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Comparison of cyanoacrylate agents VariClose® and VenaSeal™ in the treatment of insufficient saphenous veins

Peter Baláž[a,b,c], Slavomír Rokošný[a], Adam Whitley[a,d]

[a] *Division of Vascular Surgery, Third Faculty of Medicine, Charles University and University Hospital Královské Vinohrady, Prague, Czech Republic*
[b] *Cardiocentre, Third Faculty of Medicine, Charles University, Prague, Czech Republic*
[c] *Department of Vascular Surgery, National Institute of Cardiovascular Diseases, Bratislava, Slovak Republic*
[d] *Department of Anatomy, Second Faculty of Medicine, Charles University, Prague, Czech Republic*

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SOUHRN

Úvod: Cílem této studie bylo porovnat dva systémy uzavírání žil kyanoakrylátovým lepidlem, VenaSeal™ a VariClose®, v léčbě povrchové žilní insuficience.
Metody: Byla provedena retrospektivní analýza pacientů léčených od dubna 2018 do dubna 2022 kyanoakrylátovými lepidly pro insuficienci povrchových žil dolních končetin v jednom centru.
Výsledky: Systém VariClose® byl použit u 27 pacientů (30 žil) a systém VenaSeal™ u 97 pacientů (125 žil). Medián sledování pacientů léčených systémy VariClose® a VenaSeal™ dosahoval 267 (IQR 223) a 201 (IQR 280) dnů. Po roce došlo k rekanalizaci u 11 žil léčených systémem VariClose® a u 5 žil léčených systémem VenaSeal™. Míra okluze odhadnutá Kaplanovou–Meierovou metodou v 30, 90, 180 a 360 dnech činila pro žíly léčené systémem VariClose® 100 %, 96 %, 83 % a 42 % a pro žíly léčené systémem VenaSeal™ 100 %, 98 %, 96 % a 91 % ($p < 0,01$).
Závěr: Systém VenaSeal™ měl významně lepší míru okluze než systém VariClose®.

Keywords:
Cyanoacrylate
VariClose®
Varicose veins
VenaSeal™
Venous insufficiency

ABSTRACT

Objective: The goal of this study was to compare the cyanoacrylate venous sealing systems VenaSeal™ and VariClose® in the treatment of superficial venous insufficiency.
Methods: A single-centre retrospective analysis on patients treated between April 2018 and April 2022 with cyanoacrylate adhesives for lower limb superficial truncal vein insufficiency was performed.
Results: The VariClose® system was used in 27 patients (30 veins) and the VenaSeal™ system in 97 patients (125 veins). The median follow-up periods for patients treated with VariClose® and VenaSeal™ systems were 267 (IQR 223) and 201 (IQR 280) days, respectively. At one year, recanalization occurred in 11 veins treated with the VariClose® system and 5 veins treated with the VenaSeal™ system. The occlusion rates estimated by the Kaplan–Meier method at 30, 90, 180, and 360 days were 100%, 96%, 83%, and 42% for veins treated with the VariClose® system and 100%, 98%, 96%, and 91% for veins treated with the VenaSeal™ system ($p < 0.01$).
Conclusions: The VenaSeal™ system had significantly better occlusion rates than the VariClose® system.

Introduction

Treatment of superficial venous insufficiency has changed dramatically in the last decade. Endovenous laser and radiofrequency ablation are currently the most frequently used treatments and are recommended with a high level of evidence in the current clinical guidelines.[1,2] In recent years, a new non-thermal treatment called vein sealing has been gaining popularity. It consists of occlusion of insufficient truncal veins with cyanoacrylate glue and its main advantages over endovenous ablation techniques are that it does not require tumescent anesthesia or post-procedural compression.

According to current guidelines cyanoacrylate adhesive closure systems should be considered when a non-thermal non-tumescent technique is preferred.[1] The most popular cyanoacrylate adhesive closure devices are the VenaSeal™ closure system (MEDTRONIC, United States

Address: MUDr. Adam Whitley, Department of Surgery, University Hospital Královské Vinohrady, Šrobárova 1150/50, 100 34 Praha 10, e-mail: whitley.adam@gmail.com
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of America) and the VariClose® vein sealing system (BIOLAS, Turkey). The main difference between them is that the VariClose® system is associated with a shorter polymerization time.

VenaSeal™ has been shown to have occlusion rates consistently above 90%.[3] Similar excellent results have been shown for the VariClose® system. A recent meta-analysis analyzed studies investigating outcomes of treatment with the VariClose® system. Seven studies were included, and pooled occlusion rate at one year was 96.8%.[4] We published our initial experience with VariClose® in 2021 and reported a surprisingly much lower occlusion rate of 65% at six months.[5] This was the first study on VariClose® coming from outside of Turkey. Then we followed our single-centre study with a national study from four centres in the Czech Republic, with a total of 79 treated veins. The occlusion rate at 12 months was 36%, considerably lower than the previous reports in the literature.[4,6]

We now no longer use the VariClose® system and are instead using the VenaSeal™ system. The reason for performing this study was to compare the clinical efficacy of VariClose® and VenaSeal™ in terms of occlusion and complication rates from a single centre in the Czech Republic.

Material and methods

Study design and patient selection

All patients treated with VariClose® and VenaSeal™ sealing system between April 2018 and April 2022 in the Centre of Venous Surgery of the Clinic ISCARE in Prague were included in the study. Patients were offered treatment with a cyanoacrylate adhesive closure system if they presented with symptomatic insufficiency of the great saphenous vein or small saphenous vein confirmed by duplex ultrasound and did not have any contradictions to the treatment. Between April 2018 and November 2019 we used the VariClose® system. This group of patients was used in our previous two studies.[5,6] From May 2019 to April 2022 we used the VenaSeal™ system. Between May and November 2019 patients could choose either option. Contraindications to treatment with a cyanoacrylate adhesive closure system were defined as the presence of deep venous thrombosis, active superficial thrombophlebitis, hypercoagulable disorders treated with anticoagulants, a history of sensitivity to cyanoacrylate or local anesthesia, saphenous vein diameter of more than 12 mm and pregnancy.

Study and treatment plan

Before the procedures each patient underwent a focused physical examination, which included determination of the Clinical Etiology Anatomy Pathophysiology (CEAP) category and Venous Clinical Severity Score (VCSS). All patients signed informed content. Immediately after the procedure, each patient was asked about the severity of their pain during the procedure. Pain was assessed on a numerical scale where 1 indicated no pain; 2 light pain; 3 moderate pain; and 4 severe pain. Post-procedural check-ups were performed within the first month and then at 6 and 12 months. At each check-up all patients underwent duplex ultrasound examination and VCSS assessment.

Study endpoints

The primary endpoint of the study was assessment of occlusion with duplex ultrasound. The secondary endpoints were changes in VCSS before and after procedure and occurrence of postprocedural complications such phlebitis-like reactions, hematoma, and ecchymosis.

Devices and procedure

The procedures were performed in an outpatient setting without tumescent anesthesia and compression stocking were not used after procedures. The VariClose® and VenaSeal™ procedures were performed according to the instructions published by Bozkurt in 2016 and Morrison in 2015.[7,8] In brief, the micro-puncture kit was introduced percutaneously under ultrasound control at the level of the lowest insufficient point of the venous reflux. After this the 5F introducer sheath was advanced over the "J" guidewire to the saphenous-femoral/popliteal junction under ultrasound control. The delivery catheter filled with glue was connected to the injection gun and inserted into the introducer sheath and using direct ultrasound visualization positioned 3 cm distal to the saphenous-femoral/popliteal junctions when the VariClose® system was used and 5 cm when the VenaSeal™ system was used. With application of the adhesive accompanied with external pressure, the saphenous vein was sealed. Technical success was defined as occlusion of the saphenous vein with patency of the femoral or popliteal vein at the end of the procedure.

Definition of the vein occlusion

Occlusion of the treated saphenous vein was defined as absence of flow and a non-compressible vein confirmed with duplex ultrasound. The veins were occluded when flow was only present within the proximal 3 cm from the saphenous-femoral/popliteal junctions when using the VariClose® system and within the proximal 5 cm when using the VenaSeal™ system.

Statistical analysis

The normality of numerical variables was tested with the Shapiro–Wilk's test ($p > 0.05$), visual inspection of histograms, normal Q-Q plots and box plots. Descriptive statistics are expressed as mean ± standard deviation (SD) for normally distributed numeric data and median and interquartile range (IQR) for data that did not follow a normal distribution. Categorical data are expressed as percentages. The ANOVA test was used to compare the means of normally distributed data. For comparison of categorical data, the χ^2 test was used. The cumulative occlusion rate of treated vein was analyzed using the Kaplan–Meier method. Patients lost to follow-up were censored. Calculations were done using SPSS version 26 (IBM, Somers, NY, USA).

Results

Demography and baseline characteristics

One hundred and twenty-five insufficient saphenous veins in 97 patients were treated with the VenaSeal™

Table 1 – Demographic and baseline characteristics

	Total	VariClose®	VenaSeal™	*p*-value
Veins treated	155	30	125	
Number of patients	124	27	97	
Females	106 (68%)	23 (77%)	83 (65%)	0.27
Mean age	54 (SD±13)	47 (SD±12)	56 (SD±13)	<0.05
Right leg	80 (52%)	18 (60%)	62 (49%)	0.54
GSV	139 (89%)	28 (93%)	111 (89%)	0.46
Mean vein diameter (mm)	7.0 (SD±1.9)	6.3 (SD±1.5)	7.2 (SD±1.9)	0.38
CEAP classification				
C1	2 (1%)	0	2 (2%)	<0.05
C2	59 (38%)	0	59 (47%)	
C3	68 (43%)	29 (96%)	39 (31%)	
C4	7 (5%)	1 (1%)	6 (5%)	
C5	6 (4%)	0	6 (5%)	
C6	13 (8%)	0	13 (2%)	
Mean VCSS	5.2 (SD±4.9)	3.9 (SD±1.9)	5.5 (SD±5.3)	0.12

CEAP – Clinical Etiology Anatomy Pathophysiology; GSV – great saphenous vein; VCSS – Venous Clinical Severity Score.

Table 2 – Procedure characteristics

	Total	VariClose®	VenaSeal™	*p*-value
Veins treated	155	30	125	
Technical success	151 (97%)	26 (87%)	125 (100%)	<0.05
Glue amount (ml)	1.6 (IQR 0.8)	1.9 (IQR 0.4)	1.6 (IQR 0.7)	0.05
Mean pain severity	1.6 (SD±0.6)	1.7 (SD±0.7)	1.5 (SD±0.6)	0.94
Mean procedure length (min)	28 (SD±8.0)	27 (SD±9.5)	29 (SD±7.6)	0.36
Hematoma	5 (3%)	0	5 (4%)	0.36
Ecchymosis	7 (5%)	1 (3%)	6 (5%)	0.59
Phlebitis-like reactions	31 (20%)	8 (26%)	23 (18%)	0.21

system and 30 insufficient saphenous veins in 27 patients were treated with the VariClose® system.

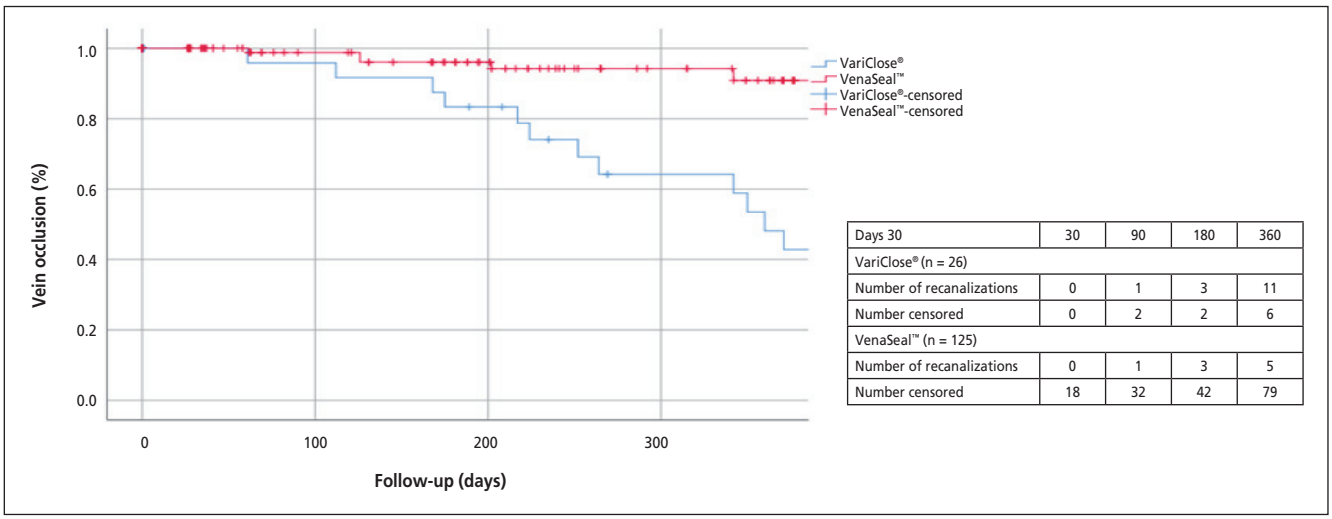
In the majority of patients (89%), the treated incompetent vein was the great saphenous vein. The mean vein diameter measured at the level of saphenous-femoral/popliteal junctions was 6.3 mm (SD±1.5) in patients treated with the VariClose® system and 7.2 mm (SD±1.9) in patients treated with the VenaSeal™ system. The average Venous Clinical Severity Score before surgery was 5.2 (SD±4.9). Detailed demographic and baseline characteristics are shown in Table 1.

Procedure

The average procedure time was 28 minutes. Technical success, defined as complete occlusion after delivery of cyanoacrylate into the vein confirmed by ultrasound at the end of the procedure, was noted in all veins treated with the VenaSeal™ system and in 26 (87%) of the 30 veins treated with the VariClose® system. The reason for technical failure was caused by polymerization of the venous glue within the delivery catheter blocking further glue from being released and resulting in incomplete ablation of the vein. These four cases were excluded from further analysis. Average pain score during the procedure was 1.6 with no significant difference between the two treatments. Detailed procedure characteristics are shown in Table 2.

Follow-up

The median follow-up period was 267 days (IQR 223) for patients treated with the VariClose® system and 201 days (IQR 280) for patients treated with the VenaSeal™. One-month follow-up visits were completed in 26 patients (26 veins) treated with the VariClose® system and in 87 patients (107 veins) treated with the VenaSeal™ system. Six-month follow-up visits were completed in 18 patients (18 veins) treated with the VariClose® system and in 49 patients (65 veins) treated with the VenaSeal™ system. Twelve-month follow-up visits were completed in 13 patients (13 veins) treated with the VariClose® system and in 31 patients (40 veins) treated with the VenaSeal™ system.



Days 30	30	90	180	360
VariClose® (n = 26)				
Number of recanalizations	0	1	3	11
Number censored	0	2	2	6
VenaSeal™ (n = 125)				
Number of recanalizations	0	1	3	5
Number censored	18	32	42	79

Fig. 1 – Kaplan–Meier curve with number of recanalized veins and patients lost to follow-up (censored) over time.

Occlusion rate

Veins were considered occluded when on duplex ultrasound examination they were non-compressible with no signs of blood flow with the exception of the proximal 3 cm from the saphenous-femoral/popliteal junctions when using the VariClose® system and the proximal 5 cm when using the VenaSeal™ system. At one-year follow-up there were a total of 11 recanalizations from 26 veins (42%) treated with the VariClose® system and 5 from the 125 veins (4%) treated with the VenaSeal™ system. The estimated occlusion rates for the VariClose® and VenaSeal™ systems calculated by the Kaplan–Meier method are presented in Fig. 1. The overall occlusion rates estimated by the Kaplan–Meier method at 30, 90, 180, and 360 days were 100%, 96%, 83%, and 42% for patients treated with the VariClose® system and 100%, 98%, 96%, and 91% for patients treated with the VenaSeal™ system. The log-rank test revealed the difference in occlusion rates between the two systems to be significant (p <0.01) (Fig. 1).

Clinical outcome

The most frequent postprocedural complications were phlebitis reactions, which occurred in a total of 31 cases (20%) without differences between the groups. Deep vein thrombosis was not confirmed in any case during follow-up. Average length of analgesia use was two days in both groups and the average number of days until returning to work was one day in both groups. Detailed clinical outcome characteristics are shown in Table 2. The mean preintervention VCSS for patients treated with the VariClose® system was 3.9 (SD±1.9) and for patients treated with the VenaSeal™ system was 5.5 (SD±5.3) (p = 0.12). At 180 days after treatment the mean VCSS score was 2.0 (SD±2.3) for the patients treated with the VariClose® system and it was 1.0 (SD±2.7) for the patients treated with the VenaSeal™ system (p = 0.34). At one-year follow-up the mean VCSS scores for patients treated with the VariClose® and VenaSeal™ systems were 2.5 (SD±2.2) and 1.0 (SD±2.7), respectively (p = 0.64). In 10 veins (38%) treated with the VariClose® system and in 2 veins (2%) treated with the VenaSeal™ system, endovenous laser ablation was performed as a reintervention due to recanalization with recurrence of symptoms.

Discussion

Four different cyanoacrylate adhesive closure systems (VariClose®, VenaSeal™, VenaBlock™, and Veinoff™) are available on the world market for the treatment of peripheral veins, but only two products, VariClose® and VenaSeal™ are registered and approved by the State Institute for Drug Control in the Czech Republic. Both sealing systems are catheter-assisted endovenous techniques that work to deliver n-butyl cyanoacrylate into the vein lumen with subsequent activation of polymerization. The main difference between them is that VenaSeal™ has a higher viscosity and takes longer to polymerize than VariClose®. Polymerization begins approximately 5 seconds after contact with blood in the VariClose® system and after 1 second with the VenaSeal™ system. Polymerization takes nearly 3 minutes to complete in the VenaSeal™ system, but in the VariClose® system it is almost instantaneous.

Even though different mechanisms of action exist between both systems data available in the literature until year 2021 revealed very similar results for the two systems. The VariClose® randomized trial, which compared radiofrequency and with the VenaSeal™ system, demonstrated a high occlusion rates of 94.4% at 36 months for the VenaSeal™ system.[9] According a meta-analysis[4] from 2019, which included all studies on the VariClose® system published at that time and analyzed a total of 918 patients (1000 limbs), the occlusion rate at 6 months was 97.3%. Good results reported in the literature was the reason for us to start using the VariClose® system. Between April 2018 and November 2019, we used the VariClose® system. Our preliminary results with VariClose® system were published in 2021.[5] We followed up our first study with a nationwide study from four centres in the Czech Republic.[6] The low occlusion rates in both studies was the impetus for us to abandon the VariClose® system and instead start using the VenaSeal™ system. This pre-

sented us the unique opportunity to compare two different cyanoacrylate adhesive closure systems, which is, to the best of our knowledge, the first such analysis. In the present study, we retrospectively analyzed 30 superficial truncal veins treated with the VariClose® system and 125 superficial truncal veins treated with the VenaSeal™ system. The majority of patients was classified as either C2 or C3 according to the CEAP classification, indicating less severe venous insufficiency. Demographic and baseline data were similar in both groups. The first noted difference was technical success of the procedure, defined as complete vein occlusion after ablation with a patent common femoral or popliteal vein confirmed by ultrasound at the end of the procedure. For the VenaSeal™ system technical success was 100%, but for the VariClose® system technical success was 87% due to failure in four patients. The failure was caused by premature polymerization of the glue within the delivery catheter preventing further glue from being administrated. These four cases of technical failure were excluded from further follow-up and are not included in the Kaplan–Meier analysis nor further clinical postprocedural assessment analysis.

Even though demographic and baseline characteristics and complications were similar in the two groups of patients, the difference in occlusion rates was dramatic. The overall occlusion rates at 1, 3, 6, and 12 months for patients treated with the VariClose® system were 100%, 96%, 83%, and 42%, respectively, which is much lower than reported in the literature prior to our previous two studies.[7,10–15] On the other hand, the occlusion rates of patients treated with the VenaSeal™ system at 1, 3, 6, and 12 months were 100%, 98%, 96%, and 91%, which are more similar to the current literature.[16,17]

One reason for the worse results of the VariClose® system may be limited experience with it. However, results from our multicentre study on the VariClose® system in the Czech Republic were also poor.[6] Additionally, we had as little experience with the VenaSeal™ system as with VariClose® before the start of the study period.

Another explanation of the different rates of occlusion rate in VariClose® group and results of previously published studies is probably due to non-uniformity in the definition of recanalization. A uniform internationally recognized definition is mandatory. In our study we define recanalization as presence of flow and vein compressibility detectable by ultrasound in any part of the saphenous vein apart from the first 3 cm for the VariClose® system and first 5 cm for the VenaSeal™ proximal to the sapheno-femoral/popliteal junctions. On the other hand, Bozkurt and Yilmaz,[7] Calik et al.,[10] and Koramaz et al.[12] define recanalization as a patent segment of saphenous vein more than 5 cm in length without regard of the location. Tekin et al.[11] define recanalization as a patent segment of the treated vein segment more than 10 cm in length, similarly without regard to location. Tok et al.,[13] Eroglu et al.,[14] and Bademci et al.[15] use the terms partial and complete occlusion without stating a definition for them. According to Bissacco et al.'s meta-analysis,[4] which included a total of 918 patients (1000 limbs) treated with VariClose®, the occlusion rate at 6 month was 97.3%, which contrasts to the 6-month occlusion rate of 83% in our study. The reported high rate of occlusion in Bissacco et al.'s meta-analysis[4] is probably due to differences in definition of recanalization and considering veins with partial flow as occluded. We believe that our definition of recanalization is clear and doesn't make confusion in reports of occlusion of treated veins.

Despite the differences in occlusion rates a decline in VCSS was noted in for both systems and the difference in reduction of VCSS was not significant between the two treatments. The explanation for this finding may be that even in recanalized veins there likely remains a variable amount of adhesive substance in the lumen, which decreases the severity of the reflux and results in some clinical improvement.

The high recanalization rates in VariClose® group and need for additional reinterventions, which was more frequently needed in for patients treated with the VariClose® system than with the VenaSeal™ system was the reason for premature termination of using VariClose® device in our centre and since December 2019 we have been using the VenaSeal™ system exclusively.

The main limitation of the present study is its retrospective, non-randomized character, and lack of complete follow-up data. Data from patients treated with the VariClose® system were used in our previous publications.[5,6] However, due to our bad experience with this venous glue we did not want to use it in more patients as we felt this would be unethical. The present study is the first comparative study of two different venous glues and one of the few analyses performed outside of Turkey demonstrating very surprising information contrasting with data presenting in the literature.

Conflict of interest
The authors declare no potential conflicts of interest with respect to the research, authorship, and publication of this article.

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Ethical statement
This was a non-experimental observational study analyzing anonymized retrospective data. Ethical approval was waived.

Guarantor
PB

Contributorship
PB – study design, data collection, statistical analysis, manuscript draft.
SR – data collection, revision of manuscript.
AW – study design, revision of manuscript.

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