Incidence of Side Effects Using Carbon Dioxide–Oxygen Foam for Chemical Ablation of Superficial Veins of the Lower Extremity


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Submitted 16 June 2009; accepted 18 April 2010
Available online 23 May 2010

KEYWORDS
Ultrasound-guided foam sclerotherapy; Side effects

Abstract  Objectives: To determine the incidence of side effects following treatment of varicose veins with carbon dioxide–oxygen (CO2/O2) foam sclerotherapy, and to compare results with historical controls using CO2- or air-based foams.
Design: Cohort study with prospective data collection, private clinic setting.
Patients: The patient population consisted of one hundred patients, 95% women, age 52 SD 13 years-old, CEAP class C2EpAsPr.
Methods: Patients underwent ultrasound-guided foam sclerotherapy following thermal ablation of saphenous trunks; 1–3% polidocanol and 70%CO2–30%O2 gas were mixed in a 1:4 proportion. Volume injected averaged 22 SD 11 (range: 2–46) mL. Vital signs were monitored for 1 h; side effects were recorded up to 24 h post treatment. Incidence of side effects was compared to CO2- and air-based foam data.
Results: Heart rate decreased from 73 SD 11 at the start to 68 SD 9 bpm (p < 0.001, paired t-test) following the procedure. Systolic and diastolic pressures, 127/75 SD 18/14 mmHg, respiratory rate, 15 SD 4 rpm and pO2, 98 SD 2%, did not change significantly. Itching (7) or leg pain (24) reporting was similar to that for air-based foam (p > NS). Lack of reported chest tightness and/or dry cough was superior to our previous data with CO2 or air foam (p < 0.05). Reporting of dizziness (1) was less than that for air-based foam (p = 0.002). The incidence of visual disturbance (2%), was comparable with that for CO2 (3%) or air (8%) foam, but too few cases were available for meaningful statistical analysis.
Conclusions: Foam sclerotherapy using CO\textsubscript{2}/O\textsubscript{2} foam was well tolerated by patients and resulted in fewer side effects than similar treatment using air foams.

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Introduction

Chemical ablation has become a valuable alternative for the treatment of valvular insufficiency of the superficial veins of the lower extremities.\textsuperscript{1–3} A wide range of venous disease has been treated with ultrasound (US) guided foam sclerotherapy (USGFS).\textsuperscript{4–16} Foam sclerotherapy can be a primary treatment, or complementary to surgical treatment or thermal ablation by radiofrequency or laser.

The gas used to prepare the foam may affect the frequency of adverse reactions associated with the USGFS. Air is used in a 4–1 ratio with a liquid sclerosant and administration of foam volumes of less than 10 mL per treatment session has been recommended.\textsuperscript{2} There is evidence that larger volumes can be injected safely and effectively if biocompatible gases (carbon dioxide, oxygen) are employed to make the foam.\textsuperscript{1,17–19} In our personal experience, the use of carbon dioxide (CO\textsubscript{2}) has reduced the incidence of side effects or complications, as compared to the use of air-based foam.\textsuperscript{1} This study investigated the incidence of adverse events during CO\textsubscript{2}/O\textsubscript{2} foam sclerotherapy.

Materials and methods

This study investigated the incidence of side effects and complications of a CO\textsubscript{2}/O\textsubscript{2}-based foam. The results were compared with previously published data for CO\textsubscript{2}- and air-based foam sclerotherapy.\textsuperscript{1} The fundamental protocols were similar for the three different types of gases used so far but the data reported here do not comprise a randomised study.

Patient population

All subjects gave written informed consent for treatment with polidocanol and for participation in a quality-assurance research program. Initially, all patients had thermal ablation of the great saphenous vein (GSV), performed either with laser or radiofrequency energy. This treatment also included ambulatory phlebectomy for the treatment of varicose veins. 100 Patients with residual or recurrent varices were treated by USGFS using CO\textsubscript{2}/O\textsubscript{2}-based sclerosant foam. Average patient age was 53 SD 13 (range 19–76) years. Women (n = 95) outnumbered men (5). The CEAP classification was C2EpAsPr for varicose veins, primary aetiology, and saphenous reflux greater than 1 s.

Contraindications

Patients with known symptomatic patent foramen ovale (PFO) were not treated. Patients with history of superficial thrombophlebitis, multiple spontaneous abortions, family history of thrombosis, previous deep venous thrombosis underwent thrombophilia screening and were treated with prophylactic low molecular weight heparin prior to thermal or chemical ablation.

Diagnostic ultrasound (US)

US was used for physiological and anatomical evaluation.\textsuperscript{20} The great, small, anterior and posterior accessory saphenous veins were examined. Findings at the saphenofemoral junction, proximal, mid and distal thigh, proximal, mid and distal calf were summarised in a formal report. Out of fascia tributaries and unusual veins were also evaluated. Perforating, intersaphenous, Giacomini, and sciatic veins were examined and noted if reflux was present. Reflux was classified as lasting for 1 sec, 2 s, 3 s or longer than 4 s.

Ultrasound-guided foam sclerotherapy (USGFS)

Ultrasound evaluation identified residual incompetent segments of the vein. A plan was then developed to a) close recanalised segments of the treated GSV, b) expand ablation distally into the GSV, c) ablate the SSV, d) close incompetent tributaries and perforating veins, and e) ablate remaining incompetent superficial veins.

Sclerosant foam preparation

The gas used in this study was a mixture of 70%CO\textsubscript{2} and 30% O\textsubscript{2}, supplied pre-mixed by the medical gas distributor. The sclerosant used was 1–3% polidocanol, mixed with gas as a 1:4 ratio. The Tessari dual syringe, three-way tap technique was employed to create the foam.\textsuperscript{21}

Access

Direct puncture of incompetent veins was performed under longitudinal or transverse ultrasound visualisation with needle diameters of 0.4 mm (27G). Ultrasound imaging was used to establish whether a further injection of foam was needed for that segment. Injections were stopped once foam approached a connection to the deep system. The GSV was usually punctured in a residual segment in the calf. SSV and tributary injection followed a distal-to-proximal approach. Treatment of perforating veins was accomplished by indirect injection into an extra-fascial tributary or saphenous vein segment. Direct injection of perforating veins was avoided. Table 1 summarises the veins that were treated. The diameter of the treated veins averaged 2.5 SD 1.2 (range 1–6) mm. Only one vein (10 mm) greater than 6 mm was treated. 2 mL of foam was used for most injections.

Patients were sometimes instructed to perform plantar and dorsiflexion of the ankle to increase blood flow via the deep veins and speed neutralisation of any foam that may have reached the deep venous system. A total of 648 injections were performed in 176 legs, averaging 6.5 per patient, or 3.7 per leg. Table 1 lists the number of injections per site. The duration of treatment varied, lasting less than 15, 30, and 45 min for 66%, 36% and 8% of the patients respectively. The total foam volume injected per patient was 22 SD 11 mL,
varying from 2 mL to 46 mL. The average foam volume injected per leg was 12 SD 6, varying from 1 to 28 mL.

**Patient monitoring**

A registered nurse (RN) monitored vital signs pre-procedure, every 15 min during the procedure, and 30 and 60 min post procedure while the patient was still in the clinic. The vital signs monitored were heart rate, blood pressure, respiratory rate, pulse oximetry (pO2), and electrocardiogram.

Side effects or adverse events were also monitored directly by the RN every 15 min during the procedure and 30 and 60 min post procedure. A telephone interview recorded the events volunteered by the patients 2, 6 and 24 h after the procedure. The expected sequelae monitored included respiratory difficulty, nausea, dizziness, circumoral paraesthesia, visual disturbance, and headache.

**TTE and TCD monitoring**

Transthoracic echocardiography (TTE) and transcranial Doppler (TCD) were undertaken for those patients with a history considered suspicious for right-to-left shunt, such as patent foramen ovale (PFO). The aim was to assess the presence of foam in the right and left heart and in the middle cerebral arteries. Asymptomatic patients who reported symptoms possibly attributable to a PFO, particularly migraine with aura, following the first injection would undergo a PFO diagnostic protocol. Further foam sclerotherapy was avoided in patients in whom a PFO was found.

**Statistical analysis**

Incidence of adverse events associated with CO2/O2 foam were documented and compared with historical data previously recorded for CO2 foam or air-based foams. Data are represented by the mean and standard deviation. Paired t-tests of statistical significance were used to compare ordinal data. Contingency table analysis was undertaken using Chi-square tests.

**Results**

There were no physiologically significant changes in vital signs or electrocardiogram (Table 2). A 5 bpm heart rate decrease at 60 min post procedure and a 2 mmHg decrease

### Table 1  Ultrasound-guided foam sclerotherapy of lower extremity veins as a complement to thermal ablation and phlebectomy (N = 100 patients).

<table>
<thead>
<tr>
<th>Injection sites</th>
<th>Number of injections</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>GSV tributaries distal to thigh</td>
<td>144</td>
<td>22.2%</td>
</tr>
<tr>
<td>GSV tributaries at mid thigh</td>
<td>106</td>
<td>16.4%</td>
</tr>
<tr>
<td>GSV tributaries at proximal thigh</td>
<td>105</td>
<td>16.2%</td>
</tr>
<tr>
<td>Distal GSV</td>
<td>75</td>
<td>11.6%</td>
</tr>
<tr>
<td>Distal SSV</td>
<td>61</td>
<td>9.4%</td>
</tr>
<tr>
<td>SSV tributaries</td>
<td>59</td>
<td>9.1%</td>
</tr>
<tr>
<td>Proximal SSV</td>
<td>54</td>
<td>8.3%</td>
</tr>
<tr>
<td>GSV at mid thigh</td>
<td>23</td>
<td>3.5%</td>
</tr>
<tr>
<td>Proximal GSV</td>
<td>18</td>
<td>2.8%</td>
</tr>
<tr>
<td>Perforating veins</td>
<td>3</td>
<td>0.5%</td>
</tr>
<tr>
<td>Total</td>
<td>648</td>
<td>100%</td>
</tr>
</tbody>
</table>

GSV: great saphenous vein; SSV: small saphenous vein.

2nd numbers is what I have in the data base.

### Table 2  Vital signs associated with chemical ablation.

<table>
<thead>
<tr>
<th>Ultrasound-guided foam sclerotherapy</th>
<th>Liquid: 1–3% polidocanol</th>
<th>Gas: 70% carbon dioxide (CO2)–30% oxygen (O2)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>pre-procedure</td>
<td>15 min into procedure</td>
</tr>
<tr>
<td>Heart rate (bpm)</td>
<td>73 SD 11</td>
<td>72 SD 10</td>
</tr>
<tr>
<td>Respiratory rate (rpm)</td>
<td>15 SD 4</td>
<td>14 SD 4</td>
</tr>
<tr>
<td>Pulse oximetry (%)</td>
<td>78 SD 2</td>
<td>78 SD 2</td>
</tr>
<tr>
<td>Systolic pressure (mmHg)</td>
<td>127 SD 18</td>
<td>125 SD 16</td>
</tr>
<tr>
<td>Diastolic pressure (mmHg)</td>
<td>73 SD 14</td>
<td>72 SD 12</td>
</tr>
</tbody>
</table>

| a | Significantly lower than pre-procedure heart rate (p < 0.001, paired t-test). |
| b | Significantly lower than pre-procedure systolic pressure (p = 0.043, paired t-test). |
in systolic pressure at 15 min into the procedure were observed.

Localised itching was reported by 7 of the 100 patients, a proportion similar to that reported by patients treated with air- (6%, \(p = NS\)) but less than that reported by patients treated with CO2 (15%, \(p < 0.05\)). Localised leg pain was reported by 24 patients, a proportion similar to that reported after air- (22%, \(p = NS\)) or CO2-based (20%, \(p = NS\)) USGFS. Two patients mentioned leg burning, two mentioned tingling, one mentioned cramping, and one complained of redness following CO2/O2-based USGFS. Discomfort from compression stockings was mentioned by 5 patients.

No patient reported chest tightness or dry cough in this series of 100 cases of USGFS using CO2/O2 gas (Table 3). This finding was a significant improvement over air or CO2 foams as previously reported (\(p < 0.05\), chi squared). Dizziness was reported once (1%), significantly less than the percentage reported following air- (12%, \(p = 0.002\)) but not statistically different from CO2-based (3.1%, \(p = NS\)) USGFS. The patient reporting dizziness also reported headache, hangover, and calf or ankle tingling, numbness and pain. The incidence of visual disturbance was comparable with that observed with CO2 and air foams (Table 3). However, the small number of events observed in these series prevented meaningful statistical comparison of these events.

Overall, 5 patients mentioned non-leg symptoms. One patient mentioned earache and another mentioned metallic/medicine tasting. There were two cases of visual disturbance and one case of dizziness, headache and hangover. All patients had received injections in proximal tributaries, accounting for 8% (5/66) of patients who received proximal tributary injections. Three of these 5 patients had injections in the proximal SSV, accounting for 7% (3/44) of patients who received proximal SSV injections. One patient received bilateral proximal GSV injections, accounting for 7% (1/14) of patients who received proximal GSV injections. 36 Further patients who received more than 25 mL of foam reported no symptom of this type.

### Table 3 Side effects following chemical ablation.

<table>
<thead>
<tr>
<th>Condition</th>
<th>Gas</th>
<th>Condition</th>
<th>Gas</th>
<th>Condition</th>
<th>Gas</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ultrasound-guided foam sclerotherapy</td>
<td></td>
<td>Liquid: 1−3% polidocanol</td>
<td></td>
<td>Liquid: 1−3% polidocanol</td>
<td></td>
</tr>
<tr>
<td>Gas: air or CO2 or 70%CO2−30%O2</td>
<td></td>
<td>Gas: air or CO2 or 70%CO2−30%O2</td>
<td></td>
<td>Gas: air or CO2 or 70%CO2−30%O2</td>
<td></td>
</tr>
<tr>
<td>Condition</td>
<td>Air</td>
<td>CO2</td>
<td>CO2−O2</td>
<td>Condition</td>
<td>Air</td>
</tr>
<tr>
<td>------------------------------------</td>
<td>--------------</td>
<td>-----------------------------------</td>
<td>--------------</td>
<td>------------------------------------</td>
<td>--------------</td>
</tr>
<tr>
<td>Chest tightness</td>
<td>9 (18%)</td>
<td>4 (3.1%)</td>
<td>0 (0%)</td>
<td>Chest tightness</td>
<td>9 (18%)</td>
</tr>
<tr>
<td>Dry cough</td>
<td>8 (16%)</td>
<td>2 (1.6%)</td>
<td>0 (0%)</td>
<td>Dry cough</td>
<td>8 (16%)</td>
</tr>
<tr>
<td>Dizziness</td>
<td>6 (12%)</td>
<td>4 (3.1%)</td>
<td>1 (1%)</td>
<td>Dizziness</td>
<td>6 (12%)</td>
</tr>
<tr>
<td>Visual disturbance</td>
<td>4 (8.2%)</td>
<td>4 (3.1%)</td>
<td>2 (2%)</td>
<td>Visual disturbance</td>
<td>4 (8.2%)</td>
</tr>
<tr>
<td>Metallic/medicine taste</td>
<td>0 (0%)</td>
<td>2 (1.6%)</td>
<td>1 (1%)</td>
<td>Metallic/medicine taste</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Nausea</td>
<td>2 (4%)</td>
<td>3 (2%)</td>
<td>0 (0%)</td>
<td>Nausea</td>
<td>2 (4%)</td>
</tr>
<tr>
<td>Circumoral paraesthesia</td>
<td>0 (0%)</td>
<td>1 (0.8%)</td>
<td>0 (0%)</td>
<td>Circumoral paraesthesia</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Respiratory difficulty</td>
<td>0 (0%)</td>
<td>1 (0.8%)</td>
<td>0 (0%)</td>
<td>Respiratory difficulty</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Total</td>
<td>49 (100%)</td>
<td>128 (100%)</td>
<td>100 (100%)</td>
<td>Total</td>
<td>49 (100%)</td>
</tr>
</tbody>
</table>

CO2: carbon dioxide.
O2: oxygen.


**Discussion**

Few reports describe the incidence and significance of side effects following USGFS with the use of biocompatible gases.\(^1\) This work makes a contribution toward an understanding of possible side effects following USGFS using a physiological gas, CO2−O2, instead of air.

In controlled clinical trials, better efficacy of foam compared to liquid sclerosant has been demonstrated.\(^{23–26}\) Pain, pigmentation or signs of inflammation, were more common after foam than after liquid injection in one report\(^{19}\) but other investigators noted no difference in ecchymosis, inflammation or other side effects or adverse reactions.\(^{23,24,26}\) Review papers have emphasised the superiority of foam versus liquid sclerotherapy for the treatment of patients with varicose veins.\(^{27,28}\) In our study USGFS was complementary to thermal ablation by radiofrequency or laser ablation.

One of the inspiring factors leading to the use of a physiological gas-based foam was CO2 angiography.\(^{29}\) Physiological gas-based foam has been injected in larger volumes than those usually recommended for air-based foam.\(^{19}\) A commercially-prepared foam, composed primarily of CO2 and O2, produced smaller bubbles, and avoided arteriolar obstruction (bubbles were seen with both foams, but did not cause obstruction with the commercial product) caused by the "home-made" air-based foam.\(^{30}\) CO2/O2-based foam is more stable than pure CO2 based foam (Personal Communication: Tessari L, Cabrera A).

The European Consensus on Foam Sclerotherapy published by Breu et al.\(^2\) made several recommendations based on the opinions of experts, since little published data existed at the time to address much of this subject. Consensus statement 1 recommends accessing the great saphenous vein at the proximal thigh. In our study, the proximal great saphenous vein had already been ablated, either surgically or thermally so we treated distal veins first. In contrast to consensus 2, we initiated SSV injections distally and found no disadvantage to this approach.
Consensus 3 recommending indirect injections for treatment of perforating veins was followed as was Consensus 4 recommending the dual-syringe technique for foam preparation. Consensus 5 mentioned air, and mixtures of CO₂ and O₂ as gases to be used to prepare the foam. We have reported the outcomes of these treatments above. Consensus 6, recommending a 1:4 liquid-to-gas ratio was followed. Consensus 7 recommended standardisation of foam preparation for trials but not for daily practice. Our quality-assurance program has been designed primarily for daily clinical practice. Consensus 8 listed concentrations of polidocanol according to specific clinical applications. Our selection of 1% polidocanol matched our primary application, treatment injection of tributary veins. Consensus 9 recommended maximum volumes per puncture up to 4 mL for small saphenous and perforating veins, 6 mL for great saphenous and tributary veins and up to 8 mL for recurrent varicose veins. Yamaki et al. have indicated that multiple small-dose injections of less than 0.5 mL can reduce the passage of sclerosant foam into deep veins.31 We injected CO₂–O₂ foam volumes of 2 mL or less. Consensus 10 and consensus 11 recommended a maximum foam volume of 10 mL per leg or per session. Foam prepared with CO₂ appears to be safe when injected in larger volumes.17–19,32 Our personal experience has indicated that side effects and adverse reactions are not related to foam volume and may occur with injections as little as 2 mL of foam.33,34 Consensus 12 recommended use of more viscous foams, such as 3% versus 1% polidocanol for large veins.35 The “3/1 study” demonstrated equivalent efficacy for 1% and 3% polidocanol foam for sclerotherapy of GSV less than 8 mm in diameter.46 In our present study polidocanol 1% was appropriate for the treatment of 2–3 mm veins which comprised almost all the veins treated. According to consensus 16, immediate compression of injected areas was not performed, foam distribution was controlled by ultrasound, and ankle dorsiflexion was performed frequently. Consensus 20 and 21 mentioned recommendations regarding patent foramen ovale. Our philosophy has been to monitor signs and symptoms early during the procedure and to have ultrasound equipment available for TTE and TCD evaluation. Evaluation for patent foramen ovale or thrombophilia before USGFS was not routine. Consensus 23 regarding the use of prophylactic low molecular weight heparin (LMWH) in selected patients was followed. Consensus 24 and 25 regarding provision of patient information on safety and efficacy and informed consent were complied with. Consensus 26 and 27 related to ultrasound guidance and interpretation criteria are routine in our practice. Consensus 28 and 29 were not directly related to this investigation; grading of results and thrombus removal recommendations have been influential in our practice.

Our observations indicated that USGFS can be performed safely. Neurological complications have been described17,38 but are rare and not exclusive to foam sclerotherapy; brain infarct has occurred following saphenous vein stripping.39 Sylvoz et al. reported a case of polidocanol induced cardiotoxicity after a 7 mL injection, and found 5 cases of cardiac toxicity reported in the literature.40 Deep vein occlusion has been reported at rates of 1.5% per treatment session or approximately 3% per patient.41 We have investigated patients with duplicated femoral vein segments: thrombosis was detected in 8.6% of the limbs or 12% of the patients (5/43).42,43 Extensive, ascending thrombophlebitis following foam sclerotherapy has been suggested as an indication to investigate for malignancy.44

**Figure 1** Transthoracic echocardiography and transcranial Doppler demonstrating bubbles in the left heart and high intensity transient signals (HITS) in the middle cerebral artery: a) four chamber view of heart; b) bubbles filling right atrium and ventricle following injection of foam sclerosant into peripheral leg vein; c) Bubbles (yellow arrow) progressing from right atrium through patent foramen ovale into left atrium; and d) HITS in the middle cerebral artery.
Bubbles, not necessarily sclerosing foam, travel to the deep system despite leg positioning, leg immobility, or volume of foam injected. Bubbles consistently reach the right chambers of the heart and may traverse to the left chambers in patients with patent foramen ovale or right-to-left pulmonary shunts (Fig. 1).22,47 HITS, commonly associated with air embolisation, have been detected in the middle cerebral artery with transcranial Doppler (Fig. 1).33,34,43 The question pertinent to this investigation is if the type of gas would influence the number of HITS.

This investigation demonstrated that USGFS using a 70–30% gas mixture of CO₂ and O₂ is at least as safe as air-based or CO₂-based foams. Vital signs were not physiologically affected during the procedure. Leg symptoms were no different from those seen with air foams but chest tightness or dry cough was reduced in patients treated with CO₂–O₂ foam. Visual disturbances were reported infrequently in this study but overall too few cases were encountered for statistical analysis.

A word of caution is warranted regarding interpretation of our findings. We have used historical data for comparison and this was not a randomised study. Factors such as patient education or awareness or even degree of Internet interaction could affect response to investigation of symptoms. However, we compared results with the same protocol for each of the patient cohorts included in the analysis presented above.

In summary, USGFS with foam prepared using a physiological mixture of carbon dioxide and oxygen was well tolerated by virtually all patients, and resulted in fewer side effects than in our historical data using air foam.

**Conflict of Interest/Funding**

None.

**Acknowledgements**

The authors thank Kathy Melphy, RN, BSN, Christine Hall, RN, BSN, Pam Norris RN, BSN, Sharon Obert, RN, BSN, Barbara Deusterman RN, BSN, Ellen Allen, RN, Janice Moreno, RN, BSN, CVN, Shanon Levin, RVT, and Kristin Hansen, RVT

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