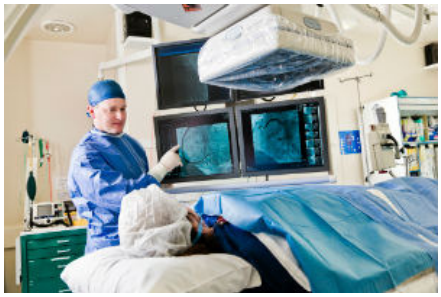
Vein Surgery for MS Fails in First Controlled Trial

This report is part of a 12-month Clinical Context series.

By John Gever, Senior Editor, MedPage Today
Published: March 15, 2013
Reviewed by Robert Jasmer, MD; Associate Clinical Professor of Medicine, University of California, San Francisco

SAN DIEGO -- Outcomes in multiple sclerosis patients were not improved with a controversial surgical procedure -- percutaneous transluminal venous angioplasty -- to improve blood flow in cerebrospinal veins, results of a small, double-blind, controlled trial indicated.



Action Points

Outcomes in multiple sclerosis patients were not improved with a controversial surgical procedure to improve blood flow in cerebrospinal veins.

The findings were especially notable because they represent the first report of a randomized, controlled, double-blind trial of the procedure, percutaneous transluminal venous angioplasty.

Among nine patients who underwent the venoplasty to clear blockages, clinical outcomes and brain lesion measures were generally worse after 6 months than in the 10 patients who received a sham procedure, Adnan Siddiqui, MD, of the State University of New York at Buffalo, and colleagues found.

Patients in the active-treatment group had a total of four clinical MS relapses during follow-up, compared with one relapse in the control group. MRI lesion volumes and numbers also were no better and, for some measures, showed strong trends toward worsened disease activity in the patients undergoing venoplasty.

Data from the study were released in advance of Siddiqui's formal presentation next week at the American Academy of Neurology's annual meeting here.

The findings were especially notable because they represent the first report of a randomized, controlled, double-blind trial of the procedure -- and also because Siddiqui and co-principal investigator Robert Zivadinov, MD, also of the University at Buffalo, have been more accepting than most U.S. neurologists of the theory underlying the venoplasty procedure.

That theory goes under the name of "chronic cerebrospinal venous insufficiency" or CCSVI. It gained worldwide prominence in 2009 when Paolo Zamboni, MD, of the University of Ferrara in Italy, reported that every MS patient he examined showed blocked veins and reduced blood flow out of the brain, whereas none of the healthy controls showed such abnormalities.

Moreover, Zamboni asserted that venoplasty in his MS patients led to dramatic relief of symptoms, amounting to a virtual cure in many of them.

But attempts to replicate the findings of Zamboni's uncontrolled, unblinded study in other settings have often failed, with neurologists elsewhere reporting either that they found CCSVI only rarely in MS patients, and/or that it was no more common in MS patients than in controls.

In the largest CCSVI study to date, conducted in Italy and using blinded central interpretation of the ultrasound scans, only 3% of MS patients and a slightly smaller percentage of controls were found to have the condition. The finding led the Italian Multiple Sclerosis Society to declare CCSVI effectively nonexistent as a cause of MS.

Nevertheless, a small industry centered on the theory has flourished, especially in Latin America, where endovascular surgeons perform venoplasty on MS patients wealthy enough to afford it -- despite official recommendations from neurology groups that such procedures hold many risks and no proven benefits.

Zivadinov, in an interview with *MedPage Today* last year, said that patients should undergo the procedure only in the context of a clinical trial. That was also the message Siddiqui conveyed with the results of their team's current study.

"This is not the last word on this endovascular treatment for MS," Siddiqui said in a press release. "This is the first word because this was the first double-blinded, randomized, sham-controlled trial on the subject. However, these findings lead us to caution strongly against the general acceptance of

this invasive procedure for MS patients."

In the study, called PREMISe (Prospective Randomized Endovascular Therapy in MS), an initial 10 patients underwent the venoplasty procedure as a phase I safety test, with no serious adverse events noted.

For the phase II efficacy trial, Siddiqui and colleagues recruited 20 patients to be randomized to the active procedure or to a sham in which patients were catheterized but no venoplasty was performed. Only the interventional surgeon -- not the investigators who evaluated outcomes -- was aware of treatment assignments.

Patients had received an initial diagnosis of CCSVI on the basis of imaging studies as well as confirmed MS of the active-relapsing, secondary progressive, or progressive-relapsing forms. Patients had EDSS disability scores of no more than 5.5.

After catheterization, all patients in both arms were confirmed by the investigators to have CCSVI using catheter venography to establish luminal diameter reductions of at least 50% in the azygous or internal jugular veins. Venography findings had to be confirmed with intravascular ultrasound.

One patient in the phase II study was found not to meet criteria for CCSVI during this procedure and was excluded, leaving 10 in the sham group and nine in the venoplasty group.

Mean EDSS scores were 3.9 in the phase II patients, with median disease duration of 9 years (range 2 to 31). Mean age at disease onset was 35; at enrollment, mean age was 46.

Besides relapses, Siddiqui and colleagues examined other clinical outcomes including EDSS score, 6-minute walk distances, and Multiple Sclerosis Functional Composite score.

None of these measures changed significantly from baseline in either group, and there were no between-group differences, the researchers indicated.

In addition to the lack of apparent clinical improvement in patients undergoing the procedure relative to controls, there was no sign that the venoplasty improved blood flow.

Both groups showed increases in venous sufficiency from baseline, according to the researchers' hemodynamic measurements, but they were virtually the same (P=0.894)

MRI measures also did not favor the venoplasty group:

- Mean cumulative new T2 lesions: 0.3 sham, 2.2 venoplasty (P=0.07)
- Mean T2 lesion volume change: -4.7% sham, 13.9% venoplasty (P=0.04)
- Mean cumulative T1 lesions: 0.2 sham, 0.8 venoplasty (P=0.14)
- Mean T1 lesion volume change: -14.6% sham, -10.2% venoplasty (P=0.81)
- Mean cumulative contrast-enhancing lesions: 0.3 sham, 2.4 venoplasty (P=0.06)

One serious adverse event was seen during the randomized phase, but Siddiqui and colleagues determined that it was not treatment-related: a cardiac event treated with a pacemaker.

A single case of swelling and soreness in the neck was considered treatment-related. However, it was rated nonserious as it did not require additional treatment, the researchers indicated.

"Our strong recommendation to patients and to practitioners, who have, in earnest, been seeking betterment for their disease and a cure for MS is that they should instead consider enrolling in trials, rather than undergoing these procedures on a fee-for-service basis," Siddiqui said in the press release.

The study was funded by Kaleida Health, the Direct MS Foundation (Canada), Volcano, ev3 , Codman & Shurtleff, the Jacquemin Foundation, and individuals.

Siddiqui reported relationships with Hotspur, Intratech Medical, Stimsox, Valor, Concentric, ev3/Covidien, GuidePoint, Penumbra, Genentech, Abbott, and Neocure. Other study investigators reported relationships with Teva, Biogen Idec, EMD Serono, Bayer, Genzyme-Sanofi, Novartis, Bracco, Questcor, Shire, Novartis, Actelion, Allergan, Nelezza, Pfizer, St. Jude Medical, Toshiba, Boston Scientific, Cordis, Micrus, W.L. Gore, and numerous other drug and device companies.

Primary source: American Academy of Neurology
Source reference:

Siddiqui A, et al "Percutaneous transluminal venous angioplasty (PTVA) is ineffective in correcting chronic cerebrospinal venous insufficiency (CCSVI) and may increase multiple sclerosis (MS) disease activity in the short term: Safety and efficacy results of the 6–month, double–blinded, sham–controlled, prospective, randomized endovascular therapy in MS (PREMiSe) Trial" *AAN* 2013; Abstract P04.273.

Related Article(s):

Radical MS Theory Stirs Interest

Largest CCSVI Study Fails to Support Theory

CCSVI in Multiple Sclerosis, A Clinical Context Report