	40 d	2 d	Topical NSAID
Male, 32	C2	Phlebitis with thrombosis of tributaries	GSV	14 d	7 d	Systemic NSAID
Male, 46	C3	Phlebitis with thrombosis of tributaries	GSV	6 m	4 d	Topical NSAID
Male, 43	C4	Phlebitis with thrombosis of tributaries	GSV	11 d	6 d	Systemic NSAID
Female, 39	C2	Cord sensation	GSV	7 d	1 m	No
Female, 68	C2	Cord sensation	GSV	7 d	1 m	No
Female, 29	C3	Cord sensation	GSV x2	1 m	3 m	No
Female, 59	C3	Cord sensation	GSV	1 m	6 m	No
Female, 40	C4	Cord sensation	GSV	1 m	4 m	No
Female, 38	C2	Cord sensation	GSV	1 m	5 m	No
Male, 41	C3	Cord sensation	SSV	5 d	3 m	No
Female, 34	C2	Glue propagation out of the junction (CFV occlusion of 25%)	GSV	1 w	9 m	No
Female, 47	C3	Glue propagation out of the junction (CFV occlusion of 25%)	GSV	1 w	6 m	No
Female, 33	C2	Glue propagation out of the junction (CFV occlusion of 50%)	GSV	1 w	12 m	Rivaroxaban 20 mg once daily for 1 m
Female, 39	C2	Paresthesia	GSV	1 d	12 m	No
Female, 34	C2	Paresthesia	GSV	1 d	12 m	No
Female, 59	C3	Paresthesia	GSV	1 d	1 m	No
Female, 42	C3	Paresthesia	GSV	1 d	3 m	No
Female, 47	C2	Hyposthesia	SSV	1 d	7 d	No
Female, 42	C3	Subcutaneous granuloma	GSV	12 d	4 m	Surgical removal
Female, 53	C2	Subcutaneous hematoma	GSV	1 d	7 d	No
Female, 48	C3	Deep vein thrombosis	GSV	4 w	3 m	Full-dose rivaroxaban for 3 months

Patient, age (y.o.)	CEAP clinical class	Type of AE	Treated vein	Time onset	Time relief	Treatment
Female, 33	C2	Allergy (local hives on both limbs)	GSV	1 d	1 d	Parenteral GCS for 3 d followed by AH for 10 d
Female, 33	C3	Allergy (local hives on the treated limb)	GSV	3 m	10 d	AH for 3 weeks
Male, 54	C4	Allergy (eczema of the treated limb)	GSV	3 m	1 m	Parenteral GCS for 10 d followed by AH for 3 w
Male, 48	C3	Allergy (hives on both libs)	GSV	1 d	3 d	Parenteral GCS once followed by AH for 3 days
Male, 44	C4	Allergy (conjunctivitis)	GSV x2	6 m	18 m	Oral and topical GCS + AH

Note. AE — adverse event; AH — antihistamine (drug); CFV — common femoral vein; GCS — glucocorticosteroid; GSV — great saphenous vein; NSAID — non-steroid anti-inflammatory drug; SSV — small saphenous vein; y.o — years old; d — day; w — week; m — month.

symptoms appeared at 24 months after bilateral CAE of the GSV. Due to the atypical presentation, the additional laboratory tests were performed. There was no D-dimer increasing, but the C-reactive protein (66,4 mg/L with the normal range of <1 mg/L) level was significantly elevated. The patient was treated with anticoagulation mg for 2 weeks and NSAIDs for 5 days with full relief of symptoms. Phlebitis with thrombosis of untreated tributaries was detected in 8 of 142 (5.6%) limbs at 7—180 days after the intervention. Four cases appeared unilateral and three cases concomitant to GSV phlebitis. All of them required treatment with systemic or topical NSAIDs until full relief within 2—7 days.

The cord sensation along the treated vein was registered in 8 (5.6%) limbs (7 GSV and 1 SSV). It was detected between 5 days and 1 month after the intervention and disappeared in all limbs within 1—6 months without specific treatment.

Glue propagation out of the SFJ with occlusion of 25—50% of common femoral vein lumen was observed in 3 (2.1%) limbs at 1 week after CAE. 50% occlusion of CFV required anticoagulation for 1 month. The two other cases were followed without specific treatment. An adhesive in the CFV resorbed within 9—12 months. No symptomatic venous thromboembolism was observed.

Sensitive disturbances was reported in 5 (3.5%) limbs. In four cases, it was represented by hyper- and paraesthesia occurred at the first day after CAE of GSV and resolved within 1—12 months. In these cases veins were cannulated at low-thigh (n=2) and upper-calf (n=2). The only case of hyposensitivity occurred after SSV cannulation at a lower calf. AE spontaneously resolved within 7 days.

A subcutaneous granuloma occurred in 1 (0.7%) limb after GSV embolization. It was detected at day 12 after the intervention at the site of vein cannulation in upper calf as a mildly painful lump with skin erythema around. DUS revealed the glue extravasation with a skin inflammatory reaction. The granuloma was followed for 4 months, no suppuration and/or extrusion were observed. Due to the persistence of symptoms, especially pain, it was removed surgically at another clinical center. Thus, information on the macroscopic structure and histological findings is not available. The complication occurred at the beginning of the learning curve and possibly was related to the glue extravasation. After that, it was decided to finish glue extraction distantly from the canulation point.

A subcutaneous hematoma was observed in 2 (1.4%) limbs at the point of cannulation. It did not require any additional procedures and spontaneously regressed within 7 days.

The symptomatic thrombosis of the peroneal and calf muscle deep veins was detected in 1 (0.7%) limb at 1 month after the intervention. Anticoagulation was prescribed for 3 months.

The non-severe systemic allergy was detected in 5 of 115 (4.3%) patients within 1 day — 6 months after embolization. In all subjects it was successfully treated with parenteral or oral glucocorticosteroids (GCS) and AH. In one patient, allergic conjunctivitis occurred at 6 months and required several courses of GCS and AH with full recovery after 18 months. Later this patient developed bilateral GSV phlebitis at 24 months as described above.

Discussion

The cyanoacrylate embolization is a reliable method to treat saphenous reflux [15]. The prospective observational study «eSCOPE» has demonstrated the 12-months occlusion rate of 93% for GSV [12]. The randomized clinical trial «VeClose» found no differences in recanalization between CAE and radiofrequency ablation (RFA) at five years [14]. The GSV occlusion rate after CAE at 1, 2, 3, and 5 years was 97.2, 95.3, 94.4, and 91.4% respectively [13, 14, 21, 22]. In the prospective cohort study «WAVES» the 12-months closure rate for GSV, SSV, and the anterior accessory saphenous vein was 100, 100, and 92%, respectively [23].

We presented the largest cohort of patients after CAE in Russia up to date. The results obtained do not differ from the previously reported and confirm the high efficacy of the method. The occlusion rate of 91% (95% CI 84.9—94.5%) at the medium follow up of 6 months may seem numerically lower than the previously reported. However, it should be considered that the mean GSV diameter in «eSCOPE» trial was 7.8±2.1 mm, «VeClose» — 6.9 mm, «WAVES» — 10.0±3.8 mm compared with the 8.7±2.6 mm in the current study. Undoubtedly, the diameter of the treated vein may affect technical success [24]. Despite the relatively long stump (16.7±9.0 mm), there was no evidence of reflux recurrence through the SFJ in the absence of recanalization. In fact, the stump length was comparable with the one in «VeClose» study after either CAE (22.5 mm) or RFA (18.9 mm).

Besides technical reliability, the other advantage of CAE is the absence of necessity for elastic compression, as was shown in the «eSCOPE» [12]. It demonstrated clinical improvement in all patients with the spontaneous regression of varicose tributaries in 40%. In the current study, the elastic compression was not used in 50 (35%) legs. The analysis of this subgroup showed CEAP clinical class reduction at 6 months in 17 of 27 (63%) followed limbs with a significant decrease of VCSS score form 6.0±2.3 to 1.4±1.4 (p<0.01). The incidence of spontaneous reduction of varicose tributaries with the cancellation of the scheduled intervention was demonstrated in the «WAVES» study [23]. Before CAE, the anticipated necessity for additional phlebectomy and sclerotherapy was 74 and 90%, respectively. However, at 3 months after the truncal embolization, it decreased to 14 and 66%, respectively. Data obtained in the current study are similar to the previously published. After 3 months, the additional sclerotherapy was required only in 27% of limbs, and 32% of limbs never needed intervention on tributaries. Clinical improvement in the VCSS score accompanied by the increase in quality of life after CAE was comparable with RFA in the «VeClose» trial [13, 14, 21, 22]. The figures of the VCSS score extracted at 6 months from the «VeClose» trial are similar to the current study.

The question of cyanoacrylate resorption is still under debate now. There is good evidence of chronic inflammatory response and appearing foreign body granulomas outside the vessel at 12 months after CAE [25], as well as anecdotical cases of saphenous vein excision at 5,5 years revealed the remnants of glue and collagenized mature fibrosis in the lumen accompanied by foreign body reaction around the vessel [26]. In the current study, it was impossible to identify the embolized GSV and/or remnant adhesive at 12—24 months in 3 limbs. This may be related to subtotal or total resorption of the glue and/or low resolution of DUS.

Phlebitis is the most common complication of CAE. It develops in up to 20% of cases [15]. It was suggested to be divided into natural phlebitis with the evidence of vein wall inflammation and hypersensitive type phlebitis (HTP) due to the immune reaction of the skin and soft tissues. The latter could occur either at the site or at the distance from embolized vein. It can be represented with the erythema, edema, pruritus, and tenderness and can be more responsive to AH than to NSAIDs. The etiology of this reaction is described as a combination of hypersensitivity of I and IV types [15]. However, in clinical practice, it is difficult to clarify the nature of the inflammatory reaction, so either natural phlebitis or HTP that occurred in the site of CAE were reported together in the current study. The observed incidence of 11,3% (95% CI 7.1—17.6%) does not exceed the previously published data. All except two phlebitis may be classified as mild as they duid not require medical treatment [27]. Oral anticoagulation was used only in one patient with bilateral phlebitis that occurred 24 months after the interventio. No severe forms with the prolonged reaction of 30 days and more or requiring vein excision was observed. The symptom onset (13±8 days) and duration (6±3 days) in 14 limbs, excluding the described atypical one, was comparable with previously reported (13±4 days and 11±5 days, respectively) [27].

The incidence of phlebitis with thrombosis of untreated tributaries of 5.6% (95% CI 2.9—10.7) did not differ significantly from previously published 3—4% [15]. This AE is usually reported as non-specific phlebitis or superficial thrombophlebitis that has no clear association with CAE. However, in the current study, 3 of 8 cases developed with the specific phlebitis of the trunk. So the real incidence of isolated lesion of varicose tributaries maybe even lower, accounting of 3.5% (95% CI 1.5—8.0%).

The other complications were rare and their incidence did not not exceed the previously published rates [15]. The glue extension, also known as «endovenous glue-induced thrombosis», was observed in 2.1% (95% CI 0.7—6.0%) and resolved within 12 months irrespective of anticoagulation. The nature of this condition is not fully understood. The raised questions are if there any thrombotic components that should require anticoagulation, or is it just an adhesive masses. However, for today the pulmonary embolism following CAE of saphenous veins has not been reported, and all glue propagations were successfully resolved [15, 28].

Subcutaneous granuloma that required surgical removal had also been described before [29]. This complication is related to suspected technical violations leading to the glue extravasation out of the vessel. In both cases, there was no evidence for spontaneous extrusion or suppuration within 3 weeks — 4 months. However, anecdotical case of granulomatous phlebitis that led to the extraction of glue from the vein lumen with skin suppuration, necrosis, and ulceration, required total removal of the embolized trunk, had been presented [30]. Such complications are rare but they need to be discussed with patients before treatment.

Limitations. The sample size was low, loss to follow up at 6 months eas relatively high. This was a cohort study wuth no controls. All this can be the reason for bias. De-

spite this, the study provides real life data about CAE, that complement previously published results.

Conclusions

Cyanoacrylate endovenous embolization is a reliable method for the treatment of saphenous veins incompetence with acceptable rates of predominantly non-severe and self-limited adverse events and low rate of re-interventions. However, the specific reactions on adhesive implantation should be discussed with the patients before the treatment. Also, specific selection criteria should be developed to determine the patients with minimal risk for adverse events.

Authors' contribution:
General responsibility — K. Lobastov
Designed the study — K. Lobastov, L. Laberko, I. Popov
Collected the data —E. Murzina, A. Bargandzhiya
Analyzed the results and wrote the manuscript draft — E. Murzina, K. Lobastov
All authors reviewed the manuscript draft and accepted it.

Conflict of interest: the study was performed without any financial or technical support. E.L. Murzina received the honoraria for master-classes from the Medtronic Company. K.V. Lobastov, A.B. Bargandzhiya, L.A. Laberko, I.B. Popov declare no conflict of interest.

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