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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[1] 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_2CO_2FS) 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).[2,3] 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_2CO_2FS (Varithena; BTG International Ltd, London, UK), although global market authorizations and approval date differences likely contributed to less O_2CO_2FS use. Polidocanol is available as Varithena O_2CO_2FS to treat incompetent great saphenous veins, accessory saphenous veins, and visible varicosities of the great saphenous vein system above and below the knee.[4] The liquid formulation of polidocanol is available as Asclera to treat uncomplicated spider veins and uncomplicated reticular veins.[5]

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[5] and Sotradecol[6] product labels under the heading Arterial Embolism.

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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[a]	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[b] (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[c]
					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[d]		Died within 48 hours (2)	2[a]	
	Not recovered (1)	1[e]	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.
[a]One case report diagnosed right ventricular arrhythmogenic dysplasia on the basis of autopsy findings.
[b]No hemodynamically significant coronary artery lesions present.
[c]This case used term *normal*, without quantification of LVEF.
[d]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.
[e]Lumbar ischemia and spinal vein occlusion without brain involvement reported as not recovered at 3-month follow-up.

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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%.[1] 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.[2-7] 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.[8] 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.[9] 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.

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