Does Venous Balloon Angioplasty Help Patients With CCSVI: Early Results Of A RCT Cast Doubt: When Will We Know?

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Background:

- Multiple sclerosis (MS) is a disease of uncertain etiology characterized by demyelinating lesions affecting the central nervous system.

- In 2009, Zamboni et al. described an association between MS and extracranial venous outflow restrictive lesions detected by extracranial and intracranial venous duplex studies.\(^1\)

- They named this venous outflow restriction chronic cerebrospinal venous insufficiency (CCSVI). In addition, they introduced endovascular treatment for CCSVI in an open-label study that included 65 MS patients with postprocedure follow-up of over 18 months.\(^2\)

- Several subsequent prospective open-label, non-randomized studies investigated safety and efficacy of venous angioplasty in MS. \(^3\)\(^-\)\(^9\) Findings from these studies have generated considerable controversy but remain unproven.

Objective:

- To investigate the safety and efficacy of percutaneous transluminal venous angioplasty (PTVA) for correcting CCSVI in MS in the setting of a prospective, double-blind, sham-controlled, randomized pilot trial.

Methods:

**Study design and patient selection:**

- The study, Prospective Randomized Endovascular Therapy in Multiple Sclerosis (PREMiSe; ClinicalTrials.gov. NCT01450072), was planned in two phases. Phase 1 was an open-label safety study of endovascular venous angioplasty with an intended enrollment of 10 MS patients with CCSVI, whereas phase 2 was sham-controlled, randomized, double-blind, including up to 20 CCSVI-MS patients undergoing either angioplasty or sham procedure. Both phases were of 6 months’ duration.

- The study was approved by the University at Buffalo Institutional Review Board and overseen by an independent data-safety monitoring committee. Written informed consent was obtained from all subjects.

- All screening, diagnostic, interventional, and follow-up procedures and visits were performed at no cost to the patients. Data were collected by the investigators and analyzed by an independent statistician.
Inclusion criteria were as follows: age 18-65 years, Expanded Disability Status Scale (EDSS) score11 of 0-8.5 (0-5.5 for phase 2), active-relapsing MS (only for phase 2) or secondary progressive and/or progressive-relapsing MS,12 and fulfilling, at the time of screening, ≥2 CCSVI venous hemodynamic (VH) duplex criteria in phase 1 and ≥2 VH extracranial criteria in phase 2.13 Active-relapsing disease was defined as one relapse within the past 12 months or presence of contrast-enhancing (CE) lesion(s) on postcontrast magnetic resonance imaging (MRI) within the previous 3 months (only for phase 2) and concomitant treatment with disease-modifying treatments excluding natalizumab (only for phase 2).

Exclusion criteria (either phase) included an acute relapse, disease progression, and/or steroid treatment within 30 days preceding study entry, pre-existing medical conditions known to be associated with brain pathology (e.g., neurodegenerative disorder, cerebrovascular disease, positive history of alcohol abuse), severe peripheral chronic venous insufficiency, severe contrast media allergy (anaphylaxis), and abnormal renal function.

Patients were also required to fulfill screening criteria on catheter venography (CV) defined as azygous vein or internal jugular vein (IJV) luminal diameter reduction ≥50%. CV findings were confirmed by intravascular ultrasound (IVUS), and both studies were performed under conscious sedation with local anesthesia, preceding the endovascular venous angioplasty treatment or sham procedure.

Randomization in phase 2 was performed by an independent statistician in 1:1 fashion, using sealed and numbered envelopes with predetermined treatments (10 angioplasty, 10 sham angioplasty). No preplanned replacement for subjects not fulfilling invasive screening criteria was included in the protocol. In phase 2, all study personnel, with the exception of the interventional neurosurgeons, were blind to the assigned procedure as were the patients.

**Sham and venous angioplasty:**

- All endovascular procedures were performed under conscious sedation with local anesthesia. The goal of angioplasty was to restore venous outflow of the stenotic IJVs and azygous vein to <50% of normal proximal venous diameter at the time of intervention. Angioplasty was performed only in the treated, not in the sham arm.

**Endpoints and follow-up assessment:**

- Primary endpoints of the study were safety at 24 hours and 1 month, venous outflow restoration of >75% at 1 month compared to baseline, as measured by changes in venous hemodynamic insufficiency severity score (VHISS), and effect of angioplasty on new lesion activity and relapse rate over 6 months. Secondary endpoints included changes in EDSS, brain volume, cognitive tests, and quality of life (QoL), including MS Functional Composite (MSFC) scores.
Results:
Screening, randomization, and blinding:
- In total, 15 patients signed informed consent in phase 1 and 30 in phase 2 after prescreening qualification procedures were completed. Of those, 5 in phase 1 and 10 in phase 2 did not fulfill noninvasive screening procedure requirements on duplex examination.

- As preplanned, 10 patients were enrolled in open-label phase 1 and 20 in sham-controlled, randomized, double-blind phase 2. Of those, 1 patient in phase 2 did not fulfill invasive screening criteria for endovascular intervention. Hence, 10 patients in the sham-treatment arm and 9 in the angioplasty-treated arm were randomized to phase 2.

Demographic, hemodynamic, MRI, and clinical characteristics at baseline:
- The sham and angioplasty treatment arms in phase 2 were well matched for various demographic, clinical, and duplex characteristics with no statistically significant between-group differences.

Safety and tolerability of treatment procedures:
- All patients in phases 1 and 2 tolerated the endovascular procedure well, and no operative or postoperative complications (vessel rupture, thrombosis, or side effects to contrast media) were identified. No serious adverse events (AEs) were detected at any time point in phase 1. Half of the patients in phase 1 reported a non-serious AE, but none were related to the treatment procedure.

Venous outflow restoration outcomes:
- Venous angioplasty restored venous outflow to at least 50% of normal proximal venous diameter in all phase 1 and 2 patients at the time of intervention.

- In phase 1, there was significant improvement of VHISS (p<0.0001) over 6-months that resulted in >75% restoration of the venous outflow compared to baseline.

- In phase 2, improvement was observed also in treatment (p=0.02) and sham (p=0.04) arms at month 1 but did not reach >75% restoration of the venous outflow compared to baseline. No differences in VHISS improvement were detected between phase 2 treated and sham groups (p=0.894).

Changes in clinical outcomes:
- No relapses occurred in phase 1. In phase 2, there were 4 relapses in the treated arm (among 3 patients) and 1 in the sham arm (p=0.389). The relapses occurred at 1, 3 (2 relapses), and 6 months in the treated arm and at 5 months in the sham arm.
• In phase 2, no significant within- or between-group changes in EDSS, MSFC, or 6-minute walked distance were detected.

• No significant between-group changes in cognitive and QoL outcomes were detected in phase 2 patients.

Changes in MRI outcomes:
• Two patients in phase 1 had findings indicative of disease activity on an MRI scan. Of nine patients in the phase 2 treated arm, five showed new CE lesions with two accounting for most of the lesion activity, and four of those five patients had new T2 lesions, whereas only two patients in the sham arm showed new lesion activity. There was a trend for higher cumulative number of new CE lesions (p=0.062) and new T2 lesions (p=0.066) in the treated compared to the sham arm over 6 months.

• Using mixed-effects ANOVA models, no significant interactions between month (postprocedure) and group or group effects were found. In separate analyses based on cumulative number of new lesions using ANCOVA, there was significant evidence that higher cumulative number of new T2 lesions was related to both larger decrease in VHISS (p=0.028) and treated arm (p=0.01) over the follow-up. There was significantly higher accumulation of T2 lesion volume (p=0.04) in the treated compared to the sham arm (phase 2) over 6 months. No differences in brain volume changes over 6 months were found.

Conclusions:
• This is the first double-blind, sham-controlled, randomized trial evaluating PTVA to address CCSVI in patients with MS.

• We found that the procedure was not associated with any serious AEs.

• However, it failed to provide any sustained improvement in venous outflow as measured through duplex and/or clinical and MRI outcomes.

• To the contrary, more sizeable change in venous outflow was associated with increased disease activity primarily noted on MRI.

• This study was a limited pilot trial, the results of which caution against widespread adoption of venous angioplasty in the management of patients with MS outside of rigorous clinical trials.

• It also provides validation for conduct of sham-controlled, double-blind trials in the evaluation of novel interventions in complex diseases.
References:


