

# Safety and efficacy of venoplasty in MS

## A randomized, double-blind, sham-controlled phase II trial

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## Abstract

### Objective

To determine the safety and efficacy of balloon vs sham venoplasty of narrowing of the extracranial jugular and azygos veins in multiple sclerosis (MS).

### Methods

Patients with relapsing or progressive MS were screened using clinical and ultrasound criteria. After confirmation of >50% narrowing by venography, participants were randomized 1:1 to receive balloon or sham venoplasty of all stenoses and were followed for 48 weeks. Participants and research staff were blinded to intervention allocation. The primary safety outcome was the number of adverse events (AEs) during 48 weeks. The primary efficacy outcome was the change from baseline to week 48 in the patient-reported outcome MS Quality of Life–54 (MSQOL-54) questionnaire. Standardized clinical and MRI outcomes were also evaluated.

### Results

One hundred four participants were randomized (55 sham; 49 venoplasty) and 103 completed 48 weeks of follow-up. Twenty-three sham and 21 venoplasty participants reported at least 1 AE; one sham (2%) and 5 (10%) venoplasty participants had a serious AE. The mean improvement in MSQOL-54 physical score was +1.3 (sham) and +1.4 (venoplasty) ( $p = 0.95$ ); MSQOL-54 mental score was +1.2 (sham) and –0.8 (venoplasty) ( $p = 0.55$ ).

### Conclusions

Our data do not support the continued use of venoplasty of extracranial jugular and/or azygos venous narrowing to improve patient-reported outcomes, chronic MS symptoms, or the disease course of MS.

### ClinicalTrials.gov identifier

NCT01864941.

### Classification of evidence

This study provides Class I evidence that for patients with MS, balloon venoplasty of extracranial jugular and azygos veins is not beneficial in improving patient-reported, standardized clinical, or MRI outcomes.

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## Glossary

**AE** = adverse event; **CCSVI** = chronic cerebrospinal venous insufficiency; **CUA** = combined unique active; **DMT** = disease-modifying therapy; **EDSS** = Expanded Disability Status Scale; **IJV** = internal jugular vein; **MS** = multiple sclerosis; **MSFC** = Multiple Sclerosis Functional Composite; **MSQOL-54** = Multiple Sclerosis Quality of Life-54; **PRO** = patient-reported outcome; **RRMS** = relapsing-remitting multiple sclerosis; **SAE** = serious adverse event; **UBC** = University of British Columbia.

Multiple sclerosis (MS) is an inflammatory and degenerative demyelinating disease of the human CNS. While abundant scientific and clinical data support the involvement of the immune system in the pathogenesis of MS,<sup>1</sup> the etiology and management of many clinical manifestations of the disease (e.g., fatigue and cognitive impairment) remain poorly understood. Chronic cerebrospinal venous insufficiency (CCSVI), described as a combination of extracranial venous structural and flow anomalies, had been proposed as contributing to the pathogenesis and disabling symptoms<sup>2</sup> in MS, and subsequently in other conditions including Alzheimer disease,<sup>3</sup> Parkinson disease,<sup>4</sup> and Ménière disease.<sup>5</sup> It had been postulated that impaired venous drainage would cause stasis leading to perivenular iron deposition triggering inflammation. This pathogenic hypothesis remains poorly supported, and venous narrowing has been found as frequently in healthy volunteers as in patients with MS.<sup>6</sup> Multiple uncontrolled, unblinded studies and case series suggested that venous dilation with or without intravascular stenting could improve symptoms and modify the disease course in MS<sup>2,7-15</sup> and Ménière disease.<sup>5</sup> These procedures were promoted through social media and were readily available through medical tourism<sup>16</sup> despite warnings by regulatory bodies including the US Food and Drug Administration about significant complications.<sup>17</sup>

We conducted a randomized, sham-controlled, double-blind, interventional trial in relapsing-remitting and progressive forms of MS<sup>18</sup> to determine short- and long-term safety and efficacy on patient-reported outcomes (PROs), and standard clinical and MRI outcomes up to 48 weeks.

## Methods

### Participants

Between May 29, 2013, and August 19, 2015, we recruited participants with relapsing-remitting MS (RRMS), secondary progressive MS, and primary progressive MS at 4 Canadian academic centers with MS clinics and interventional radiology expertise (University of British Columbia [UBC] Hospital, Vancouver; Health Sciences Centre, Winnipeg; CHUM, Hôpital Notre-Dame, Montreal; Hôpital Enfant-Jésus, Québec). The following were inclusion criteria: age 18 to 65 years, diagnosis of definite MS by the 2010 McDonald criteria,<sup>19</sup> an Expanded Disability Status Scale (EDSS)<sup>20</sup> score between 0 (i.e., minimal disability) and 6.5 (i.e., using bilateral aids to walk), neurologically stable disease within the 30 days before screening. In addition, participants fulfilled at least 2

ultrasound criteria for CCSVI defined by the Canadian Institutes of Health Research Imaging Expert Panel (appendix e-1, [links.lww.com/WNL/A720](https://links.lww.com/WNL/A720)): reflux in the internal jugular vein (IJV) and/or vertebral vein; reflux present in the deep cerebral veins; B mode IJV stenosis; absent IJV and/or vertebral vein flow; and negative IJV cross-sectional area. Participants had to have confirmation on catheter venography of >50% narrowing affecting at least 1 of 3 extracranial veins (either internal jugular and/or azygos).<sup>6</sup> Participants on standard disease-modifying therapies (DMTs) were permitted to continue on medication, and changes were allowed for on-study relapses after randomization.

Exclusion criteria included treatment with vasodilators, parasympathomimetics, sympatholytics, calcium channel blockers, previous venoplasty and/or stenting, previous jugular or subclavian central line or major neck surgery or radiation, previous contrast allergy, inability to undergo MRI, inadequate medical records confirming diagnosis and disease course, and inability to complete all study visits.

After randomization and intervention, participants were followed for 48 weeks with adverse event (AE) assessments, standardized PRO scales (72 hours and weeks 2, 12, 24, 36, and 48), Multiple Sclerosis Functional Composite (MSFC)<sup>21</sup> and EDSS scores (weeks 2, 12, 24, and 48), and MRI and ultrasound (weeks 24 and 48) assessments.

### Standard protocol approvals, registrations, and patient consents

The clinical research ethics boards at the 4 participating centers approved the study protocol. The trial was registered with [clinicaltrials.gov](https://clinicaltrials.gov) NCT01864941.

### Procedures

Personnel at all sites underwent standardized training for ultrasound (L.M.), venography (L.M.), and venoplasty (L.M. and G.S.) procedures. Venography was performed under conscious sedation, and the duration of time within the angiography suite was uniform for both venoplasty- and sham-treated participants. A 5-French diagnostic catheter was introduced through the common femoral vein to selectively catheterize the right and left IJVs as well as the azygos vein using a standardized protocol.<sup>6</sup> Venous stenosis was determined by dividing the minimum (narrowest) lumen diameter by the reference lumen diameter (normal vein diameter proximal or distal to the stenosis).<sup>6</sup> Participants with >50% narrowing of any of the 3 veins were randomized (1:1) to either sham or active balloon venoplasty of all

narrowed veins under study. The venoplasty participants were treated with an angioplasty balloon 2 mm greater than the nominal vein diameter, which was inflated for 60 seconds. A repeat venoplasty was performed for persistent narrowing >50%. The participants randomized to sham had a catheter that was advanced across the stenosis and left for 60 seconds.

### Randomization and masking

Stratified treatment randomization (RRMS vs progressive MS course<sup>18</sup>) at each site was completed by a permuted-block size of 6 to reduce the likelihood of obtaining unbalanced groups. The randomization table was generated by an independent statistician. Up to a maximum of 50% progressive disease was required for enrollment per site. Treatment assignments were sealed in individual envelopes, only opened after eligibility was confirmed, and resealed after the procedure. All participants and assessors were blinded to intervention assignment. The interventional team was not involved in any outcome assessments.

### Outcomes

The primary safety outcome included all AEs that are clinically significant and/or potentially related to study procedure and/or serious up to week 48, as determined by the principal investigators and in accordance with the International Conference on Harmonization.<sup>22</sup> The primary efficacy outcome was the change in the MS Quality of Life-54 (MSQOL-54) physical and mental composite scores<sup>23</sup> from baseline to week 48. Secondary efficacy outcomes were the changes in MSQOL-54 physical and mental composite from baseline to 72 hours to ensure an early, transient effect was not missed; Fatigue Severity Scale,<sup>24</sup> North American Research Committee on MS pain scale,<sup>25</sup> and CCSVI symptom scale<sup>26</sup> from baseline to 72 hours and week 48; and change in EDSS (median) and MSFC (mean) from baseline to week 48. Protocol-defined relapses were a 1-point increase in EDSS or a 1-point change on any functional status score representative of the relapse location. Combined unique active (CUA) lesions, defined as a contrast enhancing lesion on T1-weighted scan or a non-T1 enhancing, new/enlarging T2 lesion, compared to the previous MRI were assessed by the UBC MS/MRI Research Group from brain MRIs with contrast performed at baseline, week 24, and week 48.

### Oversight

Study data were collected and managed using REDCap hosted at the British Columbia Children's Hospital Research Institute.<sup>27</sup> Independent clinical research associates monitored source documents, case report forms, and database entries prior to database lock. An independent medical monitor (S.I.: cardiologist, UBC) reviewed all serious AEs (SAEs). An independent data safety monitoring board, which included a vascular surgeon, neurologist, ethicist, and statistician, reviewed AEs and trial progress.

### Statistical analyses

The number of participants to be included in this phase II trial was based on the primary efficacy outcome, a mean change in MSQOL-54 composite scores from baseline to week 48. Assuming an SD of 20,<sup>23</sup> 40 participants per group would give 60% power to demonstrate a difference of 10 points on the MSQOL-54 composite score (an effect size of  $10/20 = 0.5$ ) using a 2-tailed *t* test at the significance level of 0.05. At least 100 participants were randomized anticipating a potential withdrawal rate as high as 20%. The analysis plan was developed before database lock and unblinding. Analyses (safety and efficacy) were performed on the intention-to-treat population (all patients randomized) and based on data collected up to week 48. No imputation of missing values was performed. If individual patients had missing values for a particular outcome, those patients were not included in the analysis of that outcome. For the primary safety outcome (significant AEs, SAEs, and venography complications up to week 48), the distribution of the total number of AEs per participant between groups was compared with the Fisher exact test (noncontinuous variable). We also applied negative binomial regression analysis to the number of AEs per participant to estimate the relative rate; logistic regression to compare the proportion of participants having  $\geq 1$  AE; and more detailed versions of the regression analyses adjusting for covariates.

The changes from baseline for the efficacy outcomes (PROs, MSFC, and EDSS) were treated as continuous outcomes compared using a Student 2-sample *t* test. Additional regression analyses used the baseline level of the outcome as a covariate. At each follow-up time, PROs and MSFC were dichotomized as "improved" or "not improved" relative to the participant's baseline value and compared between groups using the Fisher exact test and logistic regression. Protocol-defined relapses were compared using the Fisher exact test and logistic regression analysis, and MRI CUA lesions were analyzed using the Fisher test and negative binomial regression.

The trial was conducted in accordance with the provisions of the International Conference on Harmonization Guidelines for Good Clinical Practice and the Declaration of Helsinki.<sup>22</sup> This study provides Class I evidence for assessing whether balloon venoplasty of extracranial jugular and azygous veins is beneficial in improving PROs, standardized clinical, and MRI outcomes in patients with relapsing or progressive MS.

### Data availability

Anonymized data can be made available to qualified investigators upon request to the corresponding author.

## Results

### Screening

The first participant was randomized on May 29, 2013, and the last participant completed week 48 on July 28, 2016. We

screened 274 patients, of whom 104 were randomized (49 venoplasty, 55 sham) across the 4 centers (figure 1). Failure to meet ultrasound criteria (n = 82), medical contraindications (n = 33), MRI or venography contraindications (n = 3), or insufficient medical records (n = 4) accounted for the triage of 122 patients who volunteered to participate. Sixteen participants who were potentially eligible for enrollment declined to participate in further screening with venography. One hundred thirty-six participants had venography performed, and of these, 104 (76%) fulfilled the final enrollment criteria (>50% narrowing) and were randomized. Overall retention to week 48 was 103 participants (98%). One participant randomized to sham treatment withdrew at week 24 because of a time conflict. One participant randomized to sham only completed MRI and blood work at week 48.

### Baseline

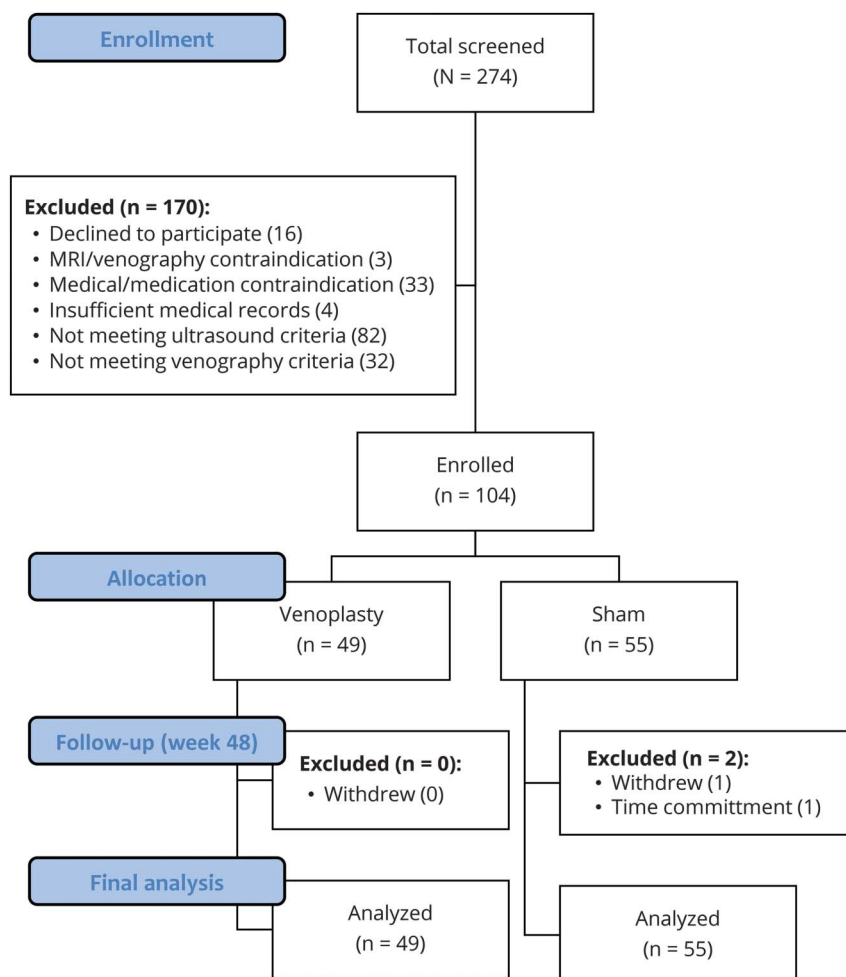
The mean age at enrollment was 50.5 years (range 33–65) with a mean disease duration of 17 years; 65% of participants were women (68/104) and 62% (64/104) had RRMS (table 1). Sixty-nine percent of participants with RRMS (44/64) were on DMTs. Characteristics were similar between

treatment groups and centers. On baseline venography, 50% of participants (32/64) with RRMS and 72% (29/40) with secondary progressive or primary progressive MS had multiple vessels with >50% narrowing.

### Efficacy: PROs

There was a transient increase in MSQOL scores within 72 hours (mental scores) and 2 weeks (physical scores) in both groups. The mean improvement from baseline to week 48 for MSQOL physical score was +1.3 and +1.4 (sham vs venoplasty  $p = 0.95$ ); MSQOL mental score +1.2 and -0.8 (sham vs venoplasty  $p = 0.55$ ); fatigue score +0.2 and +0.1 (sham vs venoplasty  $p = 0.65$ ); and pain score was +0.1 and -0.2 (sham vs venoplasty  $p = 0.19$ ). There was no significant difference in the proportion of sham and venoplasty participants who had an improvement in a PRO from baseline to week 48 (figure 2). There was no difference between sham and venoplasty groups on all PROs at 72 hours post procedure (table 2; table e-1, [links.lww.com/WNL/A719](https://www.lww.com/WNL/A719)). Improvements in the CCSVI symptom scale for limb temperature occurred in 6/50 (12%) sham and 4/48 (8%) venoplasty ( $p = 0.74$ ), limb color in 5/50 (10%) sham and

**Figure 1** Trial profile



**Table 1** Baseline demographics

Characteristic	Sham (n = 55)	Venoplasty (n = 49)	All (n = 104)	p Value <sup>a</sup>
Age, y, mean (range)	50.1 (33–65)	51.0 (35–63)	50.5 (33–65)	0.54
Female, n (%)	34 (62)	34 (69)	68 (65)	0.54
Disease course, n (%)				1.00
Relapsing-remitting	34 (62)	30 (61)	64 (62)	
Progressive	21 (38)	19 (39)	40 (38)	
Disease duration, y, mean (range)	16.2 (4–40)	18.1 (3–41)	17.1 (3–41)	0.30
EDSS score, median (range)	4 (0–6.5)	4 (0–6.5)	4 (0–6.5)	0.65
Disease-modify therapy, n (%)	24 (43.6)	20 (40.8)	44 (42.3)	0.84
Interferon beta-1a or -1b	10 (18.2)	6 (12.2)	16 (15.4)	
Glatiramer acetate	7 (12.7)	7 (14.3)	14 (13.5)	
Oral <sup>b</sup>	7 (12.7)	5 (10.2)	12 (11.5)	
Natalizumab	0	2 (4.1)	2 (1.9)	
Relapses in past year, n (%)				1.00
0	48 (87.3)	43 (87.8)	91 (87.5)	
1	6 (10.9)	6 (12.2)	12 (11.5)	
2	1 (1.8)	0	1 (1.0)	
MRI with T1 enhancing lesions, n (%)	9 (16.4)	4 (8.5) <sup>c</sup>	13 (12.7)	0.37
Venography, n (%)				0.16 <sup>d</sup>
Single vessel >50% narrowing	19 (34.5)	24 (49.0)	43 (41.3)	
Either jugular	15 (27.3)	23 (46.9)	38 (36.5)	
Azygos only	4 (7.3)	1 (2.0)	5 (4.8)	
Multiple vessels >50% narrowing	36 (65.5)	25 (51.0)	61 (58.7)	
Both jugulars	22 (40.0)	21 (42.9)	43 (41.3)	
One jugular and azygos	6 (11.0)	3 (6.1)	9 (8.7)	
All 3 vessels	8 (14.5)	1 (2.0)	9 (8.7)	

Abbreviation: EDSS = Expanded Disability Status Scale.

<sup>a</sup> Student 2-sample *t* test for continuous variables, Fisher exact test for categorical variables.

<sup>b</sup> Oral disease-modifying therapies include teriflunomide, dimethyl fumarate, and fingolimod.

<sup>c</sup> Two patients were missing these data.

<sup>d</sup> Reflects test of “single” vessel vs “multiple” vessels (not further subclassifications).

3/48 (6%) ( $p = 0.71$ ) venoplasty, brain fog in 9/50 (18%) sham and 7/48 (15%) venoplasty ( $p = 0.59$ ), and visual function in 6/50 (12%) sham and 3/48 (6%) venoplasty ( $p = 0.49$ ).

### Efficacy: Clinical and MRI outcomes

There was no improvement in MSFC from baseline to week 48 for the sham (0.0) or venoplasty (−0.4) group ( $p = 0.18$ ). There was little change in median EDSS score at week 48 in either group. Eleven participants (6 sham, 5 venoplasty) had a protocol-defined relapse ( $p = 0.91$ ); and 21 and 18 participants, respectively, had at least one MRI CUA lesion

( $p = 0.88$ ) (table 3). Of the 44 (24/55 sham, 20/50 venoplasty) participants on DMT at baseline, 1 sham participant discontinued DMT, 3 (1 sham, 2 venoplasty) switched DMTs, and 1 venoplasty participant had a temporary interruption of DMT use. Two sham participants were started on a DMT after baseline. The mean percent change from baseline to week 48 in brain volume was −0.693 and −0.707 ( $p = 0.93$ ) for sham and venoplasty groups.

Subgroup analysis of participants with the presence or absence of gadolinium-enhancing lesions at baseline, relapsing or progressive disease course, or the presence or absence of

**Table 2** Improvements in patient-reported outcomes from baseline to 72 hours

Improvement from baseline	Sham (n = 55)	Venoplasty (n = 49)	Venoplasty vs sham, estimate (95% CI)	p Value <sup>a</sup>
<b>MSQOL-54, mean ± SD</b>				
<b>Physical</b>	0.2 ± 10.4	0.6 ± 9.4	MD: 0.34 (−3.54 to 4.22)	0.86
<b>Mental</b>	4.1 ± 12.7	0.7 ± 11.8	MD: −3.35 (−8.14 to 1.44)	0.17
<b>Fatigue severity score, mean ± SD</b>	0.2 ± 1.3	0.0 ± 1.4	MD: −0.22 (−0.75 to 0.30)	0.39
<b>NARCOMS pain, mean ± SD</b>	0.1 ± 1.1	0.0 ± 1.2	MD: −0.14 (−0.60 to 0.32)	0.54
<b>CCSVI symptoms, n/n (%)</b>				
<b>Limb temperature</b>	6/47 (13)	4/44 (9)	OR: 0.69 (0.13 to 3.14)	0.74
<b>Limb color</b>	5/46 (11)	3/45 (7)	OR: 0.59 (0.09 to 3.25)	0.71
<b>Brain fog</b>	9/44 (20)	7/46 (15)	OR: 0.70 (0.20 to 2.37)	0.59
<b>Visual</b>	6/47 (13)	3/46 (6)	OR: 0.48 (0.07 to 2.43)	0.49

Abbreviations: CCSVI = chronic cerebrospinal venous insufficiency; CI = confidence interval; MD = mean difference; MSQOL-54 = Multiple Sclerosis Quality of Life-54; NARCOMS = North American Research Committee on Multiple Sclerosis; OR = odds ratio.

<sup>a</sup>Student 2-sample *t* test for scores, Fisher exact test for CCSVI symptoms.

azygos stenosis could not detect a benefit of venoplasty compared to sham on any outcome.

### Safety

No deaths occurred during the study. No periprocedural (within 48 hours) SAEs requiring hospitalization were reported. There was one asymptomatic internal jugular dissection that occurred in the venoplasty group that did not require intervention or hospitalization. Three (5%) sham and 3 (6%) venoplasty participants reported moderate or severe pain during the procedure ( $p = 0.88$ ); 6/54 (11%) and 4/49 (8%), respectively, reported postprocedure pain ( $p = 0.62$ ). Twenty of the 55 (36%) sham participants reported 37 AEs and 17/49 (35%) venoplasty participants reported 22 AEs within 48 hours. The most commonly reported periprocedural AEs were groin pain ( $n = 8/104$ , 7.7%), hematoma ( $n = 9/104$ , 8.6%), and neck pain ( $n = 6/106$ , 5.7%).

### AE to week 48

The number of participants with any AEs reported from baseline to week 48 was 42% (23/55) for sham and 43% (21/49) for venoplasty ( $p = 1$ , Fisher exact test) (table e-2, [links.lww.com/WNL/A719](https://links.lww.com/WNL/A719)). The most commonly reported AEs were gastrointestinal reflux or discomfort ( $n = 8$ ), paresthesia and/or lightheadedness ( $n = 8$ ), arthralgia ( $n = 6$ ), and general malaise ( $n = 4$ ). There were no cases of venous thrombosis up to week 48. Six (5.7%) SAEs were reported (1/55 [2%] sham, 5/49 [10%] venoplasty), none of which were related to the study procedure in the opinion of the blinded physician. The SAEs were generalized seizure (1 sham, week 17), sepsis (2 venoplasty, weeks 20 and 25), bleeding of a previously undiagnosed cerebral aneurysm (1 venoplasty, week 46), myocardial infarction (1 venoplasty, week 28), and pulmonary embolism (1 venoplasty, week 17).

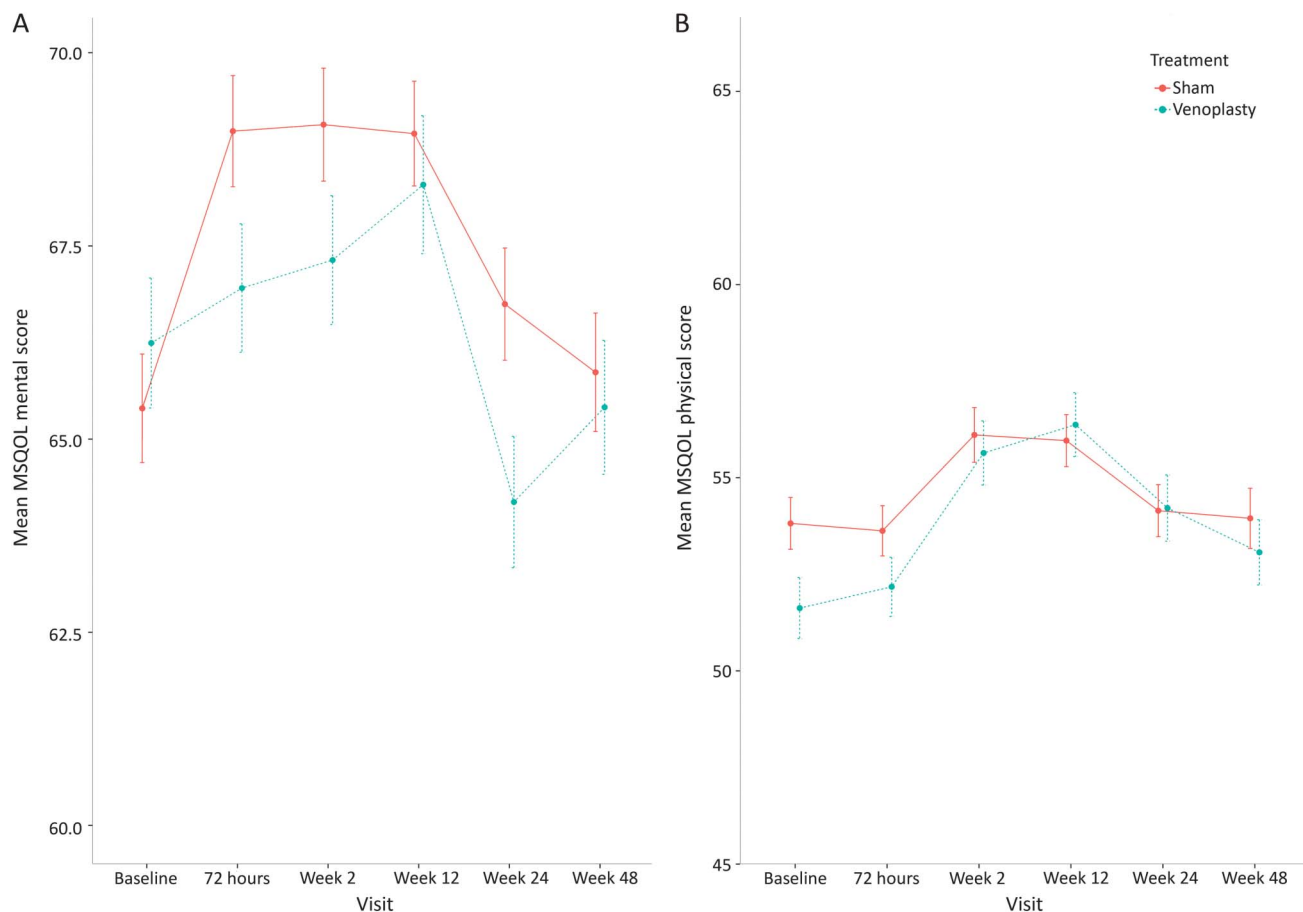
## Discussion

Before commencing this study in 2013, there were no randomized, blinded, sham-controlled trials on this topic reported since the first open-label study of 65 patients in 2009.<sup>2</sup> Eight additional open-label, uncontrolled, prospective or retrospective case series involving 1,655 patients (range 15–1,202) and unblinded evaluators have been reported.<sup>7–15</sup> The majority of these reported improvement in MS symptoms with PRO scales including MSQOL-54 and/or the EDSS. Subsequently, a retrospective cohort of 462 patients at 33 Italian centers<sup>28</sup> and a small prospective randomized study of 19 participants with MS (10 sham, 9 venoplasty) did not detect any benefit of venoplasty on clinical and MRI outcomes.<sup>29</sup>

We chose not to use vascular stents because of concerning reports of serious complications including stent thrombosis,<sup>30</sup> stent embolization, and death.<sup>15</sup> However, venoplasty alone can also be associated with SAEs, necessitating careful monitoring in this trial.<sup>31</sup> The original open-label venoplasty trial did not use intravascular stents and reported an improvement in symptoms during 18 months of follow-up.<sup>2</sup> We hypothesized that venoplasty without stenting should be sufficient to detect efficacy within 48 weeks without putting patients at greater risk of complications related to intravascular stents. Our findings support this decision, given that significant AEs were similar between the sham and venoplasty groups at 48 hours and 48 weeks post procedure, with no evidence of thrombosis up to week 48. However, SAEs were numerically higher in the venoplasty group at 10% vs 2% for sham.

There are important MS symptoms, including fatigue and pain, that are not adequately captured by routinely used clinician-assessed scales (EDSS and MSFC). Our study

**Figure 2** Patient-reported outcomes: MSQOL-54 mental (A) and physical (B) composite scores from baseline to week 48



A higher scale score indicates a higher quality of life. A similar, transient increase in scores was seen in the venoplasty and sham groups. MSQOL-54 = Multiple Sclerosis Quality of Life-54.

design ensured that we could determine whether the intervention had an early improvement on outcomes meaningful to patients as measured using validated PROs and a novel CCSVI symptom scale. Participants were reassessed over 48 weeks to determine whether any early improvements in symptoms were sustained, and to detect any delayed improvements that may have been masked by periprocedural pain or residual effects of the medications used for conscious sedation. There were no differences between the sham and venoplasty groups on the PROs throughout the 48 weeks. While it is possible that our study was underpowered to detect statistically significant differences, we had surpassed our target enrollment, 99% retention, and our cohort size was larger than the original open-label study.<sup>2</sup> We could not detect any trends in any of the PROs and either clinical or MRI outcomes.

There was no difference compared to the sham intervention or in the number of participants who had objective evidence of new inflammatory activity (MRI CUA lesion and/or confirmed clinical relapses) or improvement in disability (EDSS or MSFC). This would argue against venoplasty having a disease-modifying mechanism of action.

We took great care in standardizing the venography and intervention procedures across the 4 centers. Stratified randomization by disease type at each site reduced the likelihood of obtaining unbalanced study groups. The conscious sedation during venography, and a standardized venography procedure room experience for all participants (i.e., room setup, duration of time in the room, minimal staff present), ensured that all sham and venoplasty participants would have an identical research experience to optimize masking.

Venous narrowing >50% was present in 76% of participants, similar to earlier findings in MS.<sup>6</sup> We included participants with the progressive form of MS, i.e., those with the greatest unmet medical need for treatments that could significantly improve quality of life. Early reports<sup>2</sup> suggested that patients with RRMS were more likely to benefit from venoplasty than patients with progressive MS, but our subgroup analyses did not detect outcome differences between sham and venoplasty for either RRMS or progressive MS patients.

Extracranial venous stenosis continues to be proposed as a pathogenic disorder for a variety of neurologic conditions

**Table 3** Improvements in patient-reported and clinical outcomes from baseline to week 48; disease progression, confirmed relapses, and new MRI disease activity from baseline to week 48

Outcome	Sham (n = 55)	Venoplasty (n = 49)	Venoplasty vs sham, estimate (95% CI)	p Value <sup>a</sup>
<b>MSQOL-54, mean ± SD</b>				
Physical	1.3 ± 11.5	1.4 ± 14.0	MD: 0.17 (−4.88 to 5.22)	0.95
Mental	1.2 ± 15.2	−0.8 ± 18.7	MD: −2.02 (−8.75 to 4.71)	0.55
Fatigue severity score, mean ± SD	0.2 ± 1.65	0.1 ± 1.2	MD: −0.13 (−0.70 to 0.44)	0.65
NARCOMS pain, mean ± SD	0.1 ± 1.7	−0.2 ± 1.0	MD: −0.30 (−0.74 to 0.15)	0.19
MSFC, mean ± SD	0.0 ± 0.7	−0.4 ± 1.5	MD: −0.39 (−0.88 to 0.10)	0.12
EDSS, median ± SD	0.0 ± 0.9	−0.2 ± 0.8	MD: 0.15 (−0.18 to 0.49)	0.36
3-Mo confirmed disability progression, n (%)	3 (5)	1 (2)	OR: 0.36 (0.01 to 4.71)	0.62
Participants with relapses, n (%)	6 (11)	5 (10)	OR: 0.93 (0.21 to 3.94)	1.00
Participants with MRI CUA lesions, n (%)			RR: 0.27 (0.09 to 0.83)	0.32
1 CUA	8 (13)	3 (5)		
2 CUA	4 (9)	2 (4)		
3 CUA	1 (7)	0 (0)		
4 CUA	2 (4)	4 (8)		
5+ CUA	4 (6)	2 (4)		
Not available	3 (5)	2 (4)		

Abbreviations: CI = confidence interval; CUA = combined unique active; EDSS = Expanded Disability Status Scale; MD = mean difference; MSFC = Multiple Sclerosis Functional Composite; MSQOL-54 = Multiple Sclerosis Quality of Life-54; NARCOMS = North American Research Committee on Multiple Sclerosis; OR = odds ratio; RR = relative rate.

<sup>a</sup> Student 2-sample *t* test for scores, Fisher exact test for categorical outcomes.

(including Alzheimer, Parkinson, and Ménière diseases). It is not uncommon for patients to experience improvements in their symptoms with intervention, especially when expectations are high. Sham-controlled confirmatory trials are rarely performed for interventional procedures, but they remain necessary. Uncontrolled case series can erroneously suggest a benefit from novel but ineffective therapies.<sup>32</sup> This large randomized, double-blind, multicenter clinical trial failed to show superiority of venoplasty compared to sham intervention on patient-reported, clinical, and MRI outcomes.

In the face of extraordinary pressure to find a cure for neurodegenerative diseases, this study confirms the importance of well-designed trials to assess the safety and effectiveness of new therapies, including those that may be publicly popular and perhaps less conventional. It is critical to ensure that patients do not undergo procedures that could result in unnecessary costs or morbidity, or lose trust and hope in the vital goals of biomedical research.

### Author contributions

A.L. Traboulsee: literature search, tables, study design, data collection, data interpretation, writing, and final approval of the manuscript. L. Machan, D.K. Li, A.D. Sadovnick, S. Isserow, J. Illes, D. Klass, J.M. Girard, J. Raymond, R. Vosoughi,

B.W. Hardy, G. Siskin, F. Emond, and J.-L. Gariépy: study design, data collection, data interpretation, and final approval of the manuscript. J.N. Bone: statistical analysis, data interpretation, writing, and final approval of the manuscript.

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