Research

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Efficacy and Safety of Extracranial Vein Angioplasty in Multiple Sclerosis

A Randomized Clinical Trial

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Abbreviations: NA, not applicable; PTA, percutaneous transluminal angioplasty.

[a] All *P* values were >.99 after adjustment for multiplicity.

[b] Ratio of step length (millimeters) to step frequency (per minute).

stable and similar between the groups at 12 months, matching the composite functional outcome. The annualized relapse rate was also similar between the groups. Safety data indicated no serious adverse events attributable to venous PTA or the sham procedure.

The functional outcome explored by the trial was reduction in disability as assessed by 5 functions (ie, walking control, balance, manual dexterity, postvoid residual urine volume, and visual acuity; eMethods in Supplement 2), which are the most frequent causes of disability in MS. The hypothesis that venous PTA can significantly reduce disability is rejected by findings from this study, which not only found no difference between the groups on the functional composite measure but also no difference for any of its 5 components (Table 3).

The primary MRI outcome measure was a difference in the number of new combined brain lesions. Venous PTA had no effect on this measure (Table 2). However, at 12 months, more than 20% of patients in the PTA group were free of gadolinium-enhancing lesions compared with the sham group (OR, 2.76; 95% CI, 1.14-6.68) (Table 4). To explore this effect, which appears inconsistent with the other MRI data at 0 to 12 months, we performed an exploratory post hoc comparison of MRI findings at 0 to 6 months with those at 6 to 12 months (Table 4; eTable 1 in Supplement 2). We found a reduction in the mean number of new brain lesions (corresponding to more lesion-free patients) in the PTA group compared with the sham group at 6 to 12 months. The delayed and positive effect on the magnetic resonance biomarker suggests that PTA could affect the dynamic of the blood-brain barrier.

Gadolinium enhancement is a marker of damage to the blood-brain barrier, whose time course depends on lymphatic drainage[18] and hence on venous drainage from the skull.[19] Previous studies have reported that venous pressure is lowered[3] and cerebrospinal fluid dynamics is improved[20] after venous PTA, thereby favoring the drainage of cerebrospinal fluid into the dural veins, which depends on a pressure gradient between the subarachnoid spaces and dural veins.[21,22] Another study[23] reported that white matter lesion load was in-

Yes	31 (41)	18 (46)
No	45 (59)	21 (54)

Abbreviations: ECD, color Doppler ultrasonography; EDSS, Expanded Disability Status Scale; IJV, internal jugular vein; MS, multiple sclerosis; PTA, percutaneous transluminal angioplasty.

by a negative binomial model that compared the mean number of MRI lesions in the 2 groups at 1 year. The proportion of patients who were free of new brain lesions on MRI were compared by χ^2 test. Variables that were unbalanced at baseline were adjusted for using a logistic model on the functional end point and a negative binomial model on mean number of MRI lesions.

Relapse rates (secondary end point) in the 2 groups were compared assuming a Poisson distribution of events. Differences in EDSS scores at 1 year were compared by analysis of covariance testing, with adjustment for baseline scores. When analyzing components of the functional and MRI end points (including findings at 0 to 6 and 6 to 12 months), we adjusted for multiplicity using the Hommel method,[17] since it is reasonable to assume that variables involved could be directly related (reported as adjusted *P* value). All tests were 2-tailed, with the significance level set at $P < .05$. Analyses were performed with SAS version 9.3 (SAS Institute) and R version 3.2 (R Foundation for Statistical Computing).

Results

The Figure shows the study flowchart for patients with RRMS. A total of 177 were assessed for eligibility, and 62 were ineligible, including 47 (26.6%) who did not have CCSVI on ECD screening. One hundred fifteen patients were eligible and randomly assigned to the PTA group (n = 76) or the sham group (n = 39), which included catheter venography without venous angioplasty, between August 7, 2012, and December 15, 2014. The 2 groups were similar for baseline characteristics except that patients in the sham group had more women and longer disease duration (Table 1). No serious adverse events attributable to catheter venography or venous PTA occurred, but 2 adverse events (1.7%) did occur: 1 vagal reaction and 1 episode of transient neck pain. A total of 112 of 115 patients (97.4%) completed the 12-month follow-up, with similar proportions completing in the 2 groups. eFigure 1 in Supplement 2 shows the study flowchart for patients with secondary progressive MS.

Primary End Points

Functional end point results were available for 109 patients with RRMS (Table 2). A total of 30 of 73 patients (41%) in the PTA group and 18 of 37 (49%) in the sham group improved on

than anticipated, and patients with active disease may have been underrepresented in the study (Table 1). Finally, the fact that venous PTA was largely ineffective in restoring blood flow in nearly half the patients in the PTA group suggests that it was inadequate for exploring our initial hypothesis.

Conclusions

A number of neurologists and scientists expressed the opinion that the decision to conduct a trial on CCSVI in the absence of valid scientific evidence was unethical and a waste of resources.[28] However, we believe that the best way to provide useful information to patients (and regulatory authorities) on the benefit and safety of venous PTA was to conduct a randomized trial—as also recommended by NICE[7]—that assessed outcomes directly relevant to patients.[29] Venous PTA has proven to be a safe but ineffective technique in treating CCSVI in about half of patients. The procedure cannot be recommended for treatment of patients with MS; no further double-blinded clinical studies are needed. The delayed effect of venous PTA 6 months after the procedure on the magnetic resonance biomarker suggests a possibility that PTA may produce benefit for a subgroup of patients with MS. This should be further analyzed and investigated.

ARTICLE INFORMATION

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