Ultrasound-guided foam sclerotherapy for severe chronic venous insufficiency

Escleroterapia ecoguiada com espuma para tratamento da insuficiência venosa crônica grave

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ABSTRACT

Chronic venous insufficiency is characterized by cutaneous alterations caused by venous hypertension; in severe forms, it progresses to lower limb ulcers. Lower limb varicose veins are the main cause of chronic venous insufficiency, and the classic treatment includes surgery and compressive therapy. Minimally invasive alternative treatments for varicose veins include new techniques such as venous thermal ablation using laser or radiofrequency. The use of different methods depends on clinical and anatomical factors. Ultrasound-guided foam sclerotherapy is the venous injection of sclerosing foam controlled by Doppler ultrasound. Sclerotherapy is very useful to treat varicose veins, and probably, is cheaper than other methods. However, until the present, it is the less studied method.

Keywords: Varicose Ulcer. Varicose Veins. Venous Insufficiency. Sclerotherapy. Ultrasonography, Doppler, Duplex.

INTRODUCTION

Chronic venous insufficiency (CVI) is characterized by cutaneous alterations caused by venous hypertension. Lower limb varicose veins are the most frequent cause of CVI and the most severe form of the disease is venous ulcer. It is estimated that 30 to 40% of adult population presents varicose veins and up to 6% of patients with varicose veins will develop ulcers at some time in their lives. Up to 30% of varicose veins can progress to more severe forms of CVI. CVI causes pain, functional impairment and worsening of quality of life. Almost 1% of general population may present venous ulcer in some moment and prevalence of open venous ulcer is around 0.1% to 0.3%. In Brazil, from 2009 to 2013, 420,000 hospitalizations were caused by varicose veins and it was spent more than US$ 90 million. In the same period, more than 220,000 temporary social security assistant were granted, with an expense with venous disease of more than US$ 60 million. From 2008 to 2012, there were 5,5 thousand retirements due to incapacity and lower limb varicose veins.

Importance of great saphenous vein (GSV)

In a study of 3072 patients followed and examined for more than six years, varicose vein prevalence increased from 22.7% to 25.1% and prevalence of CVI from 14.5% to 16. Among patients with GSV reflux, 31.8% showed worsening of CVI and only 19.8% of those without reflux progressed. Reflux to great saphenous vein is the most frequent event associated to CVI and ulcer formation. In the presence of venous reflux, a long liquid column is formed, increasing hydrostatic pressure and venous hypertension. GSV reflux is identified in up to 80% of patients with CVI.

Chronic venous insufficiency evaluation

Guidelines based on evidences recommend evaluation of patients with interview and physical exam, Doppler vascular ultrasound exam (DUS) and categorization of patients using CEAP classification. CEAP classification describes systematically CVI according to clinical presentation, etiology (primary or secondary), anatomy (superficial, deep and perforating veins) and physiopathology (obstruction, reflux, or both). It guides treatment, but with low sensitivity to slight alterations.

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of the severity of the disease\textsuperscript{27}. Follow-up of treatment results must include evaluation of quality of life, severity score and anatomic and physiologic data obtained by DUS. Clinical score of severity of disease proposed by the American Venous Forum is based on signals and symptoms identified by the examiner and allows follow-up of CVI evolution\textsuperscript{28}. The score does not measure quality of life, but is sensitive to clinical presentation and is considered the best method nowadays to follow up the results of treatment\textsuperscript{4,29}. Recently, it is becoming popular the evaluation of quality of life (QL) to quantify the impact of CVI on patients\textsuperscript{30}. QL of patients with CVI is altered by physical aspect, pain, functional impairment and mobility deficit\textsuperscript{31,32}. Specific questionnaires for CVI QL evaluation are validated in English and are difficult to use in other languages, since they must be translated and validated\textsuperscript{33-35}. Charing Cross and Aberdeen question forms are translated and validated in Portuguese\textsuperscript{36,37}. Evolution of disease is best assessed when multiple instruments are used, avoiding systematic errors of single question forms\textsuperscript{37-39}. Anatomic and functional evaluation of venous system must be made by Doppler ultrasound (DUS), the ideal method, since is reproducible and non-invasive, allowing the access to venous patency or occlusion, identification and quantification of venous reflux, measure of caliber of veins and differentiation of primary and secondary venous disease\textsuperscript{40-42}. DUS does not identify venous hypertension. Venous pressure measure is invasive and in the present is not often performed\textsuperscript{43}.

**Treatment**

Clinical treatment is based in rest with elevation of lower limbs and use of compressive socks. Most patients may benefit of compressive treatment that is recommended to open or healed varicose ulcer and is not indicated to patients with arterial obstruction. Compressive treatment improves symptoms and is efficient for ulcer healing, but with low adherence. Clinical treatment does not eliminate varicose veins and does not alter anatomic basis of venous hypertension. Rate of recurrence of ulcer in one year reaches 70%, and 35% of patients have four or more episodes of ulcer\textsuperscript{44,45}. Obese and older patients have difficulty to wear elastic stockings, 15% are not capable to use them and 26% need help to wear them\textsuperscript{46,47}. Low adherence to treatment is responsible for ulcer recurrence\textsuperscript{48}. Single compressive therapy is not efficient for patients with varicose veins and CVI\textsuperscript{49-52}.

In our country, the most common treatment for varicose veins and GSV reflux is surgical (proximal ligature and flebo-extraction of great saphenous vein)\textsuperscript{1,2,53}. In patients with GSV reflux and intact deep venous system, surgery is efficient and indicated to avoid recurrence of varicose ulcer\textsuperscript{5,54}. In the ESCHAR randomized study, surgery and clinical treatments were equivalent: 65% of ulcer healed in 24 weeks. Surgery was not able to heal ulcers more rapidly, but, after 12 months, recurrence was 28% in the group without surgery and 12% in the surgical group\textsuperscript{55,56}. Surgery improves quality of life\textsuperscript{12}, but cannot be performed in a considerable amount of patients. In randomized trials, up to 25% of patients refuses surgery\textsuperscript{45,56}. Surgical patients present more pain and post-operatory discomfort and delay resuming work activities\textsuperscript{57}. In five years, recurrence, with new indication of surgery, is 6%-58. Complications such as deep venous thrombosis (DVT) may occur in 5% of patients, saphenous nerve lesion in 7% and hematoma in 33\%\textsuperscript{59}. Worse surgical results are related to pre-operatory factors such as body mass index superior to 29kg/ m\textsuperscript{2}, previous pregnancies, recurrent varicose veins, CVI with eczema and healed ulcers\textsuperscript{50-52}.

Among minimally invasive techniques for the treatment of varicose veins and reflux of GSV it is included ultra-sound guided foam sclerotherapy (UFS) and thermal ablation using radiofrequency or laser. Thermal ablation is performed by inserting a thermal element catheter in the distal part of GSV by puncture. The procedure is performed with femoral blockage or with local anesthesia. Catheter must progress proximally inside the vein, in all extension to be treated. Thermal energy released by the catheter destroys venous endothelium. Veins with excess tortuosity, occluded segments, stenotic, or with parietal irregularities may impair progression of catheter. Big diameter veins are challenging for thermal ablation, since they distance thermal element from endothelium. Excessively superficial veins increase the risk of thermal lesion of skin. Finally, costs of catheters and generators limit their use. Minimally invasive treatments present advantages such as rapid recovery of patients and possibility of ambulatory treatment. These modali-
ties have good relation cost/efficiency and complication rate similar to conventional surgical treatment. According to recommendations of the British National Institute for Health and Clinical Excellence, these treatments must by primarily used in relation to conventional surgery. Patients with worse quality of life had better benefits when submitted to minimally invasive techniques, regardless the one used. Ultrasound guided foam sclerotherapy is less expensive than other methods, but cost analysis in Brazil is lacking.

History

Elsholz (1623-1688) was the first to perform injection in humans and Zollikofer (1682) was the first to perform sclerotherapy. Since XVII Century, several sclerosing agents were used, and many of them were toxic. Varicose veins sclerotherapy was used and favored until XIX Century. In the XX Century, surgical technique developed and became the treatment with better results; therefore, sclerotherapy for trunk veins was abandoned. Also, during XX Century, many reports of the use of detergent sclerosing agents were published, with higher sclerosing power, forming foam when mixed with gas. In 1937, Biegeleisen used etanolamine; in 1946, Reiner used tetracycl sodium sulfate and, in 1963, Henschel described sclerotherapy with polidocanol. The first description of foam sclerotherapy was in 1939. In 1944, Orbach described the technique of blood displacement with air bubble to treat varicose veins with diameter of up to 4mm, and, in 1956, Fluckiger described that foam reached distant places from the point of injection by manual massage orientation. The ultrasound-guided venous puncture and, in 1993, Schadeck described that foam was visible at ultrasound, allowing observation of its progress. In 1995, Cabrera described good results for ultrasound guided sclerotherapy using foam, that was patented for use in saphenous vein. In 2000, Tessari described reproducible low cost technique to produce foam using syringes connected to three-way stopcock, mixing liquid and air at a 1:4 proportion, displacing the mix from one syringe to another at least for ten times. Tessari method produces an homogenous and stable foam that popularized foam sclerotherapy.

Foam sclerotherapy results

In 2000, Cabrera et al. published a retrospective study of 500 patients with GSV reflux treated by UFS and reported occlusion of 81% of treated veins. They did not report any severe complication. Wright et al., in 2006, treated 437 patients, 70.9% with GSV reflux. They reported elimination of reflux in 83.9% of treated veins with UFS in one year. Foam sclerotherapy was inferior to surgery to eliminate venous reflux, but patients returned to daily activities more rapidly. Rasmussen et al., in 2011, studied 580 limbs with GSV reflux, randomized for surgical treatment, thermal ablation or UFS. 1443 were submitted to foam sclerotherapy and, after one year of treatment, 16.3% maintained reflux, an index superior to other groups. Patients had faster recovery with less pain than those treated by surgery. There was no statistical difference among complications of studied groups. Brittenden et al., in a randomized trial, compared foam, surgery and thermal ablation in 785 patients. 280 patients were submitted to foam sclerotherapy. In six months, 63% of veins eliminated reflux. UFS result was inferior to surgical and thermal ablation groups. Wright, Rasmussen and Brittenden studies, as well as most studies on foam sclerotherapy, are characterized by the small proportion of patients with open or healed ulcer. Rate of occlusion of treated veins in several studies varied from 53 to 85%. Myers studied 1189 sclerotherapies in 489 patients; 454 GSV were treated and 53.1% of veins occluded after one single session of sclerotherapy. Occlusion rate of tributary veins was higher than of GSV. Veins with diameter higher than 6mm had worse results than those with five or lower diameter. Best results were observed with foam sclerotherapy, with more than 12ml of volume and with sclerosing agents with higher concentration.

Interest of foam sclerotherapy of varicose veins in patients with severe CVI is justified since frequently these patients are older and less prone to surgical treatment. Few randomized studies compared UFS to clinical treatment for ulcer healing and casuistic is small. There are evidences of favoring it in detriment to surgical treatment. In a meta-analysis Mauck identified less recurrence of varicose ulcers when venous reflux was
surgically removed. Mauck results were similar to those of ESCHAR study. Several authors that study healing of varicose ulcers following UFS report healing rates higher than those of ESCHAR study, however, there is a predo-
minance of non-comparative studies. O’Hare reported 91.2% rate of healing in 24 weeks, Kulkarni 71.1% in 24 weeks, Campos 91.3% after one year and Cabrera 83% in six months. Campos, in 2014, randomized 49 patients with ulcer and GSV reflux for surgery or UFS. Twenty three limbs were submitted to UFS and healing occurred in 91.3% after one year of treatment. There were no severe complications or differences in relation to surgical group. Ulcer healing rate, clinical improvement and of QL were similar. Silva identified healing of 84.2% of ulcers. Randomized studies report similar healing of ulcers with surgery, thermal ablation or UFS, with numerous casuistic studies. Brittenden showed improvement of QL, however, less intense in patients treated by UFS when compared to surgery.

Safety

Wright reported an incidence of deep venous thrombosis (DVT) in 5.3% of patients after injection of 60ml of foam, and the author decided to reduce maximum volume to 30ml. After reduction, 95 patients were treated without new episodes of DVT. According to European consensus, foam volume should be limited to 10ml per session. Yamaki affirms that equivalent volumes injected fractioned caused less progression of foam to deep venous system evaluated by Doppler. When foam volume used is reduced, the procedure is safer, but requires a higher number of treatment sessions to eliminate numerous and bulky varicose veins. Some authors use the maneuver of elevation the limb to reduce venous volume and allow contact of lesser volume with endothelium.

More frequent side effects following UFS are phlebitis and cutaneous pigmentation. There are a few reports of severe complications such as DVT, pulmonary thromboembolism, stroke and cerebral embolization in patients with permeate oval foramen. Severe complications are rare (<0.1%) states that women have more side effect reactions than men, specifically cutaneous pigmentation. Cavezzi and Paras estimates the occurrence of pigmentation in 10% to 30% of patients, with resolution in 12 months. Jia in a systematic review of more than 9000 sclerotherapies describes the most frequent complications: 4.7% of phlebitis, 17.8% of cutaneous pigmentation and 25.6% of local pain. He also observed less than 1% of deep venous thrombosis and pulmonary embolism, and 1.4% of visual disturbances.

Current Recommendations

Laser or radiofrequency ablation is recommended by guidelines of “American Venus Forum” (AVF) and British National Institute for Health and Clinical Excellence (NICE) as first choice of treatment of saphenous veins with reflux. There are evidences that treatment avoids ulcer recurrence and speeds recovery with less pain than conventional surgery. AVF states that evidences on UFS are insufficient. According to NICE, evidences on safety and efficacy of UFS are adequate and recommends that foam sclerotherapy must be offered primarily than surgical treatment. European guidelines published in 2014 considered UFS evidences adequate and recommend the method to treat saphenous veins and varicose collateral veins.

Patients submitted to UFS present better QL than surgical patients after four weeks of treatment due to less pain. After one year of treatment, surgical patients show better QL, but with higher rate of recurrence of varicose veins than those submitted to UDS. UFS has lower cost and the procedure is faster, without the need of anesthesia. It is reported higher recurrence rate of varicose veins and lower occlusion rate of treated veins with UDS, when compared to thermal ablation and surgical treatment. However, meta-analysis have identified similar efficacy of minimally invasive methods and surgical treatment. According to guidelines of Brazilian Society of Vascular Surgery, UDS may be used as an alternative to surgery in patients with primary CVI.

Critical Opinion

CVI is prevalent and causes important economic and social burden. Most studies primarily access patients with less severe disease and, rarely, results are categorized according to clinical class. Patients with severe CVI are usually older and less prone to surgical procedure. Sclerotherapy may replace surgical treatment.
of varicose veins in many patients. Main limitations of method include cutaneous pigmentation (frequent and usually compromise esthetical result), and the need of repeat treatment until total elimination of varicose veins. Patients must be warranted that esthetical result of foam sclerotherapy is less predictable than surgical resection. Low efficacy of a single session of sclerotherapy may be solved by subsequent sessions. Those enhance costs, but have no additional technical difficulty. After surgery of varicose veins, in case of necessity of reoperation, the presence of scars and adhesions may difficult technically the procedure or cause iatrogenic lesions. The main interests of UFS are its low cost, the easy application and low limitation in relation to other therapeutic methods. In literature, most studies show reduced evidence due to bias of selection and randomization and long term results are still lacking and must be checked by controlled randomized trials.

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Received in: 02/03/2017
Accepted for publication: 22/06/2017
Conflict of interest: none.
Source of funding: none.

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