Meta-Analysis of CSF Diversion Procedures and Dural Venous Sinus Stenting in the Setting of Medically Refractory Idiopathic Intracranial Hypertension

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ABSTRACT

BACKGROUND AND PURPOSE: In medically refractory idiopathic intracranial hypertension, optic nerve sheath fenestration or CSF shunting is considered the next line of management. Venous sinus stenosis has been increasingly recognized as a treatable cause of elevated intracranial pressure in a subset of patients. In this article, we present the results of the largest meta-analysis of optic nerve sheath fenestration, CSF shunting, and dural venous sinus stenting. This is the only article that compares these procedures, to our knowledge.

MATERIALS AND METHODS: We performed a PubMed search of all peer-reviewed articles from 1988 to 2014 for patients who underwent a procedure for medically refractory idiopathic intracranial hypertension.

RESULTS: Optic nerve sheath fenestration analysis included 712 patients. Postprocedure, there was improvement of vision in 59%, headache in 44%, and papilledema in 80%; 14.8% of patients required a repeat procedure with major and minor complication rates of 1.5% and 16.4%, respectively. The CSF diversion procedure analysis included 435 patients. Postprocedure, there was improvement of vision in 54%, headache in 80%, and papilledema in 70%; 43% of patients required at least 1 additional surgery. The major and minor complication rates were 7.6% and 32.9%, respectively. The dural venous sinus stenting analysis included 136 patients. After intervention, there was improvement of vision in 78%, headache in 83%, and papilledema in 97% of patients. The major and minor complication rates were 2.9% and 4.4%, respectively. Fourteen additional procedures were performed with a repeat procedure rate of 10.3%. Three patients had contralateral stent placement, while 8 had ipsilateral stent placement within or adjacent to the original stent. Only 3 patients required conversion to CSF diversion or 2.2% of patients with stents.

CONCLUSIONS: Patients with medically refractory idiopathic intracranial hypertension have traditionally undergone a CSF diversion procedure as the first intervention. This paradigm may need to be re-examined, given the high technical and clinical success and low complication rates with dural venous sinus stenting.

ABBREVIATIONS: BMI = body mass index; IIH = idiopathic intracranial hypertension; ONSF = optic nerve sheath fenestration

Idiopathic intracranial hypertension (IIH), previously referred to as pseudotumor cerebri and benign intracranial hypertension, is a syndrome defined by elevated intracranial hypertension without radiographic evidence of a mass lesion in the brain. The overall prevalence of IIH in North America has been estimated to be 0.9–1.07/100,000; however, in women with obesity between 20 and 44 years of age, the prevalence rises to 15–19/100,000.

Although headache is the most common presenting symptom, seen in 92%–94% of patients, IIH also represents a significant cause of chronic headaches. In some patients, there may be vision changes, which, if not corrected, may progress to permanent visual loss.

The standard medical treatment includes weight loss, acetazolamide, diuretics, and repeat high-volume lumbar punctures. In patients with medically refractory IIH or progressive visual loss, a CSF-diversion procedure (lumboperitoneal shunt, ventriculoperitoneal shunts, or optic nerve sheath fenestration) is considered the next line of management.

CSF diversion procedures in the setting of medically refractory IIH have been described in the literature dating back to 1955, by
Jackson and Snodgrass. These studies are level 3 evidence, comprising case series and individual case reports. There are no prospective randomized controlled studies on lumbo-peritoneal shunt, ventriculoperitoneal shunts, or optic nerve sheath fenestration, to our knowledge.

Venous sinus stenosis has been increasingly recognized as a treatable cause of elevated intracranial pressure. Venous sinus stent placement was first described by Higgins et al. During the past 20 years, an increasing number of case reports and larger case series have described dural venous sinus stent placement, and reported high rates of technical success and favorable clinical outcomes.

In this article, we present the results of the largest meta-analysis of optic nerve sheath fenestration, CSF diversion procedure, and venous sinus stent placement for medically refractory IIH from 1988 to present. We then compare these interventions with a focus on symptom improvement, complications, and the need for repeat procedures.

MATERIALS AND METHODS

Search Criteria
We performed a PubMed search of all peer-reviewed articles from 1988 to date with a combination of key words including “Idiopathic Intracranial Hypertension,” “Pseudotumor Cerebri” and “Benign Intracranial Hypertension” and “Lumbo-peritoneal Shunts,” “Ventriculoperitoneal Shunts,” and “Optic Nerve Sheath Decompression” and “Intracranial Venous Shunts.” References from the articles that were identified in the initial search were also reviewed for extraction of additional studies.

Eligibility Criteria
Studies reporting patients with IIH and other secondary causes of increased intracranial pressure were separated into 2 groups, and only the patients with IIH who had undergone a procedure were included.

Because these studies were conducted with different aims and protocols, some data on visual acuity, visual fields, CSF pressure, and mean body mass index (BMI) were not available. We attempted to standardize the data as much as possible. The means, ranges, and percentages were calculated for the combined subset of patients with data available for each parameter or outcome. Patients without adequate data were excluded from the analysis to avoid bias and to produce reliable results. Symptom-resolution analysis was performed for only those patients with reported data. Symptom resolution and improvement are presented as improvement in visual acuity, visual fields, CSF opening pressure, and mean body mass index (BMI) were not available. We attempted to standardize the data as much as possible. The means, ranges, and percentages were calculated for the combined subset of patients with data available for each parameter or outcome. Patients without adequate data were excluded from the analysis to avoid bias and to produce reliable results. Symptom-resolution analysis was performed for only those patients with reported data. Symptom resolution and improvement are presented as improvement in visual acuity, visual fields, CSF opening pressure, and mean body mass index (BMI) were not available. We attempted to standardize the data as much as possible. The means, ranges, and percentages were calculated for the combined subset of patients with data available for each parameter or outcome. Patients without adequate data were excluded from the analysis to avoid bias and to produce reliable results. Symptom-resolution analysis was performed for only those patients with reported data.

Exclusion
All studies written before 1988; series with <9 patients for venous sinus stent placement, <6 for ONSF, and <7 for CSF flow diversion; non-English articles; and reports with inadequate information regarding patient selection and follow-up were excluded.

Data Extraction
Effort was made to standardize the data for ease of comparison among treatment modalities with a focus on the following end points:

- Presenting symptoms and patient characteristics (BMI and CSF opening pressure).
- Resolution of symptoms (including headache and visual loss).
- Resolution of papilledema.
- Revision rates of the CSF flow-diversion procedures.
- Complication rates.
- Technical success.

In the analysis of CSF-diversion procedures, patients needing revisions were considered as having complications because they needed repeat procedures, though indications were variable.

RESULTS

Optic Nerve Sheath Fenestration
ONSF (On-line Table 2) is usually the intervention of choice for patients with medically refractory IIH presenting with severe visual loss but minimal headache. The procedure has been shown to rapidly improve visual function (both visual acuity and visual fields) and stabilize the visual changes, thus preventing progression.

Our PubMed search identified 18 clinical studies with patients undergoing ONSF, including 712 patients and 1153 eyes. The mean age at presentation was 32.4 years (range, 4.4–74 years), and the mean follow-up period was 21 months (range, 0–160 months).

Sixty percent of patients presented with headaches, 92% presented with visual acuity changes, and 86% presented with visual field change. Females represented 82% (391/476 patients). Unilateral surgeries (53%, 252/476 patients) were slightly more common than bilateral surgeries. Eighty-nine percent of patients (389/439) had ONSF as their first surgical procedure for medically refractory IIH.

After optic nerve sheath fenestration, visual acuity improved in 59% (152/257 eyes) and improved or remained stable in 95% (1011/1066 eyes). Visual fields improved in 68% (470/688 eyes). Headache improved in 44% (56/127 patients), and papilledema improved in 80% (76/95 patients).

In the total 712 patients who underwent ONSF, there were 128 documented complications. Complications included diplopia (35%; 43%), pupillary complications (32; 25%), late failure (13; 10%), and dellen (shallow excavations along the outer edge of the cornea caused by localized dehydration) (8; 6%).

The total average complication rate (including major and minor complications) was 18% (128/712). We defined major complications as esotropia, exotropia, retrobulbar hemorrhage, orbital hematoma, orbital apex syndrome, orbital cellulitis, and traumatic optic neuropathy. The rate of major complications was 1.5% based on the total number of patients in the study group, 712. We defined minor complications as diplopia, late failure, dellen, synchiae, atonic pupil, tonic pupil, anisocoria, pupillary dysfunction, periligmal conjunctival bleb, peripapillary hemorrhages, disc hemorrhage, cyst formation, and conjunctival abscess. The rate of minor complications was 16.4%.
On the basis of the total number of procedures performed, 14.86% required a repeat procedure: 9.21%, repeat ONSF and 5.65%, CSF diversion. In the series of Spoor et al.,26 31.4% (11 of 35) of patients with acute presentation required a second procedure (but a total of 16 procedures if both eyes were included in some patients).

Because all the data were not available for all the cases, denominators used in the calculation for percentages differed.

Unfortunately, BMI was only available for 1 study included in the analysis, Gupta et al.,35 with an average BMI of 24.4. Opening pressures were only available in 2 studies (Thuente et al.,33 and Gupta et al.,36), with 30 patients and a mean opening pressure of 29.28 cm H2O (range, 13–70 cm H2O).

**CSF Flow Diversion**

Seventeen studies with a CSF-diversion (On-line Table 3)8,40-46,48,55-60 procedure meeting the inclusion criteria were analyzed, including 435 patients; 85% (310/363) were females. Sex was not reported in 3 studies (Abubaker et al.,46 Tulipan et al.,43 and Rosenberg et al.,41). The mean age was 31.9 years (range, 6 months to 68 years).

The mean follow-up time was 41 months (range, 1–278 months). Eighty-six percent (164/190) of patients had CSF diversion as their first surgery. The mean CSF opening pressure, reported in 120 cases, was 41.4 mm Hg (range, 29–60 mm Hg). After the procedure, headache improved in 80% (231/287) of cases. Papilledema improved in 70% (107/153) of cases. Visual acuity improved after treatment in 54% (104/193).

Forty-three percent of patients required at least 1 additional surgery. Most surprising, 154 of 435 patients undergoing CSF flow diversion underwent an additional 428 procedures (not reported in 2 studies: Thambisetty et al.,47 and Tarnaris et al.,48) or 2.78 additional procedures for each failure. These additional procedures were mainly revisions of the shunt. The most common reason for the shunt revision was shunt obstruction (41%), followed by low-pressure headache (15%), shunt failure (11%), radicular pain (3%), and others (25%), which included abdominal pain, tonsillar herniation, valve dysfunction, shunt disconnection, shunt malposition, subdural hematoma, and CSF fistula.

The rate of major complications was 7.6% (33/435). We defined major complications as shunt infection, tonsillar herniation, subdural hematoma, and CSF fistula.

The rate of minor complications was 32.9% (143/435). We defined minor complications as abdominal pain, valve dysfunction, radicular pain, shunt disconnection, shunt malposition, low pressure headache and/or CSF leak, and catheter migration. In Rosenberg et al.,41 operative complications (2/37 patients) were not clearly defined.

**Venous Stent Placement**

Our meta-analysis of dural venous sinus stent placement (On-line Table 4)17,16-21 included 8 studies with 136 patients. Eighty-eight percent were female (119/136 cases). The mean age was 34.5 years (range, 10–64 years), and the mean follow-up time was 22.9 months (range, 1–136 months). The mean BMI was 34 kg/m2 (range, 22–73 kg/m2). The mean CSF pressure was 34.3 mm Hg (range, 22–73 mm Hg). Seventy-three percent (88/121 cases) of patients who were medically refractory underwent venous stent placement as the first intervention.

Nearly all of the stents used were self-expanding nitinol stents; however, C.5% of studies described placement of balloon-mounted stents. Stents included the following: Bridge X3 stent (Medtronic, Santa Rosa, California),34 S.M.A.R.T. stent (Cordis, Fremont, California),36 Complete SE stent (Medtronic),19 Zilver biliary stent (Cook Medical, Bloomington, Indiana),5,20,21 (Worthington Biochemical, Lakewood, New Jersey), Precise self-expanding stent (Cordis),25 or Acculink stent (Guidant, St. Paul, Minnesota).21

After the intervention, headache improved in 83% (101/121 cases) and papilledema improved in 97% of patients (104/108 cases). Visual acuity changes improved in 78% (40/51 cases) after treatment. The mean poststen pressure gradient was 20.6 mm Hg (range, 4–50 mm Hg), and the mean poststent pressure gradient was 2.7 mm Hg (range, 0–23 mm Hg). Sixty-seven percent (n = 83) of stents were placed in the right transverse sinus, 29% (n = 36) of stents were placed in the left transverse sinus, and 4% were not specified. Stent location was not reported in 16 cases (Higgins et al17 and Ahmed et al19).

Of the 136 patients who underwent stent placement, 7.4% (10/136 cases) had complications, though no fatalities were reported. The major complication rate was 2.9% (4/136) and was defined as a subdural hematoma. The minor complication rate was 4.4% (6/136) and was defined as transient hearing loss, femoral pseudoaneurysm, retroperitoneal hematoma, urinary tract infection, and syncope.

Fourteen additional procedures were performed; therefore, the rate of repeat procedures was 10.3% (14/136). Additional procedures were performed in 8% of patients. Contralateral stent placement was performed in 3 patients, and additional ipsilateral stent placement at or near the original stent for restenosis, in 8 patients. Conversion to CSF diversion was seen in only 3 patients or 2.2% of total patients initially receiving stents.

Here again, similar to the ONSF studies, because all data were not available for all the cases, denominators used in calculation for percentages differed.

**DISCUSSION**

Idiopathic intracranial hypertension has been described dating back to 1893, by Quinke, who proposed the term “meningitis serosa.”49,50 The presenting symptoms included headache, blurred vision, and vomiting. The clinical syndrome was later described as “pseudotumor cerebri” by Nonne in 190449 and then “benign intracranial hypertension” by Foley in 1955.10,49,50 The inclusion of “benign” in the description was challenged in 1969 by Buchheit et al.,49,51 who recognized that papilledema was present in almost 95% of the patients, which, if untreated, could progress to optic atrophy and irreversible blindness. The term “idiopathic intracranial hypertension” was introduced in 201150 and may be increasingly used because the etiology and pathophysiology are poorly understood.

Idiopathic intracranial hypertension is currently defined by the Modified Dandy Criteria1,9 and includes an elevation of intracranial pressure with a normal composition of CSF and no intra-
cranial mass or venous sinus thrombosis. By using the Modified Dandy’s Criteria, patients with a heterogeneous group may potentially be combined, confounding management and outcomes.

The underlying pathophysiology of elevated intracranial pressure can be divided into 2 groups, CSF overproduction and decreased CSF absorption. Some early hypotheses for IH included serious meningitis resulting in decreased CSF outflow (Quinke), increased CSF in the subarachnoid space (Passot), hydrocephalus due to remote effects of bacterial toxins or otitis media (Warrington), and altered vasomotor control of the intracranial vascular bed (Dandy).52

The mainstays of conservative therapy include weight loss, medications to reduce CSF production, and repeated high-volume lumbar punctures. Despite these measures, some patients may have progressive symptoms or develop visual changes. Patients who fail conservative measures are generally referred for CSF flow-diversion procedures such as lumboperitoneal shunting, ventriculoperitoneal shunting,13,14 or optic nerve sheath fenestration. More recently, dural venous sinus stent placement has been described in the literature.

ONSF appears to have the highest success rate in patients with visual field changes or vision loss, 86%-92% compared with CSF flow diversion or sinus stent placement, 58% and 65%, respectively. ONSF was associated with the lowest improvement of headache, 60%, compared with sinus stent placement (89%) or CSF flow diversion (80%). ONSF was also associated with a lower major complication rate of 2%, a minor complication rate of 16%, and a revision rate of 15%. From a practical standpoint, ONSF may not be as readily available, and recovery from the procedure should be considered.

The most common indication for CSF flow-diversion procedures is severe headache or progressive visual change. There was a major complication rate of 8% and a minor complication rate of 33% in the 435 patients included. Considering this young population, with an average age of 31.9, the high reported repeat procedure rate of 43% is concerning. Most repeat procedures were shunt revisions. Forty-three percent of patients ultimately needed an additional procedure during the average follow-up period of 41 months. Of 358 patients (some patients were excluded in the denominator because of missing data), 154 patients underwent 428 additional procedures, or 2.78 additional procedures in >43% of patients undergoing CSF flow diversion.

There is limited but growing literature for dural venous sinus stent placement in the setting of elevated intracranial pressure and dural venous sinus stenosis. Dural venous sinus stenting may cause elevated intracranial pressure by 2 different mechanisms. The first is an increased gradient between the CSF space and the cerebral venous sinuses. A second is decreased CSF absorption by the arachnoid granulations, which are pressure-sensitive.3,12,16,17,20 Stent placement has been hypothesized to lower intracranial pressure by removing a Starling-like resistor, thereby removing the positive feedback loop.19

With noninvasive imaging, such as contrast-enhanced MRV, 3 patterns of dural venous sinus stenting may be amenable to sinus stent placement:

- Bilateral transverse/sigmoid sinus stenosis.
- Unilateral transverse/sigmoid sinus stenosis with contralateral hypoplasia/aplasia.

Although most patients with stents included in this meta-analysis underwent stent placement as the first intervention for medically refractory IIH, 10.3% of patients underwent stent placement as a second procedure. Dural venous sinus stenting could be considered in patients who have failed the traditional CSF-diversion procedure.

Given the cost and morbidity of repeat procedures, CSF shunting as the criterion standard treatment should be re-evaluated. Ahmed et al53 reported that in their health care system in Australia, the cost of the initial dural venous sinus stent placement was similar to the cost of the initial CSF flow-diversion procedure; however, when one took into account the cost of revisions, the total cost of CSF flow diversion was 5 times higher. Although CSF flow diversion is commonly performed, the literature regarding outcomes and high rates of revision does not compare favorably with recent data on venous sinus stent placement when using strict patient selection, dual antiplatelet therapy, and modern devices. We would argue that evaluation for underlying venous sinus stenosis should be undertaken with MRV (and confirmed, if present, with conventional catheter-based venography and pressure measurements) before any CSF flow-diversion procedure.

Limitations

Meta-analysis by definition is limited by a retrospective design; therefore, data collection was inconsistent and/or incomplete for both pre- and postoperative parameters. This was further compounded by inclusion of different surgical modalities and specialists. Ophthalmologists focused on vision, and most ONSF studies lacked CSF pressure and BMI. Neurosurgeons focused on headache, while neurointerventionists focused on headaches and papilledema. All studies lacked consistent data on visual acuity and field changes. Different studies had different definitions for improvement, indications for surgery, and variable long-term follow-up (1–278 months). Although there were fewer patients included in the dural venous sinus stenting group than in the others, 136 patients who met inclusion should generate reliable data for comparison.

Despite these challenges, we summarized the available data as rigorously as possible, with an emphasis on presenting symptoms, resolution of presenting symptoms, repeat procedure rates, and complication rates.

In the CSF flow-diversion group, some pediatric patients were included because they could not be separated because individual data were not available.8,40,42,44,47,54-56 In the ONSF studies by Corbett et al24 and Spoor et al,26 complications were given in terms of eyes and not patients. We considered the number of eyes as the number of patients for calculation consistency. Nithyanandam et al58 reported complications in terms of percentages, which we had to convert.

In studies in which values of certain parameters were marginally available (eg, CSF pressure >40 cm of H2O in 73% of cases in the CSF diversion study by El-Saadany et al,57), values were pre-
sented as “NR” or not reported in On-line 3 and excluded from the mean CSF pressure.

Future Directions
Surgery for medically refractory IIH is performed by different specialties; therefore, the data are inconsistent. Future CSF flow-diversion, ONSF, and dural venous sinus stenting studies for IIH should include documentation of the following:

1) Patient characteristics (age, comorbidities, BMI, symptoms, medications).
2) Formal ophthalmologic examination (pre- and post-intervention).
3) CSF studies (pre- and post-intervention).
4) For dural sinus stent placement, angiography confirming stenosis and pressure gradients.
5) Long-term clinical follow-up and stent patency.

CONCLUSIONS
Patients with medically refractory idiopathic intracranial hypertension have traditionally undergone CSF flow-diversion procedures as the first intervention. On the basis of our meta-analysis comparing traditional CSF flow-diversion procedures with venous sinus stent placement, this paradigm may need to be re-examined, given high technical and clinical success with low complications and low repeat-procedure rates associated with stent placement compared with traditional surgical interventions.

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