Ultrasound-Guided Gas Sclerotherapy

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ABSTRACT: Ultrasound-guided gas sclerotherapy (UGGS) is a new method for sclerosing varicose veins. The objective of this method is to increase sclerosant contact with the venous endothelium to obtain the best sclerosing effect, achieved by a depletion of blood within the vein. This is accomplished by quickly injecting a bolus of CO₂ prior to the sclerosant injection at selected points of venous reflux. The initial multi-year research defined the parameters for the safe use of UGGS. In total, 780 lower limbs with important degrees of venous insufficiency were treated using UGGS; the estimated 1-year occlusion persistence was 92% in a smaller number of treated patients with venous incompetence screened for follow-up. Additional monitoring was not possible because a majority of patients did not attend their annual appointment. UGGS is a very effective varicose vein treatment that is easily performed in an office procedure with basic sterility, and offers versatility that allows the treatment of large vein trunks, as well as any branch from the same point of injection. Of note, it is also inexpensive and repeatable as needed. Given the body’s relatively high-volume tolerance for CO₂, this volume might be used in other medical procedures.

Key words: UGGS, sclerotherapy, ultrasound, varicose vein treatment, polidocanol, insufficient GSV, SSV, SFJ

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he epidemiology of chronic venous disease (CVD) has been reviewed and published by several authors, all of whom report a high incidence mainly in the western world, with a prevalence in women; CVD results in varying degrees of disability, from physical discomfort and incapacity for normal living to life-threatening conditions.1-4 Patient activity and personal productivity varies from physical discomfort and incapacity for normal living to life-threatening conditions.1-4 Patient activity and personal productivity levels are therefore affected — hence, the importance of adequate treatments for this condition. For a long time, saphenectomy and ligation were the only surgical methods available to treat CVD, along with sclerotherapy, which also has relevance in the treatment of varicose veins. Over the last decades, methods such as endovascular laser, radiofrequency, and other variants aimed to use heat to destroy the main trunk of the great saphenous vein (GSV) in its thigh trajectory. The VenaSeal closure system (Medtronic), which uses a proprietary cyanoacrylate medical adhesive delivered endovenously to close the vein, is also now available; however, we do not yet have long-term results on this system, and all of the above require special equipment.5-11

The new VenaSeal modality requires sophisticated equipment. In the case of heat methods at the thigh level, they cannot be applied if the varices are tortuous and superficial. In addition, if there are at the same time, varices under the knee have to be treated surgically or sclerosed. In addition, the difference in cost of sclerotherapy for large varicose veins as compared with the newest method of treatment is economically significant in many countries.

Sclerotherapy began in France in 1920 when Sicard and Linser accidentally discovered that a varicose vein could be sclerosed. However, its history dates back to the era of Hippocrates.12

There have been several sclerosing agents, many of them discarded due to undesirable side effects. Sotradecol has been widely used in the United States and other countries, but it has a high reported incidence of hyperpigmentation and tissue necrosis. Polidocanol was recently approved in the United States and has been in use for a long time in many other countries; it is the sclerosant used in the method described herein, and has a weaker effect than sotradecol but with fewer side effects. Both polidocanol and sotradecol are categorized as detergents and interfere with endothelial cell lipids, causing damage — a mechanism different from other sclerosant agents. Thus, the type of sclerosing agent must be considered, as well as the volume administered, the concentration, and the vein diameter and length, as parameters of reference for the dose of sclerosant to be administered. Cabrera et al reported on a microfoam sclerotherapy that increases the contact time with the vascular endothelium and consequently has an increased sclerosant effect, which has been widely recognized. The UGGS method has been designed to achieve the maximum possible contact with the vessel wall that is even more intensive than foam, which has become evident with the results obtained.

With the implementation of ultrasound-guided sclerotherapy, with or without foam, a large step of efficacy in treating varicose veins has been reached, and sclerotherapy stands out in its relevance for those who cannot afford another method.

As mentioned above, volume and concentration of the sclerosant must be taken into account when performing sclerotherapy. Another important consideration is to reach the higher points of reflux in order to lower venous pressure, as stated by the well-known phlebologist Pauline Raymond-Martimbeau. The UGGS method described herein enhances the contact of the sclerosing solution with the venous endothelium due to depletion of the blood vessel by injecting a CO₂ bolus before application of the sclerosant solution.

The UGGS method presented herein may provide the greatest contact of the sclerosant with the vein wall, is highly effective at a lower sclerosant solution concentration, and also offers the versatility of diverting the injected substances (in this case, CO₂ gas and the sclerosant polidocanol) forward, backward, or to any lateral direction where there are varicose vein tributaries requiring treatment. There are reports in the literature regarding the safe use of CO₂ angiography.13,14 On the other hand, this is the only method using
reasonable to consider whether the concentration of CO2 remains the lungs ranges from 20-50 mm Hg or from about 2.7% to 7.5%, it is adverse effects in human, and that physiological CO2 level in the can withstand, which is yet unknown.18

The transportation of CO2 in the blood is easier than oxygen (O2); even in advanced abnormal conditions, CO2 is transported within safe physiological limits when using the UGGS method. In- deed, fatalities and severe complications have been reported during scanning multiples varicose branches, rapid performance, no related important side effects, and easy repeatability in time. The consideration that CO2 should not be used in the thoracic aorta, the coronary arteries, and the cerebral circulation due to risk of neurotoxicity and cardiac arrhythmias, and said by some others not to use it above the diaphragm at large volumes, is something unrelated to the UGGS method, provided that intracardiac shunting is discarded. Knowing that very large volumes of CO2 produce adverse effects in human, and that physiological CO2 level in the lungs ranges from 20-50 mm Hg or from about 2.7% to 7.5%, it is reasonable to consider whether the concentration of CO2 remains within safe physiological limits when using the UGGS method. Indeed, fatalities and severe complications have been reported during laparoscopy when the accidental puncture of a vessel allowed CO2 to enter in large amounts into the portal system and moved to the right atrium and pulmonary artery, blocking the entire circulation of blood at that level15-17 and resulting in the sudden and eventual appearance of systolic heart murmurs.

Consequently, it is necessary to be conscious that the circulatory system has a limit to the amount of CO2 or any other gas that it can withstand, which is yet unknown.18

With the UGGS method, it may be assumed that the venous blood velocity should be exceeded, with the rapid injection of 60 mL CO2 performed in approximately 2 or 3 seconds. The instantaneous duplex image obtained about 30 cm from the injection point shows mixed color turbulence, likely showing that CO2 displaces the blood, with the effect of exposing the endothelium to more contact with the sclerosant, which is immediately injected (Figure 1).

The first follow-up occurs in 5 days for any missing sclerosed segment or segments that might need to be treated again. Five days later, another check-up occurs and the procedure is repeated again

Methods
Research conducted to determine the maximum volume of CO2 for use in patients was tested for years, progressively increasing the volume of CO2 with increasing varicose vein sizes. The determined maximal volume was 300 mL; however, larger CO2 volumes were not tested due to patient safety, since the maximum limit is still unknown. The initial experience was not ultrasound guided, and only clinically evaluated.

Safe parameters for the UGGS method have been obtained over the last 14 years. The procedure takes between 20 to 45 minutes. The first follow-up occurs in 5 days for any missing sclerosed segment or segments that might need to be treated again. Five days later, another check-up occurs and the procedure is repeated again.
if necessary, up to three times total. In the current study, a total of 780 lower limbs were treated with UGGS. The study group included 82 men and 308 women. Both limbs were treated in 107 patients, all belonging in CEAP class C2 or higher. A total of 76 limbs suffered from varicose ulcers. In great saphenous vein (GSV) patients, insufficiency was present in 673 lower limbs and small saphenous vein (SSV) insufficiency was present in 107 lower limbs; some patients presented with GSV insufficiency in the same limb or in the other limb of the same patient. Mean patient age was 52 years (range, 27 to 88 years; mode, 56 years).

All patients were informed about the need for removing a large varicose vein and about the options for treatment. In addition to the conventional options, the patients were informed about the UGGS treatment, based on experience gained through a significant number of patients successfully treated. No patient was pressured to choose the UGGS method, and all were informed that the most definitive treatment was surgical saphenectomy. All patients were also informed about the other available procedures. Those who selected UGGS were informed about the expected and variable duration of results and the need for annual monitoring, as well as about the easy repeatability if needed. Most of the patients who wanted UGGS were influenced by a fear of surgical procedures and the high cost of surgery and other available procedures. All UGGS patients provided informed consent.

The development and practice of this procedure relied upon the previous knowledge of known intravenous volumes of CO$_2$ already used in medical procedures; at that point, CO$_2$ volume was increased from 20 mL, then at 20 mL increments thereafter to achieve the volumes we use at present, without secondary effects. During the initial years, we only treated CEAP class C2 patients without ultrasound guidance, and only after clinical evaluation. Isolated varicose veins, showing through the skin, of short, medium, and (later in the study period) large size, and without symptoms or other visible alterations related to venous insufficiency, were treated with increasing volumes of CO$_2$ according to size. At the same time, the concentration of polidocanol was maintained between 0.25% to 2%, also according to the vein diameter. The criterion concerning the diameter of the vein was changed after the results obtained by the UGGS presented here. The concept of injecting at the higher point of reflux and selecting C2 or higher class with abundant and large varicose veins led to management of the situation with ultrasound-guided sclerotherapy with the conventional protocol for this treatment, but with an additional element. The UGGS method consists of injecting a bolus of CO$_2$ followed immediately by a dose of sclerosant solution using a three-way stopcock connected linearly with a 60 mL luer-lock syringe charged with CO$_2$, and laterally connected to a 10 mL syringe charged with sclerosant solution at the chosen concentration. While in standing position, 21 gauge butterfly needles are strategically located at the higher points of reflux at the trunk of the main incompetent veins, tributaries, and other additional convenient locations of high reflux. This is relevant because there is significant vessel constriction in response to the injection of polidocanol, and the butterfly needles allow the operator to remain within the venous pathway. Then, boluses of CO$_2$ at variable volumes according to the length of the path to be treated are injected with the maximal pressure exerted by the operator through a 21 gauge butterfly needle and a 60 mL syringe at recumbent position, followed by the injection of the sclerosant. Jelcos (21 gauge) were also used in less superficial veins.

The combination of a 60 mL syringe and a 21 gauge butterfly needle provides a CO$_2$ injection pressure that is adequate for this method. Compared with conventional ultrasound-guided sclerotherapy, less sclerosant is necessary because of the versatility of the UGGS method. For example, if you find a convergence of tributaries at some level of the GSV trunk, you can compress digitally just above the tributary’s end at the GSV trunk; by injecting at that level, the sclerosant will be redirected toward those tributaries. The same procedure can be performed at any other varicose vein with additional tributaries. In 115 cases, incomplete vein closure necessitated a second complementary higher-concentration injection; in 46 cases, a third higher concentration injection was required. None of the cases presented a complete lack of sclerosing effect.

The volume of CO$_2$ used varies between 120 mL and 300 mL; this range of volumes did not produce any significant secondary effect. This upper limit was established once it became sufficient to treat all patients, without any threatening signs that might represent some risk for them. Knowing that the maximal tolerance of CO$_2$ volume for humans is unknown, larger volumes of CO$_2$ were not used. The concentration of the sclerosing solution varied from 0.62% to 2.5%, with the vast majority of cases (94%) treated with 0.62% to 1.5%.

The body complexion was considered for the volumes of CO$_2$ to administer (in accordance with the abundance of varicose veins to treat), but a correlation was not established between patient body weight and CO$_2$ volumes. After injection, the patients are placed in a recumbent position for 30-45 minutes to alleviate some common effects. Then, they are released home and normal activities are permitted. Patients are asked to return for check-up in 5 days; in the event of any persistence of symptoms, the procedure is repeated as required with a concentration of sclerosing solution increased by 50%. Five days later, if the situation persists, the patients are treated again, increasing the concentration by 50% each time, up to three times.

No specific patient preparation is required except for 1.5 hours of fasting before the procedure, and shaving the leg hair in men.

Considering that many apparent varicose vein tributaries are not eliminated with saphenectomy, and that there are many varicosities dependent on insufficient perforators, and varicose veins that connect the GSV and SSV systems (Giacommini veins and others), as well as the known crossover between the GSV and the SSV behind the limb and below the knees, these areas were also evaluated with Duplex ultrasound to determine the appropriate injection point before proceeding with UGGS, as well as the perforators present.

In the case of the GSV, usually 1 or 2 butterfly needles are placed at the upper and lower thigh segments, and others (1 to 3 or more) are placed in locations selected from the above evaluation in the entire limb, mostly below the knee.

The site of the upper thigh is the first to be injected, with a complete bolus of 60 mL of CO$_2$ rapidly follow by 2-3 mL of sclerosant solution. This is assumed to sclerose at the thigh, the upper part
of the varicose GSV, and backward, partial, or total lower part. If there is interest in treating an important insufficient saphenofemoral junction (SFJ) during part of the injection procedure, compression is applied above the inguinal ligament for a few seconds to attain a maximal effect at that level, which is also useful in case there are one or more varicose tributaries between the upper butterfly needle and the inguinal region. A second injection is made at the inferior thigh to essentially cover the lower thigh and the upper leg (by compressing immediately above the injection point), which is also useful for invading any other tributary below that location. In the event another injection point is needed, the location is at the discretion of the operator. In regard to the SSV, it was initially injected in the mid-calf with only one point of injection, while directing the gas and liquid in both directions, at the same time that upper popliteal fossa compression is applied.

Lately, whenever a superficial varicose vein in the posterior leg is identified as a tributary of the SSV, an injection from the tributary with 60 mL or less of CO₂ and 3 to 4 mL of solution while blocking the upper popliteal fossa is enough to obtain complete occlusion of the insufficient SSV as well as the tributary, without the need to directly approach the SSV.

There is some disagreement in the literature32-35 regarding whether or not neovascularization is a cause of varicose vein recurrence. Whatever the cause, recurrence is not unusual, and the UGGS method easily occludes the vein without complicated surgical intervention by injecting one or two prominent vessels.

During the UGGS procedure, most of the insufficient perforators became sclerosed; if not, they were subsequently sclerosed selectively.

Lower concentrations of sclerosant were chosen for larger-diameter varicose veins, with the opposite chosen for smaller-diameter veins. After sclerotherapy was completed, conventional compression systems were used. Easy home or work activities were recommended, but no extreme activities or exercising were encouraged. On day 5 post procedure, the patient is checked clinically and by ultrasound to evaluate the treatment outcome; in the absence of adequate response, treatment is repeated at the segments required. Use of a compression stocking was a general recommendation for every patient.

Immediately after treatment, the patient must lie flat for 20 to 45 minutes, depending on the amount of CO₂ injected. The feeling of chest pressure and cough are common during the first minutes, but decrease and almost disappear in 15 to 30 minutes. Visual disturbances may also appear; these vision changes were once thought to relate to transient ischemic attacks, but lately have been considered related to migraine with aura. The sclerosant dose has been dependent on body complexion, but it must also be dependent on the abundance of varicose veins; however, body type is considered in order to avoid large doses. Nonetheless, in approximately 16% of cases, considering the maximal recommended dose by weight, larger doses were injected when large and abundant varicose veins were present, exceeding the conventional dose in 20% to 30% without any secondary effects, either initially or at second and third follow-up visits, as assessed clinically with basic blood tests including liver and renal values, which were selected to assess any harmful effects. Lumpiness in the leg after sclerotherapy is easy to reduce if the vein lies on a bone by using dental rolls placed along the vein and applying compression against the bone with a wide adhesive tape for 3 days. At thigh locations, infiltration with CO₂ is performed along the lumps, just below the skin, followed by cold saline injected in the space produced by the previous CO₂ injected. This helps to hide the bulging varice to some degree, and the other conventional compression methods, including high-compression stockings, were also used.

Also, in relation to the concentrations and doses of polidocanol used, the concentration was below the usual standards for large varicose veins, but the entire dose exceeded in some cases the traditionally recommended dose, mainly when sclerosing abundant and large varicose veins was required, and follow-up after treatment for 2 weeks showed no abnormalities in the most important blood test parameters.

Administration of high-volume CO₂ dose was well tolerated, as was exceeding conventional doses of polidocanol in some patients.

**RESULTS**

The results at 1 year were similar or better compared with conventional ultrasound-guided sclerotherapy. Longer follow-up was not possible due to a large number of patients who did not return during the second and third year after the procedure; there were too few patients to establish a percentage estimation. A result was considered successful if total vein occlusion was achieved, or if significant reduction in the diameter and correction or improvement of the reflux zone was achieved, which was seen in some cases that also had other segments of occlusion. That effect of diameter reduction was considered an interesting finding, and was seen in about 6 cases. A second complementary higher-concentration injection was required for incomplete closure of the vein in 115 cases, while a third higher-concentration injection was required in 46 cases. None of the cases presented a complete lack of sclerosing effect. Therefore, polidocanol has enough effect for treating any varicose vein with this method without exception, demonstrating the enhancing contact effect of the sclerosant due to the previously injected CO₂.

One-year follow-up results were obtained in 660 male and female patients; 92% of veins were still occluded at this point. After this point, a very small number of patients attended their subsequent appointments; thus, longer-term follow-up results aren’t available. Isolated patients appeared over the years; some presented with closed varicose veins and some had reopened varicosities. The patients with varicose ulcers who could be followed for 1 year presented with ulcer healing in 43 legs and significantly decreased size in 33 legs, but a great variability existed in the initial size. In the cases where polidocanol dose was exceeded, follow-up after treatment for 2 weeks showed no abnormalities in the most important blood test parameters.

**DISCUSSION**

The UGGS method is a new way to perform sclerotherapy. Our extensive experience showed an excellent rate of sclerosed
varicose veins by using an injection of a bolus of \( \text{CO}_2 \) prior to the sclerosing solution to empty the vein of blood. This method enhances sclerosis effect in two ways: first, there is no (or very little) sclerosant dilution with blood; second, there is more intimal contact of the sclerosant with the vein wall. This allows a substantial sclerosing action on the varicose vein endothelium with a relatively weak sclerosing agent that was once preferred only for small-diameter telangiectasias and reticular veins. This method also results in few side effects. It is likely that a sclerosing agent other than polidocanol would be equally effective using the UGGS method.

This experience using up to 300 mL of intravenous \( \text{CO}_2 \) indicates that \( \text{CO}_2 \) can be useful for other medical procedures where this gas, at these volumes, has never being considered. Certainly, with the availability of appropriate equipment and test facilities, more prominent research can be done. It is quite likely that both inferior varicose limbs might be treated the same day without any problem, which was not done in the current experience due to lack of controlled facilities.

With the use of the propelled injection of \( \text{CO}_2 \) followed by the sclerosant, larger vein segments are exposed to treatment, allowing the planning of only a few points of injection while obtaining the desired result. The UGGS method is also versatile because it can deviate the sclerosant flow to any other varicose vein connected to the main flow, and is thus less time consuming and less costly in terms of resources. It can be repeated in a phlebology consultation or complemented as indicated by the follow-up results. No anesthesia is needed, and this is an office-based ultrasound-guided procedure, with basic sterility.

Upon the normal inhalation of \( \text{O}_2 \), \( \text{CO}_2 \) is produced by cell metabolism in the mitochondria. It is transported to the lungs, dissolved in solution 7%, buffered with water as carbonic acid, and bound to hemoglobin.

Normally, 200 mL of \( \text{CO}_2 \) are excreted per minute from the alveoli to the blood in the steady state. With exercise, the incremental metabolism increases the production of \( \text{CO}_2 \) several times. In this case, tachypnea allows the excretion of the excess of \( \text{CO}_2 \) production. Tachypnea was not clinically evident in the UGGS method.

Sensors in the brain, the carotid artery, and the aorta detect \( \text{CO}_2 \), which disappears after several minutes. Hypothetically, because the injected \( \text{CO}_2 \) reached the lungs without affecting mitochondrial production, it was not recognized by the specific sensors, and there was thus no tachypneic response (as happens with exercise). The overload of \( \text{CO}_2 \) in the alveoli, which causes the mentioned symptom, might be due to overload of \( \text{CO}_2 \) in the alveoli that also invade the bronchioles. This hypothetical scenario will perhaps prove to be an adequate explanation in time. 34-36

General experience indicates a need to increase the sclerosing agent concentration with larger-diameter veins. 30,37-39 Histologically, varicose veins present an important alteration. The intima may be intact, but usually alternates with areas of intimal thickening and/or dispersed fibrosis, increased collagen deposition, and plaques below the endothelial lining, as well as circular muscle fiber disruption in the media. 40,41 The sclerosant acts upon that damaged endothelium, respecting veins with intact endothelium, as occurs with the deep venous system. Thus, possibly because of this method, an inverse relationship between the vein diameter and the required sclerosant concentration is frequently observed.

Apparently, with the initial injection of a bolus of \( \text{CO}_2 \), the blood is pushed into the vein, conserving the laminar organization with a parabolic front, where the most effectiveness occurs peripherally due to slower velocity, and this effect is greater in larger-diameter veins than in smaller-diameter veins, where center and periphery are too close to generate a difference in blood velocity. Another argument is that the more dilated the vein, the more likely the damage of its wall. This problem is addressed by the SofMedica’s ClariVein device, which combines a mechanical destruction of the endothelium with a sclerosant infusion 42 for obtaining better results.

Ceulen et al 43 attempted to develop a safety measure to prevent foam from flowing into the deep venous system, with blockage of the saphenofemoral junction to reduce flow into the deep system using a mix of 1% polidocanol foam and radioactive pertechnetate; this method did not prevent entirely (but may have reduced) the flow of foam into the femoral vein. In the UGGS method, this maneuver was intended to delay the sclerosant in the insufficient SFJ and prolong its effect. When the compression was performed, no tendency to deep venous thrombosis was detected, probably because upon compression release, the retained flow is diminished into the femoral vein, as happened with the aforementioned findings.

There is no need for Tessari method. Instead of foam, liquid solutions are used.

The UGGS technique is presented here as originally created. However, there are many possibilities for optimization; for example, by testing other concentrations and volumes, using a variable injection pressure, using automatic injection systems, monitoring closed capnography or serial determinations of pH, etc. The experience presented herein has provoked great interest in a future area of study; namely, the addition of some medication or procedure that brings about selective fibrotic changes in the thrombus occluding the veins after sclerotherapy to obtain a definite seal of the venous lumen in the treated varicose veins.

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