Communication

Early Results of the Sandwich Technique Using Cyanoacrylate Glue and Polidocanol Foam Sclerotherapy for the Treatment of Varicose Veins

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Early Results of the Sandwich Technique Using Cyanoacrylate Glue and Polidocanol Foam Sclerotherapy for the Treatment of Varicose Veins

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Abstract: Background. This is a retrospective analysis of the results of treatment for varicose veins using the sandwich technique with cyanoacrylate glue and foam sclerotherapy. This novel method allows for substantial reduction of amount of glue needed for the vein closure, and minimizes the risk of granuloma formation and allergic reaction related to the epifascial administration of cyanoacrylate. **Methods:** This technique was used in 60 patients, 77 intrafascial veins were managed. Vein closures were performed with Venex cyanoacrylate glue and 1-3% polidocanol foam. All procedures were done under ultrasonographic control, though direct percutaneous punctures of target veins. Follow-up were scheduled 1-3 week after the procedure. If revealed, unclosed segments of the target veins were obliterated at these follow-up visits, with glue and/or sclerotherapy. **Results.** There were no serious adverse events intra- or postprocedurally. The technical success rate was 100%. The primary success rate at 1-3 week follow-up was 84.4%. The primary assisted success rate, after additional closures, was 100%. **Conclusions.** We demonstrated that the treatment for varicose veins, using sandwich technique, which combines cyanoacrylate glue and foam sclerotherapy, can be safe and efficient.

Keywords: cyanoacrylate glue; foam sclerotherapy; varicose veins

1. Introduction

From the beginning of the 21st century there was a substantial change in the treatment for varicose veins — a shift from traditional surgical excision to the less invasive techniques, primarily endovenous ones [1,2]. At the same time, the long-term results of treatment improved, while the procedures became more acceptable for patients. At the moment, there are two main modes of the treatment for lower extremity varicosities: endothermal techniques, comprising laser, radiofrequency and steam ablations of incompetent superficial veins; and non-thermal methods, comprising liquid or foam sclerotherapy, mechanical occlusion chemically assisted endovenous ablation (MOCA) [3] and endovenous application of cyanoacrylate glue. While the thermal methods are more efficient in the long-term, they can be associated with an injury to the adjacent nerves [4–7]. In comparison with thermal ablations, non-thermal methods are associated with higher rates of varicose vein recurrences, especially if large diameter saphenous veins are managed. This particularly concerns sclerotherapy; therefore this method is not recommended for the management of intrafascial incompetent veins that are wider than 6 mm.

Cyanoacrylate glues have already been used for the embolization of small aneurysms, endoleaks, bleeding esophageal varices, gastrointestinal bleeding and vascular malformations. These procedures have been demonstrated to be relatively safe and efficient. During the last decade cyanoacrylates have been introduced to the varicose veins management [8–12]. Recent trials have demonstrated that the treatment with glue can be as effective as thermal methods, but without the risk of nerve injury [13–18]. The procedure for varicose veins with the use of N-butyl cyanoacrylate is quite simple: the glue is delivered via catheters or by percutaneous injection, and the target vein is compressed for a short time until the glue polymerizes. Side effects are infrequent and usually mild. The most common complication, occurring in about 10% of patients, is phlebitis, which typically is transient, low-symptomatic and does not require intervention. Severe side effects comprise allergic

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reactions, granuloma formation at the side of glue injection, protrusion of glue into the deep veins, and distal embolization [4,19–23]. These serious complications are rare, yet they are potentially life-threatening [24]. Although a high-quality evidence coming from clinical trials in terms of risk factors of these side effects is lacking, data from open-label studies and case series suggest that these dangerous adverse events are primarily associated with extravasal application of cyanoacrylate, glue embolization of epifascial varicose veins, large volumes of injected glue and the treatment in patients with known hypersensitivity to chemical compounds (not only to cyanoacrylates).

In this retrospective analysis we present results of the treatment for varicose veins with the use of a novel technique: application during the same procedure of cyanoacrylate glue and foam sclerosant, using the sandwich technique. This new method allows for substantial reduction of amount of glue needed for the vein closure, and minimizes the risk of granuloma formation and allergic reaction related to the epifascial administration of cyanoacrylate.

2. Materials and Methods

We have performed the closure of varicose veins using the sandwich approach in 60 patients, 23 males and 37 females. In 10 patients both legs were addressed during the same procedure. In total, 81 intrafascial veins were managed. Since the treatment of varicose veins with endovenous glue is not reimbursed in our country, all patients were self-referred. For the treatment of varicose veins with this particular method, there were included only those patients who presented with incompetent intrafascial veins, which were wider than 6 mm in the ultrasonographic examination performed in the standing position. Maximal diameter of the target veins revealed by ultrasound in this patient series varied from 8 mm to 18 mm.

The so-called intrafascial veins of the lower extremity comprise the great saphenous vein, the small saphenous vein, the anterior accessory saphenous vein and the Giacomini vein. These veins are enclosed by two fibrous sheaths: the membranous layer of the subcutaneous tissue and the muscular fascia; these two layers separate the vein from the adjacent subcutaneous tissue and skin [25]. Intrafascial veins are the blood vessels that are most commonly affected by varicose vein disease. In this patient series we also included patients presenting with huge neovascularization networks in the groin, resulting from previous unsuccessful open surgical treatment. These neovascularizations are located, at least partially, intrafascially. Anatomical distribution of incompetent veins managed with our novel technique of glue ablation is presented in Table 1.

Table 1. Anatomical location of intrafascial veins treated with cyanoacrylate glue.

Target vein	No of patients
Right lower extremity	
Great saphenous vein	32
Small saphenous vein	6
Great saphenous vein + Small saphenous vein	1
Great saphenous vein + Anterior accessory saphenous vein	1
Great saphenous vein + neovascularization in the groin	2
Anterior accessory saphenous vein	2
Neovascularization in the groin	2
Great saphenous vein + Giacomini vein	2
Small saphenous vein + Giacomini vein	2
Small saphenous vein + Anterior accessory saphenous vein	1
Both great saphenous veins	1
Both small saphenous veins	6
Both anterior accessory saphenous veins + Great saphenous vein	3
	1

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Left lower extremity	31
Both lower extremities	19
	10

All procedures were performed under ultrasonographic control, with the use of 8-11 MHz linear probe. No anesthesia was needed. After mapping of incompetent superficial veins and planning the procedure, firstly the incompetent intrafascial veins (great saphenous vein, small saphenous vein, anterior accessory saphenous vein, Giacomini vein or intrafascially located neovascularizations) were addressed. Cyanoacrylate glue was injected into the most critical locations, like the area 2-4 distally from the saphenofemoral or saphenopopliteal junction, connection of intrafascial segment of the incompetent saphenous vein with epifascial incompetent tributary, or most severe dilatations of saphenous vein. N-butyl cyanoacrylate glue (Venex, Vesta Medical Devices, Ankara, Turkey) was used. This endovascular glue is registered for the closure of varicose veins. Of note, this particular cyanoacrylate glue, after contacting with water, polymerize within few seconds, allowing for very precise administration, with minimal risk of undesired closure far away from the site of injection. The glue was administered from 1mL tuberculin syringe in small drops, 0.1-0.2 mL each, under ultrasonographic control, through direct puncture using a 25G (0.50 mm) needle. The length of the needle depended on the depth of the target vein. We used 16 mm, 25 mm or 50 mm long needles. In general, the needle had to be as short as possible to facilitate the administration of hyperviscous glue. After injection of the glue and needle withdrawal, this area was gently pressed with the ultrasonographic probe for about 60 s. Maximal volume of the glue administered during the procedure was 1.0 mL, usually it was 0.8-0.9 mL. Remaining unclosed segments of the target vein and epifascially located varicosities were managed with foam sclerotherapy. For this purpose we used 1%-3% polidocanol (Aetoxysklerol, Kreussler Pharma, Wiesbaden, Germany) mixed with room air in proportion 1:4, using the standard Tessari method to obtain the sclerosing foam. All foam injections were performed under ultrasonographic control, through a 26G (0.40 mm) needle. Foam was firstly administered in 0.5-1.0 mL boluses between previously injected drops of cyanoacrylate glue. In this way a "sandwich" consisting of glue drops and sclerosing foam completely closed the target intrafascial vein. If needed, in order to close fragments of the vein that still remained open, additional small volumes of glue were injected. Then, polidocanol foam was administered to the varicosities located epifascially. If the intrafascial vein was managed with 2% or 3% polidocanol, usually for the closure of superficial varicose veins less concentrated sclerosant was used (e.g. 1%). The total volume of administered sclerosing foam was usually about 5 mL, and never exceeded 10 mL. If larger volumes of sclerosing foam were needed to close the varicosities, it was postponed until the follow-up. Duration of the treatment, including pre- and postprocedural ultrasonographic screening, was usually about 15 minutes. After completion of the procedure, elastic adhesive bandages were applied, and the patients were recommended to wear these bandages for at least 2 days. In a case of large epifascial varicosities, in order to minimize the risk of painful phlebitis, patients were recommended to wear bandages until the next visit. Except for bandages, patients were allowed to walk normally and execute their normal daily activities.

Typically, follow-up was performed 2 weeks after the procedure. Still, if it was inconvenient for the patient, or an earlier control seemed desirable, follow-up was scheduled 1 week earlier or later. At the follow-up detailed ultrasonographic examination of the treated lower extremity was performed. This check-up, in addition to the assessment of the closure of previously managed incompetent veins, was focused at revealing possible deep venous thrombosis, protrusion of injected glue into the deep venous system, and other complications related to the procedure. If there were unclosed segments of the target veins, they were closed–either with additional small volumes of glue, additional foam sclerotherapy, or combination of both. Besides, unclosed epifascial varicosities were managed with foam sclerotherapy. Patients with partially successful primary procedure were then scheduled for second follow-up, also performed about 2 weeks later. During this second follow-up the patients underwent the same assessment as during the first one. If needed, additional foam

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sclerotherapies were performed. The same regarded the patients who required more sessions to completely close the remaining small varicosities.

For the purpose of this survey, we defined the primary success rate as completely closed target intrafascial vein(s) at the first follow-up (1-3 weeks after the procedure), regardless of the presence of remaining small epifascial varicosities that still required foam sclerotherapy. Similarly, we defined the assisted primary success rate as completely closed target intrafascial vein(s) at the second or third follow-up.

3. Results

In all patients the procedures underwent uneventfully. There were no allergic reactions, severe pain associated with punctures, bleeding, nor other adverse events during the procedure. Similarly, there were no complications associated with foam sclerotherapy, including neurologic symptoms. Immediately after the procedure all target intrafascial veins were contracted, filled with the glue and sclerosing foam. There were no remaining patent segments of these veins visible on ultrasound. Deep veins of the managed extremity were patent, with no signs of thrombosis or protrusion of the glue into them. Thus, the technical success rate was 100%, without any concerns regarding the safety.

Out of 60 patients, 2 of them did not show at the follow-up. Therefore, early results of the treatment could be evaluated in 58 cases. In all 58 patients ultrasonographic examination performed during the first follow-up did not reveal deep vein thrombosis. Neither there were protrusions of injected glue into the deep veins. Patients did not report any serious adverse events occurring between the procedure and the first post-procedural follow-up. Only a few patients reported moderate pain at the site of managed intrafascial vein, still such a pain was transient and did not require intervention, except for mild analgesics. Similarly, there were neither severe phlebitis associated with sclerotherapy, nor inflammatory skin reactions suggesting hypersensitivity to the injected cyanoacrylate.

In 49 cases at the first post-procedural follow-up the target intrafascial veins were completely closed. Thus, the primary success rate was 84.4%. In 27 patients (55.1%) an additional foam sclerotherapy of remaining small varicosities was performed. Other 22 patients (44.9%) did not require further treatments. The remaining 9 patients underwent additional closures of the patent venous segments. Two of them were managed with additional cyanoacrylate glue injection, 6 with foam sclerotherapy, and 1 patients with glue combined with sclerotherapy. At the second follow-up only 2 patients required additional foam sclerotherapy for unclosed vein segment. At the third follow-up all these patients had their target veins completely closed. Thus, the assisted primary success rate was 100%. There were no serious adverse events related to all these additional procedures.

Table 2 summarizes early results of the treatment. In this table we present success rates in particular veins. Of note, since in many patients more than one anatomical location was addressed, more veins than patients have been assessed.

Table 2. Early results of the treatment.

Vein [1]	No of veins managed	Primary success rate	Primary assisted success rate
Great saphenous vein	50	92.0%	100%
Small saphenous vein	14	85.7%	100%
Anterior accessory saphenous vein	6	100%	100%
Giacomini vein	3	100%	100%
Neovascularization in the groin	4	25.0%	100%

[1] Only 58 patients who came for postprocedural follow-up are included; since in some patients more than one anatomical location was addressed, in total there are more veins than the patients.

4. Discussion

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In this retrospective analysis of patient series we demonstrate that the treatment for varicose veins using our novel sandwich technique, which combines cyanoacrylate glue and foam sclerotherapy, can be safe and efficient. Our early results are comparable to the treatments that utilized N-butyl cyanoacrylate only, administered through dedicated applicators [8,9,21]. A similar sandwich technique has already been reported by *Sakakibara et al.* [26], who used this approach in a case of very superficially located incompetent intrafascial veins. A combined use of cyanoacrylate glue and sclerotherapy has also been reported as a conference abstract by *Giovanni et al.* [27], still no technical details have been given. There are also unpublished communications of the simultaneous administration of cyanoacrylate glue and sclerosing foam through special needles, yet no data regarding safety and efficacy of such procedures are available.

In our patient series there were no serious adverse events associated with the treatments, while early results of these procedures were very good, with 100% technical success rate and 100% primary assisted success rate in 77 veins managed. There were, however, some differences regarding primary success rate in particular intrafascial veins. All anterior accessory saphenous veins and Giacomini veins were completely obliterated during the first procedure. Primary success rate was also high regarding the great and small saphenous veins, whereas complete closure of neovascularization networks developed after unsuccessful surgical treatment was low (25%). Still all of these incomplete closures were successfully managed during redo procedures. This relatively low efficacy in this specific location probably resulted from the fact that small volumes of the glue were injected into these neovascularization networks. This was because of the direct proximity with the saphenofemoral junction and considerable risk of glue migration into the deep venous system, or even of a distal embolization. Since all these incompetent neovascularized veins were safely obliterated at follow-ups, most likely in these patients more aggressive management during primary procedure is not necessary.

In our method, in contrast to the traditional treatments with cyanoacrylate glue, which typically utilizes long catheters and dedicated applicators for glue injections (e.g.: VenaSeal Closure System, Medtronic, Minneapolis, MN, USA; VenaBlock Vein Sealing System, Invamed, New York, NY, USA; Venex Sealing System, Vesta Medical Devices, Ankara, Turkey; VariClose Vein Sealing System, Biolas, Ankara, Turkey) there is no risk of cyanoacrylate placement into the epifascially located veins. Also, the total amount of glue can be substantially reduced, since less critical segments of incompetent veins are closed with sclerosing foam. Epifascial application and large volume of cyanoacrylate glue are already known to be associated with a higher risk of clinically relevant phlebitis and/or foreign body reactions [13,21]. In addition, our combined technique allows for reducing the volume of sclerosing foam, thus minimizing the risk of neurologic adverse events that are primarily associated with the migration of large volumes of foam into the cerebral circulation [28]. In the already mentioned study by *Sakakibara et al.* [26], the Authors needed larger volumes of cyanoacrylate (mean: 2.6 mL) to manage incompetent veins. By contrast, in our patients it was never necessary to inject more than 1 mL of glue, even in the patients with bilateral varicosities. Although details of the procedures are not given in this communication, since it was a conference abstract [26], perhaps the difference resulted from the use of less concentrated sclerosant (0.5% polidocanol). We typically utilized 2% or 3% polidocanol, and such a concentrated foam after the injection evokes the spasm of vein, reducing the volume of subsequent glue and sclerosant injections. Besides, we injected the glue with small tuberculin syringes that allowed us for a precise placement of very small drops of glue, which is quite difficult to achieve with an applicator or larger syringes.

It should also be mentioned that small volumes of injected glue, without the use of an applicator, reduced the total cost of procedure, since medical glue, as well as applicators, are quite costly. On the other hand however, precise placement of glue drops with a needle can be technically more challenging in comparison with the use of dedicated applicator.

We acknowledge that there are several weak points of our study. Firstly, it was a retrospective survey of patient series. Besides, only early results of the treatments were available. Since this study was not planned to be prospective, it was not possible to evaluate the patients over a longer time, except for those who visited the clinic because of varicose vein recurrences or other reasons.

Obviously, further prospective studies are needed to assess the long-term results and to compare our technique with other modalities of cyanoacrylate glue application, and also with other minimally invasive techniques for the treatment of varicose veins.

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