

Safety of Endovascular Treatment of Chronic Cerebrospinal Venous Insufficiency: A Report of 240 Patients with Multiple Sclerosis

Kenneth D. Mandato, MD, Paul F. Hegener, MD, Gary P. Siskin, MD, Ziv J Haskal, MD, Meridith J. Englander, MD, Sreenivas Garla, MD, Nancy Mitchell, NP, Laura Reutzell, NP, and Christopher Doti, NP

ABSTRACT

Purpose: To evaluate the safety of outpatient endovascular treatment in patients with multiple sclerosis (MS) and chronic cerebrospinal venous insufficiency (CCSVI).

Materials and Methods: A retrospective analysis was performed to assess complications occurring within 30 days of endovascular treatment of CCSVI. The study population comprised 240 patients; 257 procedures were performed over 8 months. The indication for treatment in all patients was symptomatic MS. Of the procedures, 49.0% (126 of 257) were performed in a hospital, and 51.0% (131 of 257) were performed in the office. Primary procedures accounted for 93.0% (239 of 257) of procedures, and repeat interventions accounted for 7% (18 of 257). For patients treated primarily, 87% (208 of 239) had angioplasty, and 11% (26 of 239) had stent placement; 5 patients were not treated. Of patients with restenosis, 50% (9 of 18) had angioplasty, and 50% (9 of 18) had stent placement.

Results: After the procedure, all but three patients were discharged within 3 hours. Headache after the procedure was reported in 8.2% (21 of 257) of patients; headache persisted > 30 days in 1 patient. Neck pain was reported in 15.6% (40 of 257); 52.5% (21 of 40) of these patients underwent stent placement. Three patients experienced venous thrombosis requiring retreatment within 30 days. Sustained intraprocedural arrhythmias were observed in three patients, and two required hospital admission. One of these patients, who was being retreated for stent thrombosis, was hospitalized because of a stress-induced cardiomyopathy.

Conclusions: Endovascular treatment of CCSVI is a safe procedure; there is a 1.6% risk of major complications. Cardiac monitoring is essential to detect intraprocedural arrhythmias. Ultrasonography after the procedure is recommended to confirm venous patency and to identify patients experiencing acute venous thrombosis.

ABBREVIATIONS

CCSVI = chronic cerebrospinal venous insufficiency, MS = multiple sclerosis

Multiple sclerosis (MS) is a chronic inflammatory disease characterized by demyelination of the central nervous system. This potentially debilitating disease affects millions of people

worldwide and is the most frequent nontraumatic disabling neurologic disease in young adults (1). It has been estimated that 12,000 new cases of MS are diagnosed annually in the United States (2). The etiology of MS is uncertain, but it is thought to be immune-mediated at the present time.

Chronic cerebrospinal venous insufficiency (CCSVI) is a recently described condition that is believed to correlate symptoms and possibly the pathogenesis of MS with extracranial venous outflow obstruction (3,4). Early reports by Zamboni et al (5) described high rates of clinical improvement in patients with MS after angioplasty of stenotic internal jugular and azygos veins. The purpose of the present study was to assess specifically the safety and adverse event rates of catheter-directed interventions in a large cohort of patients with MS and CCSVI.

From the Department of Radiology (K.D.M., P.F.H., G.P.S., M.J.E., S.G., N.M., L.R., C.D.), Albany Medical Center, MC-113, 47 New Scotland Avenue, Albany, NY 12208; University of Maryland (Z.J.H.), Baltimore, Maryland. Received January 27, 2011; final revision received September 19, 2011; accepted September 20, 2011. Address correspondence to G.P.S.; E-mail: sisking@mail.amc.edu

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MATERIALS AND METHODS

A retrospective study was performed to evaluate the safety of outpatient angioplasty to treat CCSVI in patients with MS. The study received institutional review board approval. All procedures were performed at one of two sites. The first site (site 1) is a 651-bed, tertiary-care university medical center, and the second site (site 2) is an outpatient interventional radiology office located in a multispecialty health setting. The study included all consecutive patients treated between February and October 2010. All treated patients had neurologist-confirmed diagnoses of MS and related symptoms. The indication for venography and subsequent endovascular treatment was the presence of symptomatic MS.

Three physicians performed the procedures in an identical manner at both sites. All patients received intravenous hydration before, during, and after the procedure. Continuous cardiac monitoring and oxygen sensitometry was employed in all patients. Patients received either oral sedation with diazepam (Valium; Roche Pharmaceuticals, Nutley, New Jersey) or intravenous conscious sedation with midazolam hydrochloride (Versed; APP Pharmaceuticals LLC, Schaumburg, Illinois) and fentanyl citrate (Sublimaze; Taylor Pharmaceuticals, Buffalo Grove, Illinois).

Unilateral common femoral venous access was obtained in all patients using micropuncture technique under ultrasound guidance. An 8-F introducer sheath (Terumo Medical Corporation, Elkton, Maryland) was used in all patients. To catheterize the internal jugular veins and azygos veins, 5-F Glidecatheters (Terumo Medical Corporation) with a Headhunter or Berenstein configuration were used. A technically successful procedure was defined as the ability to catheterize selectively and image the right internal jugular vein, left internal jugular vein, and azygos vein. After the internal jugular veins were selectively catheterized, venography was performed in a minimum of three projections (anteroposterior, lateral, and ipsilateral anterior oblique). Two projections (left anterior oblique and lateral) were used to visualize the azygos vein.

Angioplasty was performed when a significant stenosis or flow abnormality was identified. Although a luminal diameter reduction of 50% was frequently used as a threshold for angioplasty, lesser degrees of stenosis were treated when seen in conjunction with a flow abnormality including reflux (defined as retrograde flow of contrast material during venography) or stasis (defined as prolonged opacification of the vein being evaluated after injection of contrast material). Lesser degrees of stenosis were treated when seen in conjunction with difficulty passing a guide wire through the valve in the proximal internal jugular or azygos veins because such difficulty might be attributed to a valvular abnormality or an intraluminal web or membrane, both of which have been described in association with this condition (4,5).

Balloon selection was based on the location and maximum visualized diameter of the vein being treated. Gen-

erally, balloons capable of high-pressure inflation (Dorado PTA Dilatation Catheter, Atlas PTA Balloon Dilatation Catheter; Bard Peripheral Vascular, Tempe, Arizona) were used to treat stenoses in the proximal portions and midportions of the internal jugular veins, and low-pressure balloons (Fox Cross PTA Catheter; Abbott, Santa Clara, California) were used to treat stenoses in the azygos vein and distal portion of the internal jugular vein. Stent placement was performed when a venous occlusion or a venous dissection with a reduction in blood flow was seen after angioplasty or when an inadequate response to angioplasty was seen. Manual pressure was applied for a minimum of 10 minutes in all patients after sheath removal.

After the procedure, all patients were observed and monitored in the recovery room of each site for approximately 2 hours. Patients were kept supine for 1 hour with gradual head elevation over the course of the second hour. Vital signs with direct observation of the femoral venous access site were performed at 15-minute intervals during the recovery period. After 2 hours, patients able to ambulate did so under direct observation. All patients were eligible for discharge after 2 hours if they were clinically stable and without distress. Patients were discharged to home if they lived locally or to a hotel if they had traveled > 1 hour for this procedure. Patients treated with angioplasty were discharged with the recommendation that they take aspirin 325 mg daily for 6 months and to decrease that dose to 81 mg daily after that time. Patients treated with stent placement were discharged with the recommendation that they take clopidogrel (Plavix; Bristol Meyers Squibb, New York, New York) 75 mg daily for 6 months and to change that to aspirin 81 mg daily after that time. Follow-up ultrasonography was performed in most patients within 24 hours of the procedure to assess patency of the internal jugular veins after intervention. All patients either were seen in our office or were contacted by phone or e-mail within 30 days of the procedure.

RESULTS

Over the course of the 8-month study period, 257 procedures were performed in 240 patients. The characteristics of the study population are summarized in **Table 1**. Serum creatinine levels before the procedure were > 1.5 mg/dL in two patients. Repeat creatinine levels performed 30 days after the procedure in these two patients showed unchanged renal function.

The procedures were divided almost equally between the in-hospital and outpatient settings, with 126 (49%) performed at site 1 and 131 (51%) performed at site 2. The technical success rate of the procedure in the study population was 99.2% (255 of 257); the azygos vein was unable to be catheterized in one patient, and the right internal jugular vein was unable to be catheterized in another patient who had a history of prior tunneled catheter placements in that vein. Primary procedures, defined as the first catheter-

Table 1. Patient Characteristics

Total No. Patients	240
Total No. Procedures	257
Mean Patient Age	49.1 y (range 25.7–70.2 y)
Female	64.6% (155/240)
Male	35.4% (85/240)
Relapsing remitting MS	62% (149/240)
Secondary progressive MS	28% (67/240)
Primary progressive MS	8% (19/240)
Unknown	2% (5/240)

MS = multiple sclerosis.

based therapy for CCSVI, were performed in 93% of cases (239 of 257). Secondary (reintervention) procedures were performed after a failed primary or secondary intervention within our practice (17 of 18) or elsewhere (1 of 18). Of the 239 patients who underwent primary treatment, 208 (87%) were treated with angioplasty only, and 26 (11%) were treated with adjunctive stent placement of at least one vessel owing to immediate recoil, thrombosis, or flow-limiting dissection despite repeat angioplasty; there was no significant difference in the incidence of immediate recoil, thrombosis, or flow-limiting dissection after angioplasty when comparing the two sites of treatment ($P = .6803$). Five patients (2%) underwent diagnostic venography alone. Nine patients (50%) undergoing reintervention had angioplasty of at least one vessel, and nine (50%) received at least one stent. The balloon sizes included lower internal jugular veins (10–18 mm), mid–internal jugular vein (8–14 mm), upper internal jugular vein (6–10 mm), and azygos vein (8–12 mm). Two patients underwent inadvertent catheterization of the common femoral artery; percutaneous closure devices were used without further sequelae. Of patients, 98.8% (254 of 257 procedures) were discharged within 3 hours of vascular sheath removal.

Adverse Events

Puncture site bleeding during the observed recovery period occurred after 0.8% (2 of 257) of procedures (**Table 2**); one of these patients developed a small asymptomatic hematoma that resolved spontaneously. There was no rebleeding after discharge. Minor allergic reactions (hives) to iodinated contrast occurred in 2.7% (7 of 257) of cases; these were treated with intravenous diphenhydramine (Baxter Healthcare Corporation, Deerfield, Illinois).

During the 30 days after the procedure, a transient headache was reported by 8.2% of patients (21 of 257 cases). One patient (0.4%), after a secondary placement of an internal jugular vein stent, reported a persistent headache lasting > 30 days. A neurologist was unable to find an explanation beyond the placement of this stent to explain the patient's headache. This patient was treated with pain medication, and the headache resolved over 3 months. One other patient (0.4%) reported unilateral orbital pain, which

Table 2. Adverse Events after Endovascular Intervention for Chronic Cerebrospinal Venous Insufficiency

Adverse Event	Incidence
Minor Complications	
Contrast reaction (eg, hives)	2.7% (7/257)
Transient headache (< 30 days)	8.2% (21/257)
Persistent headache (> 30 days)	0.4% (1/257)
Transient neck pain (< 30 days)	15.2% (39/257)
Orbital pain	0.4% (1/257)
Puncture site bleeding or hematoma	0.8% (2/257)
Postangioplasty thrombosis or dissection	10.1% (26/257)
Cardiac arrhythmias	1.2% (3/257)
Major Complications	
Postprocedural venous thrombosis (< 30 days)	1.2% (3/257)
Stress-induced cardiomyopathy	0.4% (1/257)

lasted > 30 days but resolved within 60 days. Neck discomfort or pain was reported after 15.6% (40 of 257) of procedures. These patients all were treated with oral pain medication as needed. Of these 40 patients, 52.5% (21 of 40) had undergone internal jugular vein stent placement (vs angioplasty alone); transient neck discomfort or pain occurred more often in patients treated with stent placement than with angioplasty alone ($P < .0001$). There was no significant difference in the incidence of transient headaches or neck pain when comparing a hospital or office-based site of treatment ($P = .3055$).

Three patients (1.2%) were found to have thrombosis of the internal jugular vein within 30 days of the procedure. In two cases, thrombosis was identified on the ultrasound scan obtained 24 hours after the procedure (one after angioplasty and one after stent placement). The patient with acute thrombosis after angioplasty was treated the next day with stent placement. The patient experiencing acute stent thrombosis was treated with additional angioplasty. The third patient presented 1 week after stent placement with the abrupt onset of recurrent MS symptoms. That stent was not restored to patency because of a sustained cardiac arrhythmia.

Sustained cardiac arrhythmias were observed in 1.2% (3 of 257) of cases—two during primary intervention and another during an attempted thrombectomy of a subacute stent thrombosis. The tachyarrhythmias experienced by the two patients with primary intervention resolved; one patient with a supraventricular tachycardia that progressed to atrial fibrillation was discharged after a 23-hour observation period. In these two patients, > 90 days have passed since the procedures, and neither patient has experienced any additional arrhythmias in that time. The third patient developed acute tachycardia during stent recanalization in which both jugular access and femoral access were required. After the procedure, the patient experienced severely depressed left ventricular systolic function with segmental wall motion

abnormalities and an estimated ejection fraction < 25%. She was subsequently intubated and required norepinephrine bitartrate (Levophed, Hospira, Inc., Lake Forest, Illinois) for intravenous blood pressure support. These changes were attributed to a stress-induced (takotsubo) cardiomyopathy (6). Coronary angiography showed no limiting stenoses. There was no evidence of myocardial infarction. The patient was discharged after 4 days in the hospital, at which time her estimated ejection fraction was > 55% with normal left ventricular systolic and diastolic function. No segmental wall motion abnormalities were seen at that time. No significant sequelae from this complication occurred within the subsequent 90 days.

Using the Society of Interventional Radiology (SIR) Classification System for Complications (7), major complications included venous thrombosis requiring additional treatment (n = 3) and significant cardiac arrhythmia requiring therapy (n = 1). The rate of major complications was 1.6% (4 of 257 cases) within 30 days of outpatient endovascular treatment of CCSVI.

DISCUSSION

The work of Zamboni et al (5) regarding the evaluation and treatment of CCSVI has generated a great deal of interest among patients with MS and the physicians who treat them. Their report of 65 treated outpatients suggested that endovascular treatment of stenoses of the internal jugular and azygos veins may lead to sustained clinical improvement in patients with MS, in particular, patients with relapsing-remitting forms. The reported complications, including puncture site hematomas and transient headaches, all resolved spontaneously. Ludyga et al (8) reported their experience with 331 MS patients with CCSVI undergoing 344 interventions (angioplasty in 192 cases and stent placement in at least one vein in 152 cases). Complications in this series included early stent thrombosis (1.2%), difficulty with removal of the angioplasty balloon or delivery system (1.5%) with one patient requiring a surgical cutdown to remove an angioplasty balloon, transient atrial fibrillation (0.6%), and local bleeding from the groin (1.2%) with two patients having a pseudoaneurysm requiring a thrombin injection for treatment. One patient in this series experienced gastrointestinal bleeding that was attributed to administration of clopidogrel after the procedure. These reports support the safety of venous angioplasty to treat CCSVI.

CCSVI and the procedure described by Zamboni et al (5) for treatment of this condition are controversial because results from multicenter prospective controlled trials have not yet been published. The SIR recently issued a position statement supporting the conduct of high-quality research in this area and convened an interdisciplinary research consensus panel on this topic (9). As a part of any clinical research, larger scale validation of the safety of this procedure at multiple centers is needed. Although prior studies

have shown the safety of outpatient angioplasty and stent placement (10–16), research confirming the safety of this procedure would also serve to define the setting (ie, outpatient vs inpatient, freestanding center vs hospital) where treatment might be best performed.

The present study shows that in the hands of experienced operators, CCSVI interventions can be performed with low complication rates in an outpatient setting. Although some of the complications seen after this procedure are possible after any vascular intervention (eg, risk of contrast allergy, puncture site hematoma), the most common unique adverse events in this series were neck pain (15.6%) and headache (8.2%), both of which resolved spontaneously within 30 days in all but one patient.

Cardiac arrhythmia and venous thrombosis appear to represent the most significant complications seen in this series of patients. Venous thrombosis after endovascular intervention in the venous system has been described by Kolbel et al (17) and Neglen et al (18) in association with the treatment of lower extremity deep venous thrombosis, by Rizvi et al (19) in association with the treatment of superior vena cava syndrome, and by Bakken et al (20) in association with hemodialysis-related venous outflow stenoses. Both angioplasty and stent placement place a low-flow vein at risk for subsequent intimal irregularity, increasing the possibility of restenosis and thrombosis. In this series, three patients were found to have immediate thrombosis detected on an ultrasound scan performed 24 hours after the procedure; this shows the importance of imaging evaluation after the procedure to facilitate retreatment as rapidly as possible. In addition, anticoagulation after the procedure is important for prevention of this potential complication.

The occurrence of cardiac arrhythmias in association with venous catheterization has been described with both venous access device placement (21,22) and pulmonary arteriography (23). Because this procedure involves passage of catheters and guide wires from the inferior vena cava into the superior vena cava, patients must be carefully monitored so that early recognition and prompt treatment are possible. In the two patients experiencing supraventricular tachycardia, the arrhythmia started during balloon angioplasty of the azygos vein. As described, one patient in this series experienced a stress-induced cardiomyopathy, which was life-threatening; this is a rarely described event that would most likely be a rare complication seen in association with this procedure. However, undergoing a new treatment for a debilitating disease such as MS can induce stress even in the strongest of patients, which means that any condition induced by stress is possible in this patient population. In this particular case, the procedure in question was the third procedure for a patient who had experienced significant clinical benefit after angioplasty and was now facing treatment of a thrombosed stent. The stress of this situation, which worsened as the procedure became more complex, likely precipitated this event. The interventional team must be prepared for this type of ad-

verse reaction when considering the performance of this procedure in both the hospital and the outpatient setting. Given the fact that the most severe complications occurred in the context of complex repeat interventions, consideration should be given to performing this subset of procedures in a hospital setting.

In conclusion, the correlation between MS and CCSVI is a new theory that may represent a contributing factor to some of the symptoms experienced by patients with MS. Future research must be performed to show the effectiveness of endovascular treatment in these patients and to validate the results of Zamboni et al (5). This study was not designed to assess clinical outcomes after endovascular treatment of CCSVI. Instead, it was designed as a focused evaluation of the intraprocedural and short-term risks associated with this procedure because information regarding safety is important for future trial design as research moves forward in this area. This study has shown that outpatient angioplasty is a safe procedure with a low risk of significant complications when performed to treat CCSVI in patients with symptomatic MS.

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