Kontothanassis, et al., J Blood Lymph 2018, 8:4
DOI: 10.4172/2165-7831.1000231

Journal of Blood & Lymph

Research Article Open Access

Effects of Mesoglycan Treatment in the Prevention of Venous Thrombosis after Superficial Vein Surgery

Kontothanassis D[1], Bissacco D[2*], Oberto S[1], De Zolt P[1], Camporese G[3] and Bortoluzzi C[4]

[1]*Italian Vein Institute, Padua, Italy*

[2]*Department of General and Oncology Surgery, University of Milan, Milan, Italy*

[3]*Department of Angiology, University Hospital of Padua, Padua, Italy*

[4]*Department of Internal Medicine, Venice Hospital, Venice, Italy*

[*]**Corresponding author:** Daniele Bissacco, Department of General and Oncology Surgery, University of Milan, Milan, Italy, Tel: +39 340 7729070; E-mail: danielebissaccomd@gmail.com

Received date: Dec 11, 2018; **Accepted date**: Dec 17, 2018; **Published date**: Dec 24, 2018

Abstract

Aim: To demonstrate the effectiveness of a two months treatment with Mesoglycan after superficial vein surgery in the prevention of superficial vein thrombosis (SVT) and deep vein thrombosis (DVT).

Methods: From January 2014 to April 2015, all patients underwent superficial vein surgery were enrolled and analyzed. Clinical examination through CEAP class identification, Venous Clinical Severity Score (VCSS), and color Duplex ultrasound scanning (CDUS) were performed before treatment, two days post-operatively and at the 2 month follow-up time. Prophylaxis with heparin was given for 1 week after treatment. Mesoglycan 50 mg tablet BID was continued for 2 months. Primary endpoint was Mesoglycan side effect rate. Secondary endpoints were postoperative DVT and/or SVT, endovenous heat induced thrombosis (EHIT) after laser treatment and recanalization/recurrence rate.

Results: 381 venous interventions in 334 consecutive patients were performed. After exclusion of 18 patients, 363 veins were treated in 361 enrolled patients. Female were 242 (76.6%), mean age was 52 years and mean BMI was 25.2 kg/m^2. Sixty patients had a history of venous thrombosis (18.9%); 17 had thrombophilia (5.3%). CEAP classification was C2 130 (36.1%), C3 138 (38.2%), C4 77 (21.3%), C5 7 (1.9%) and C6 9 (2.5%) patients. Surgical techniques performed were endovenous laser ablation, sclerotherapy, crossectomy, perforator ligation and/or phlebectomies. All patients enrolled complete the Mesoglycan 2-months therapy. Mesoglycan side effects were referred in 4 patients (1.2%).

At the 2 days FU, CDUS evidenced pathological conditions in 3 cases (0.8%): 1 contralateral SVT, 1 EHIT of the great saphenous vein, and 1 ipsilateral SVT associated to a perforator vein thrombosis. No deep venous thrombosis were documented at the 2 months FU.

Conclusion: Mesoglycan 50 mg tablet BID is a safe and well tolerated therapy after superficial venous ablation procedures with very low thrombotic complications rate at the 2 month postoperative follow-up time.

Keywords: Mesoglycan; Venous thromboembolism; Vein surgery; Endovenous laser ablation

Introduction

Venous thrombosis and thromboembolism are still not so rare as complication after superficial vein surgery, even if correctly performed (5.3-16% of patients) [1-10]. Postoperative superficial vein thrombosis (SVT) and deep vein thrombosis (DVT) can affect all venous treatments. Furthermore, thermal techniques as Endovenous Laser Ablation (EVLA) and Endovenous Radiofrequency Ablation (EVRA) are related to Endovenous Heat Induced Thrombosis (EHIT), in which the thrombus is extended from the superficial venous system into the deep venous system close to the site of the recent ablation. The incidence of this complication is referred to be 0,2-8% [9,11,12].

Mesoglycan is a pharmacological treatment approved for Chronic Venous Disease (CVD). It is a sulphated polysaccharide compound designed for the treatment of vascular disease with an associated thrombotic risk. Mesoglycan is extracted from porcine intestinal mucosa and it is composed of heparan sulphate (47.5%), dermatan sulphate (35.5%), electrophoretically slow-moving heparin (8.5%) and chondroitin sulphate (8.5%).

Heparan and dermatan sulphate are thrombin inhibitors acting through complementary antithrombin III and heparin cofactor II pathways [13,14]. Mesoglycan has been documented to inhibit neutrophil adhesion and activation, to decrease capillary permeability, to enhance systemic fibrinolysis, and to prevent venous thrombus formation [15]. In medical literature, no data are available about the utility of postoperative Mesoglycan treatment in the prevention of venous thrombosis and thromboembolism after intervention on superficial venous system for CVD.

The aim of this study was to demonstrate the safe and effectiveness of a 2 months therapy with Mesoglycan after superficial venous interventions.

Methods

Patients with Clinical, Etiologic, Anatomic, and Pathophysiologic (CEAP) C class 2 or higher, treated for CVD, from January 2014 to April 2015, were examined.

Accurate clinical examination, Venous Clinical Severity Score (VCSS), and color Duplex ultrasound (CDUS) scan analysis of the lower extremity veins were performed prior to treatment, at 2-day and at 2-month follow-up time.

Vein incompetence was assessed with reflux in response to manual calf compression or Valsalva maneuver with the patient standing, and reflux was defined as evidence of reverse flow >500 ms in a vein segment. Patients were thoroughly informed about surgical procedure, operation risks, recurrence. All patients signed a written informed consent form before the procedure.

In case of EVLA, the target vein was cannulated percutaneously just below the knee under ultrasound guidance. A 5F introducer sheath was positioned and a J guide wire was inserted into the treated vein. The correct position of the fiber tip was confirmed by ultrasound imaging. The laser wavelength was 1470 nm diode. Laser energy was always delivered with a pull-back rate of about 60 J/cm under ultrasound guidance to make the procedure safe and assist the vein obliteration. The immediate occlusion of the treated vein was confirmed by ultrasound imaging.

Crossectomy was performed with a small incision at the groin under ultrasound guidance. Ultrasound Guided Foam Sclerotherapy (UGFS) was obtained with the use of Lauromacrogol (Atossisclerol) at the percentage of 0.5%, 1%, 3% according to the diameter of the treated vein.

All patients received local anesthesia with mild sedation using midazolam (2 or 3 mg) or diazepam (2 mg) before starting the treatment.

In case of tumescent anesthesia, it was infused with an 18 gauge needle under ultrasound guidance with a mixture of about 500 cc of normal saline and local anesthetics consisting of 2% lidocaine (10 mg); enough fluid was infused to encircle completely the whole vein segment to be treated. The temperature of the fluid was 4°C to cause local anesthesia and significant spasm of the vein and perivenous vessels. At the end of the operation the limb was wrapped with an elastic bandage for about 2 hours. Afterwards elastic compression (class II) was applied for 15 days. An ice pack was used immediately on the limb and for few days after surgery when necessary. Postoperative analgesia with nimesulide (Diclofenac 150 mg every 24 hours) was given when necessary.

Prophylaxis with low molecular weight heparin (LMWH, Parnaparin 4250 UI), was given to all patients for 1 week.

Mesoglycan treatment with 50 mg tablet BID was started 7 days after the operation and continued for 2 months. Patients with thrombophilia received a first dose of LMWH the day before surgery, and continued this treatment for 15 days after surgery.

Each patient was assessed by clinical examination and CDUS analysis at 2-day and 2-month follow-up time. During the visit, patients were asked about postoperative complications, Mesoglycan compliance and adverse effects.

CDUS was performed to detect SVT/DVT, recanalization rate after EVLA and UGFS, hematoma, residual varicose disease and reflux at the treated areas. Thrombosis was detected by the non-compressibility of the vein and filling defects on color mode.

Preoperative, intraoperative and postoperative data were collected prospectively by using a custom made database.

Results

During study period, 381 venous interventions in 334 consecutive patients were performed. Eighteen treatments in 18 patients were excluded from the study: 4 patients because of a co-diagnosis of angiomyolipoma, and 14 because of an incomplete 2-month follow-up.

After this exclusion, 316 patients were enrolled, 242 females (76.6%) and 74 males (23.4%). Mean age was 52 years (range 16-86), mean BMI was 25.2 kg/m^2 (range 17.6-38.4). Seventy-two patients (22.7%) were positive for cardiovascular disease. Sixty patients (18.9%) had a positive history of venous thrombosis: 50 SVT (42 ipsilateral, 6 contralateral, and 2 bilateral); 10 DVT (8 ipsilateral and 2 contralateral in 2 cases complicated by pulmonary embolism). Seventeen patients had diagnosis of thrombophilia (5.3%).

Clinical preoperative evaluation also included stratification of CVD according to the CEAP classification and VCSS Score. Before surgery, the mean VCSS was 5.9 (range 2-14); CEAP classification result is reported in Table 1.

CEAP clinical classification	N (%)
C2	130 (36.1%)
C3	138 (38.2%)
C4	77 (21.3%)
C5	7 (1.9%)
C6	9 (2.5%)

Table 1: CEAP clinical class.

In summary, 233 great saphenous veins (GSV, 64.2%), 19 anterior accessory saphenous veins (AASV, 5.2%), 39 small saphenous veins (SSV, 10.8%), 3 Giacomini's veins (GV, 0.8%), 10 perforators veins (PV, 2.8%), 27 tributaries (7.4%), and 32 recurrences varicose veins (RVv, 8.8%) were treated. Surgical techniques chosen are reported in Table 2.

Surgical technique	N (%)
EVLA	3 (0.8%)
EVLA+phlebectomies	231 (63.9%)

EVLA+phlebectomies+UGFS	56 (15.5%)
EVLA+crossectomy+phlebectomies	2 (0.6%)
Phlebectomies+UGFS	45 (12.4%)
Crossectomy+phlebectomies+UGFS	2 (0.6%)
phlebectomies	16 (4.4%)
HL+S	2 (0.6%)
Perforator ligation+phlebectomies	4 (1.2%)

Table 2: Surgical techniques performed.

Abbreviations: EVLA: Endovenous Laser Ablation; UGFS: Ultrasound Guided Foam Sclerotherapy; HLS: High Ligation +Stripping.

No complications or other adverse reactions occurred intraoperatively. Immediate occlusion of the treated veins after EVLA and UGFS were confirmed in all limbs by intraoperative CDUS. The mean time for patient discharge from the hospital was 3 hours (range 3-5 hours).

After 2 days, ecchymosis were documented in 52 operations (14.4%). Hematoma occurred in 6 cases (1.6%) but no one required any invasive treatment for its drainage. No bleeding, skin burns or paranesthesia were occurred. LMWH therapy was well tolerated by the entire population. No recanalization was documented.

Venous thrombosis occurred in 3 cases (0.8%): 1 contralateral SVT, 1 EHIT, and 1 ipsilateral SVT associated to a perforator vein thrombosis. Detailed characteristic of patients affected by postoperative thrombosis are reported in Table 3.

Case	Sex	Age	BMI	CEAP "C"	VCSS	Intervention	Complication	Treatment	Follow-up
1	F	45	38.4	3s	7	EVLA	Contralateral SVT	LMWH+painkillers	Resolved at 30 days
2	M	45	39.4	3s	9	EVLA+phlebectomies	EHIT type II	LMWH	Resolved at 30 days
3	M	65	26.1	4s	11	Perforator ligation	Perforator thrombosis	LMWH	Resolved at 30 days

Table 3: Details regarding patients with postoperative thrombosis.

Abbreviations: EVLA: Endovenous Laser Ablation; SVT: Superficial Vein Thrombosis; EHIT: Endovenous Heat Induced Thrombosis; LMWH: Low Molecular Weight Heparin.

No patient developed major bleeding or heparin induced thrombocytopenia as a consequence of prophylactic treatment with LMWH. After two months, only 2 veins operated with endovascular treatment (0.6%), demonstrated an early recanalization after EVLA: both patients remained asymptomatic. No new episodes of DVT or SVT were detected. All the patients started and continued the treatment with Mesoglycan for two months; in only 4 cases (1.2%) minor side effects (stomach ache) was registered.

Discussion

EVLA and RFA are recommended by international guidelines for the treatment of saphenous reflux, but when endovascular techniques can't be performed, traditional surgery with high ligation and stripping and sclerotherapy under CDUS guidance may be a valid alternative [10,16]. According to the current guidelines, we used endovascular techniques in 292 operations (80.8%) to treat the reflux of GSV, AASV, SSV and RVv. In most cases EVLA was used in a hybrid approach, in association to other techniques in order to correct all the sources of vein reflux: phlebectomies, UGFS or crossectomy. In 69 cases (19.2%) EVLA was contraindicated, because of anatomical variabilities, presence of dilatation and tortuosity. In all cases, superficial varicose veins were removed by phlebectomies. No intraoperative complication was documented. At the 2 days follow-up time we registered only 52 ecchymosis (14.4%), 6 hematomas (1.6%), and 3 venous thrombosis (0.8%): no patients required invasive treatment and all the symptoms solved in few days. At the 2 months after treatment, CDUS evidenced 2 early recanalization, in both cases asymptomatic. Our data confirms that EVLA is a safe and effective treatment for superficial vein reflux of the lower limbs. Endovascular techniques are more linked to postoperative thrombotic complications, due to EHIT, so the prevention of this events presents a great relevance.

SVT and DVT remain possible complications in the postoperative period after superficial vein interventions, even if it is correctly performed. Currently, international guidelines recommend a LMWH thromboprophylaxis only with patients with an increased risk of venous thrombosis: patients with thrombophilia, with a history of SVT

or DVT, and in obese patients [10,17,18]. Based on our experience, we recommend the use of a post-operative thromboprophylaxis with LMWH in all cases.

SVT, DVT and pulmonary embolism are rare but occasionally serious complication [4,8,10,19]. The risk is higher with endovascular treatment, due to EHIT. Even if the EHIT mechanism is not fully understood, factors which may increase its developing include elderly population, undiagnosed hypercoagulable states, severity of CVD [9,11,12] and in treated veins with a diameter of >8 mm [20,21]. For these patients a preventive dose of LMHW before or at the beginning of surgery was suggested but there are only few data about the effectiveness of this procedure [12]. Our case of EHIT was degree 2 according to Kabnick classification [22]. According to the literature, in our patients, EHIT happened in an obese patient with a mean diameter of the GSV of 12 mm and severe CVD (CEAP class C4).

In our experience, all the surgical procedures (EVLA, EVRA, UGFS, and even crossectomy) are performed under CDUS guidance: this allows a complete examination that helps in the control of intra-operative and post-operative complications. We had a low rate of postoperative ipsilateral SVT, 0.6%: this can be related to the fact that during surgery our policy is to remove all the superficial varicose veins in association to the treatment of the saphenous reflux. Before surgery, all the varicose veins that are present on the treated limb are precisely evidenced with the use of CDUS and laser trans-illuminator, and then are completely removed by phlebectomies; this may justify the correct pathway that leads to reduction of the rate of superficial vein thrombosis on residual varicose veins.

Mesoglycan is reported to have several favorable actions on the fibrinolytic system, on microrheological and macrotheological parameters [13,14]. Due to these proprieties, the use of Mesoglycan is approved for the treatment of chronic venous ulcers resulting in faster and more frequent healing [23], in the secondary prevention of long term sequelae after DVT [24], and in patients with CVD [25]. It has been demonstrated that Mesoglycan is effective for the prevention of postoperative venous thromboembolism in patients with cancer [26], but there are no data about its use in the prevention of SVT and DVT. In our patients, all the SVT and DVT were diagnosed at the 2 days control, during LMWH therapy and before starting Mesoglycan therapy. At the 2 month follow-up control, after 2 month of Mesoglycan therapy, no new case of vein thrombosis was detected.

Our study was limited by the lack of a control group. However, it showed a very low thrombotic rate (0.8%) compared to the other cases presented in literature: furthermore, all cases resolved in short period.

Conclusion

We present a wide range of venous treatments with a low postoperative complication rate. Mesoglycan 50 mg BID for two months seem to be a valid option during the postoperative period, due to low adverse effect rate, low incidence of thrombotic complications and safe profile.

Conflict of Interest

None. Publication costs was covered by IFI – Italian Phlebological Institute.

References

1. Van Rij AM, Chai J, Hill GB, Christie RA (2004) Incidence of deep vein thrombosis after varicose vein surgery. Br J Surg 91: 1582-1585.
2. Puggioni A, Kalra M, Carmo M, Mozes G, Gloviczki P (2005) Endovenous laser therapy and radiofrequency ablation of the great saphenous vein: analysis of early efficacy and complications. J Vasc Surg 42: 488-493.
3. Agus GB, Mancini S, Magi G, IEWG (2006) The first 1000 cases of Italian Endovenous-Laser Working Group (IEWG). Rationale, and long-term outcomes for the 1999-2003 period. Int Angiol 25: 209-215.
4. Kabnick LS (2006) Complications of endovenous laser therapy: statistics and treatment. Vascular 14: S31-32.
5. Jia X, Mowatt G, Burr JM, Cassar K, Cook J, et al. (2007) Systematic review of foam sclerotherapy for varicose veins. Br J Surg 94: 925-936.
6. Kontothanassis D, Di Mitri R, Ferrari Ruffino S, Ugliola M, Labropoulos N, et al. (2007) Endovenous thermal ablation. Standardization of laser Energy: literature review and personal experience. Int Angiol 26: 183-188.
7. Kontothanassis D, Di Mitri R, Ferrari Ruffino S, Zambrini E, Camporese G, et al. (2009) Endovenous Laser Treatment of the Small Saphenous Vein. J Vasc Surg 49: 973-979.
8. Myers KA, Jolley D (2009) Outcome of endovenous laser therapy for saphenous reflux and varicose veins: medium-term results assessed by ultrasound surveillance. Eur J Vasc Endovasc Surg 37: 239-245.
9. Marsh P, Price BA, Holdstock J, Harrison C, Whiteley MS (2010) Deep Vein Thrombosis (DVT) after Venous Thermoablation Techniques: Rates of Endovenous Heat-induced Thrombosis (EHIT) and Classical DVT after Radiofrequency and Endovenous Laser Ablation in a Single Centre Eur J Vasc Endovasc Surg 40: 521-527.
10. Gloviczki P, Comerota AJ, Dalsing MC, Eklof BG, Gillespie DL, et al. (2011) The care of patient with varicose vein and associated chronic venous diseases: clinical practice guidelines of the society for Vascular Surgery and the American venous Forum J Vasc Surg 53: 2S-48S.
11. Hingorani AP, Ascher E, Markevich N, Schutzer RW, Kallakuri S, et al. (2004) Deep venous thrombosis after radiofrequency ablation of greater saphenous vein: a word of caution. J Vasc Surg 40: 500-504.
12. Puggioni A, Kalra M, Carmo M, Mozes G, Gloviczki P (2005) Endovenous laser therapy and radiofrequency ablation of the great saphenous vein: analysis of early efficacy and complications. J Vasc Surg 42: 488-493.
13. Ofosu FA, Modi GJ, Smith LM, Cerskus AL, Hirsh J, et al. (1984) Heparan sulfate and for dermatan sulfate inhibit the generation of thrombin activity in plasma by complementary pathways. Blood 64: 742-747.
14. Tollefsen DM (1995) Insight into the mechanism of action of heparin II. Thromb Haemost 74: 1209-1214.
15. De Donato G, Sangiuolo P (1986) Instrumental evaluation of the effects of mesoglycan in phlebopathic patients. Minerva Med 48: 77-85.
16. Creton D, Uhl JF (2007) Foam sclerotherapy combined with surgical treatment for recurrent varicose veins: short term results. Eur J Vas Endovasc Surg 33: 619-624.
17. Abbott D, Dharmarajah B, Davies AH (2007) Varicose vein surgery and deep vein thrombosis prophylaxis. Phlebology 22: 1-2.
18. Guyatt GH, Akl EA, Crowther M, Gutterman DD, Schuünemann HJ, et al. (2012) Antithrombotic Therapy and Prevention of Thrombosis Panel Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. Chest 141: 7S-47S.
19. Huisman LC, Bruins, RM, Van der berg M, Hissink RJ (2009) Endovenous laser ablation of the small saphenous vein: prospective analysis of 150 patient, a cohort study. Eur J Vasc Endovasc Surg 38: 199-202.
20. Lawrence PF, Chndra A, Wu M, Ridberg D, DeRubertis B, et al. (2010) Classification of proximal endovenous closure levels and treatment algorithm. J Vasc Surg 52: 388-393.

21. Sufian S, Arnez A, Labropoulos N, Lakhanpal S (2015) Endovenous heat-induced thrombosis after ablation with 1470 nm laser: Incidence, progression, and risk factors. Phlebology 30: 325-330.

22. Kabnick LS, Ombrellino M, Agis H, Mortiz M, Almeida J, et al. (2006) Endovenous heat induced thrombus (EHIT) at the superficial deep venous junction: a new post-treatment clinical entity, classification and potential treatment strategies. 18th Annual Meeting of the American Venous Forum, Miami, Florida; 2006.

23. Arosio E, Ferrari G, Santoro L, Gianese F, Coccheri S, et al. (2001) Placebo-controlled, Double-blind Study of Mesoglycan in the Treatment of Chronic Venous Ulcers Eur J Vasc Endovasc Surg 22: 365-372.

24. Prandoni P, Cattelan AM, Carta M (1989) Long-term sequelae of deep venous thrombosis of the legs. Experience with mesoglycan. Ann Ital Med Int 4: 378-385.

25. Andreozzi GM (2007) Effectiveness of mesoglycan in patients with previous deep venous thrombosis and chronic venous insufficiency. Minerva Cardioangiol 55: 741-753.

26. Di Carlo V, Agnelli G, Prandoni P, Coccheri S, Gensini GF, et al. (1999) Dermatan sulphate for the prevention of postoperative venous thromboembolism in patients with cancer. Thromb Haemost 82: 30-34.