

## REFERENCES

1. Bounds MC, Endean ED. Treatment of postoperative high-volume lymphatic complications using isosulfan blue. *J Vasc Surg Venous Lymphat Disord* 2018;6:737-40.
2. Akhan O, Karcaaltincaba M, Ozmen MN, Akinci D, Karcaaltincaba D, Ayhan A. Percutaneous transcatheter ethanol sclerotherapy and catheter drainage of postoperative pelvic lymphoceles. *Cardiovasc Intervent Radiol* 2007;30:237-40.
3. Johnson OW, Chick FJ, Chauhan NR, Fairchild AH, Fan CM, Stecker MS, et al. The thoracic duct: clinical importance, anatomic variation, imaging, and embolization. *Eur Radiol* 2016;26:2482-93.
4. Hill H, Srinivasa RN, Gemmete JJ, Hage A, Bundy J, Chick JF. Lymphangiography and cyanoacrylate glue embolization for the treatment of postoperative lymphatic leak after robot-assisted laparoscopic pelvic resection. *J Endourol Case Rep* 2018;4:66-71.

<https://doi.org/10.1016/j.jvsv.2018.11.001>

### Regarding “Retrograde administration of ultrasound-guided endovenous microfoam chemical ablation for the treatment of superficial venous insufficiency”



We read with interest Dr Deak's case series<sup>1</sup> of 250 patients treated with U.S. Food and Drug Administration (FDA)-approved polidocanol microfoam 1% consisting of 65% oxygen and 35% carbon dioxide (O<sub>2</sub>CO<sub>2</sub>FS) containing <0.8% nitrogen. The absence of neurologic or cardiac adverse events (NCAEs) in Dr Deak's community practice case series is consistent with the absence of clinically important neurologic events in the Efficacy and Safety Study of Polidocanol Injectable Foam for the Treatment of Saphenofemoral Junction Incompetence (VANISH-1) and Polidocanol Endovenous Microfoam Versus Vehicle for the Treatment of Saphenofemoral Junction Incompetence (VANISH-2).<sup>2,3</sup> We recently reviewed leg vein sclerosant-associated NCAEs to see whether foamed preparation contributed to postmarketing reports of NCAEs. We searched the FDA Adverse Event Reporting System database and MEDLINE for NCAEs using any formulation of polidocanol or sodium tetradecyl sulfate (STS) for leg vein sclerotherapy. Search dates were from March 30, 2010, for all polidocanol products (U.S. approved date for Asclera) and from January 1, 1968, for STS (introduction of the FDA Adverse Event Reporting System database) through September 19, 2017, for these products. We included only NCAEs with onset within 24 hours of the sclerotherapy procedure so as to exclude secondary or cascade events not directly attributable to sclerotherapy.

NCAEs attributable to pulmonary embolus, deep venous thrombosis, and anaphylaxis were excluded, as these have previously been labeled in the polidocanol and STS package inserts. Cases reported as vasovagal reactions were also excluded.

We retrieved 83 reports of polidocanol and 57 reports of STS. After applying the inclusion and exclusion criteria, we identified 23 leg vein sclerotherapy NCAE cases (Table). Patent foramen ovale or right to left shunt was documented in 11 cases, including all but one STS neurologic case. Physician-compounded foamed sclerosant, generally with room air, was documented in 10 patients. Twelve cases did not report the presence or absence of foam. One case documented liquid formulation associated with lumbar ischemia and spinal vein occlusion without brain involvement. NCAE onset occurred within 30 minutes after the sclerosant injection in 18 cases. Of the 13 patients with brain ischemia, 9 patients had complete clinical recovery within 3 days, and 6 patients had documentation of intracranial intra-arterial air. Coronary artery imaging showed no hemodynamically significant coronary artery disease in any of our cardiac cases. One cardiac arrest case reporting death before hospital arrival did not provide coronary artery information.

Our case series, which excluded pulmonary embolus and deep venous thrombosis, found no NCAEs for O<sub>2</sub>CO<sub>2</sub>FS (Varithena; BTG International Ltd, London, UK), although global market authorizations and approval date differences likely contributed to less O<sub>2</sub>CO<sub>2</sub>FS use. Polidocanol is available as Varithena O<sub>2</sub>CO<sub>2</sub>FS to treat incompetent great saphenous veins, accessory saphenous veins, and visible varicosities of the great saphenous vein system above and below the knee.<sup>4</sup> The liquid formulation of polidocanol is available as Asclera to treat uncomplicated spider veins and uncomplicated reticular veins.<sup>5</sup>

Mitigation potential exists for NCAEs associated with leg vein sclerotherapy paradoxical embolism of room air. The safety and efficacy of polidocanol or STS foamed with room air has not been established and its use should be avoided. This statement was recently included in the Asclera<sup>5</sup> and Sotradecol<sup>6</sup> product labels under the heading Arterial Embolism.

The authors would like to thank Mary Ross Southworth, PharmD (Office of New Drugs, Center for Drug Evaluation and Research, Food and Drug Administration, Silver Spring, Md), for her thoughtful suggestions in preparing this manuscript.

**Table.** Case series clinical characteristics

Neurologic cases (n = 14)				Cardiac cases (n = 9)			
		Polidocanol (n = 9)	STS (n = 5)			Polidocanol (n = 7)	STS (n = 2)
Events	Stroke/TIA (13)	8	5	Events	Cardiac arrest (2)	2 <sup>a</sup>	0
	Spinal ischemia (1)	1	0		NSTEMI, STEMI (3)	2	1
					SC/TTS per reporter (4)	3	1
Formulation	PCFS (6)	3	3	Formulation	PCFS (4)	3	1
	Un-foamed liquid (1)	1	0		Un-foamed liquid (0)	0	0
	NR (7)	5	2		NR (5)	4	1
Air embolism	ICA on imaging (6)	1	5	Coronaries	Normal <sup>b</sup> (8)	6	2
	NR (8)	8	0		NR (1)	1	0
PFO/RLS	Found (9)	5	4	PFO/RLS	Found (2)	1	1
	Not found (3)	2	1		Not found (1)	1	0
	NR (2)	2	0		NR (6)	5	1
Time to onset	Within 30 minutes (11)	6	5	Time to onset	Within 30 minutes (7)	6	1
	30 minutes to 3 hours (1)	1	0		30 minutes to 3 hours (1)	1	0
	NR but <24 hours (2)	2	0		NR but <24 hours (1)	0	1
				LVEF at time of acute presentation	Range	24%-50%	45% to normal EF <sup>c</sup>
					Mean	38%	—
					NR	3	—
Time to complete neurologic recovery	3 days or less (9)	5	4	Time to normalization of LV wall motion	9 days or less (4)	2	2
	4-14 days (2)	2	0		<3 months (2)	2	0
	<3 months (2)	1	1 <sup>d</sup>		Died within 48 hours (2)	2 <sup>a</sup>	
	Not recovered (1)	1 <sup>e</sup>	0		NR (1)	1	

ICA, Intracranial intra-arterial air; LV, left ventricle; LVEF, left ventricular ejection fraction; NR, not reported; NSTEMI, non-ST elevation myocardial infarction; PCFS, physician-compounded foamed sclerosant; PFO/RLS, patent foramen ovale/right to left shunt; SC/TTS, stress cardiomyopathy/Takotsubo syndrome; STEMI, ST elevation myocardial infarction; STS, sodium tetradecyl sulfate; TIA, transient ischemic attack.

<sup>a</sup>One case report diagnosed right ventricular arrhythmogenic dysplasia on the basis of autopsy findings.

<sup>b</sup>No hemodynamically significant coronary artery lesions present.

<sup>c</sup>This case used term *normal*, without quantification of LVEF.

<sup>d</sup>National Institutes of Health Stroke Score (NIHSS) 1 at 1-month follow-up. Patient initially presented with NIHSS 16, which had been acutely treated with microcatheter aspiration of air from middle cerebral artery.

<sup>e</sup>Lumbar ischemia and spinal vein occlusion without brain involvement reported as not recovered at 3-month follow-up.

Daniel Woronow, MD

Thao Tran, PharmD

Amy Chen, PharmD

Monica Muñoz, PharmD, MS

Cindy Kortepeter, PharmD

Division of Pharmacovigilance

Office of Surveillance and Epidemiology

Center for Drug Evaluation and Research

U.S. Food and Drug Administration

Silver Spring, Md

The views expressed are those of the authors and not necessarily those of the U.S. Food and Drug Administration.

## REFERENCES

1. Deak ST. Retrograde administration of ultrasound-guided endovenous microfoam chemical ablation for the treatment of superficial venous insufficiency. *J Vasc Surg Venous Lymphat Disord* 2018;6:477-84.
2. King JT, O'Byrne M; VANISH-1 Investigator Group. Treatment of truncal incompetence and varicose veins with a single

administration of a new polidocanol endovenous microfoam preparation improves symptoms and appearance. *Eur J Vasc Endovasc Surg* 2015;50:784-93.

3. Todd KL 3rd, Wright DI: VANISH-2 Investigator Group. Durability of treatment effect with polidocanol endovenous microfoam on varicose vein symptoms and appearance (VANISH-2). *J Vasc Surg Venous Lymphat Disord* 2015;3:258-64.e1.
4. U.S. Food and Drug Administration. Varithena. Full prescribing information. U.S. Department of Health and Human Services. Available at: [https://www.accessdata.fda.gov/drugsatfda\\_docs/label/2017/205098s0261bl.pdf](https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/205098s0261bl.pdf). Accessed July, 2018.
5. U.S. Food and Drug Administration. Asclera. Full prescribing information. U.S. Department of Health and Human Services. Available at: [https://www.accessdata.fda.gov/drugsatfda\\_docs/label/2018/021201s0021bl.pdf](https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/021201s0021bl.pdf). Accessed July, 2018.
6. U.S. Food and Drug Administration. Sotradecol. Full prescribing information. U.S. Department of Health and Human Services. Available at: <https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=f1756c28-dcd2-4b49-be62-07ca20682018>. Accessed July, 2018.

<https://doi.org/10.1016/j.jvsv.2018.09.014>

## Reply



I thank Dr Woronow and colleagues for their letter to the Editor recognizing the absence of neurologic and cardiac adverse events (NCAEs) in my recently published case series regarding outcomes from 250 patients treated with Food and Drug Administration-approved polidocanol microfoam 1%.<sup>1</sup> The safety profile demonstrated in phase 3 clinical trials was the rationale for incorporating this treatment in my practice in place of physician-compounded foam (PCF). The analysis in Dr Woronow's letter revealed 23 leg vein sclerotherapy NCAE cases with use of PCF. NCAE cases are likely the result of gas emboli that occur in using foams made with room air that have a high nitrogen content. Polidocanol microfoam 1% has a low nitrogen content (<0.8%) to reduce the risk of neurologic complications.

Before adopting polidocanol microfoam 1% in my practice, I refrained from using PCF because of the published reports of patients who suffered significant neurologic events after treatment, including stroke, seizure, and transient ischemic attack.<sup>2-7</sup> I also noted that the existence of a patent foramen ovale (PFO) may contribute to the increased risk of NCAE. In the analysis performed by Dr Woronow, more than half of the patients with NCAEs had a PFO. This incidence was similar to an analysis of 82 patients undergoing polidocanol microfoam 1% ablation of the great saphenous vein.<sup>8</sup> In that study,

61% of the patients were PFO positive. In another study, middle cerebral artery bubbles were detected during polidocanol microfoam 1% ablation in 89% of the PFO-positive patients and 29% of PFO-negative patients. No patients displayed evidence of cerebral or cardiac microinfarction 30 days after treatment, nor did they display any adverse neurologic signs or elevated cardiac troponin I.<sup>9</sup> Therefore, if arterial bubble emboli are unavoidable during the injection of sclerosant foam, it is critical to select a Food and Drug Administration-approved formulation that minimizes risk to the patient.

I have since treated 420 patients with polidocanol microfoam 1%. My patients continue to benefit from treatment, with no NCAEs reported.

Steven Deak, MD, PhD

Deak Vein NJ Clinic  
Somerset, NJ

## REFERENCES

1. Deak ST. Retrograde administration of ultrasound-guided endovenous microfoam chemical ablation for the treatment of superficial venous insufficiency. *J Vasc Surg Venous Lymphat Disord* 2018;6:477-84.
2. Asbjornsen CB, Rogers CD, Russell BL. Middle cerebral air embolism after foam sclerotherapy. *Phlebology* 2012;27:430-3.
3. Bush RC, Derrick M, Manjoney D. Major neurological events following foam sclerotherapy. *Phlebology* 2008;23:189-92.
4. Hill DA. Neurological and chest symptoms following sclerotherapy: a single centre experience. *Phlebology* 2014;29:619-27.
5. Parsi K. Paradoxical embolism, stroke and sclerotherapy. *Phlebology* 2012;27:147-67.
6. Engelberger RP, Ney B, Clair M, Dabiri A, Alatri A, Mazzolai L, et al. Myocardial infarction after ultrasound-guided foam sclerotherapy for varicose veins—a case report and review of the literature of a rare but serious adverse event. *Vasa* 2016;45:255-8.
7. Malvey MA, Asbjornsen C. Transient neurologic event following administration of foam sclerotherapy. *Phlebology* 2017;32:66-8.
8. Wright DD, Gibson KD, Barclay J, Razumovsky A, Rush J, McCollum CN. High prevalence of right-to-left shunt in patients with symptomatic great saphenous incompetence and varicose veins. *J Vasc Surg* 2010;51:104-7.
9. Regan JD, Gibson KD, Rush JE, Shortell CK, Hirsch SA, Wright DD. Clinical significance of cerebrovascular gas emboli during polidocanol endovenous ultra-low nitrogen microfoam ablation and correlation with magnetic resonance imaging in patients with right-to-left shunt. *J Vasc Surg* 2011;53:131-7.

<https://doi.org/10.1016/j.jvsv.2018.10.003>