Venous sinus stenting lowers the intracranial pressure in patients with idiopathic intracranial hypertension

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ABSTRACT

Aims We report the cerebrospinal fluid opening pressure (CSF-OP) measurements obtained before and after venous sinus stenting (VSS) in 50 patients with idiopathic intracranial hypertension.

Methods The CSF-OP was measured with a spinal tap 3 months before and 3 months after treatment. All data were prospectively collected and included patient demographics, weight (kg), body mass index (BMI), acetazolamide daily dosage (mg), procedural details, complications, venous sinus pressures (mm Hg), trans-stenotic pressure gradient (mm Hg), transverse sinus symmetry, and type of venous sinus stenosis.

Results The average pretreatment CSF-OP was 37 cm H₂O (range 25–77) and the average post-treatment CSF-OP was 20.2 cm H₂O (range 10–36), with an average reduction of 16.8 cm H₂O (P<0.01). The post-treatment CSF-OP was less than 25 cm H₂O in 40/50 patients. The average acetazolamide daily dose decreased from 950 mg to 300 mg at the time of 3-month follow-up (P<0.01). No patient required an increase in acetazolamide dose 3 months after VSS. The average weight before treatment was 95.4 kg with an average BMI of 35.41. There was an average increase in body weight of 1.1 kg at the 3-month follow-up with an average increase in BMI of 0.35 (P=0.03).

Conclusions We provide evidence that there is a significant decrease in CSF-OP in patients with idiopathic intracranial hypertension 3 months after VSS, independent of acetazolamide usage or weight loss.

INTRODUCTION

Since the first reported case in 2002, venous sinus stenting (VSS) has gained increased acceptance as a minimally invasive surgical option for patients with idiopathic intracranial hypertension (IIH) and significant cerebral venous sinus stenosis (CVSS). The objective of VSS is to alleviate significant stenosis typically found at the transverse–sigmoid sinus junction, thereby reducing intracranial pressure (ICP) and alleviating the symptoms of IIH.

Despite the overall positive clinical results of VSS reported in the literature, pre- and post-treatment ICP has been documented in only a minority of cases. More specifically, only four studies in the literature documented cerebrospinal fluid opening pressure (CSF-OP) by lumbar puncture (LP) before and after treatment, if not in all, at least in the majority of patients. Two other groups reported measurements obtained from an ICP monitor that was implanted before and after the stenting procedure. As the VSS procedure has not yet been evaluated in randomized controlled or sham procedure trials, our group believes that objective data such as CSF-OP are necessary, both for selecting patients for treatment and also to demonstrate a successful treatment effect as this treatment continues to be evaluated. In this paper we report the CSF-OP measurements obtained before and after treatment in our patient cohort.

METHODS

This analysis was approved by our institution’s IRB.

Patient population

Sixty-three patients who met the criteria for diagnosis of IIH were treated with VSS in our institution from January 2012 to June 2017. Our protocol required a 3-month post-stenting LP for CSF-OP measurements. Of the 63 patients, 50 had both pre- and post-treatment LP with CSF-OP measurements and they constitute the cohort of this analysis. Of the 13 subjects excluded from the analysis, seven refused a post-treatment LP due to a history of symptomatic CSF leak from a prior procedure. Among these seven patients, four had papilledema that resolved after VSS and three had symptomatic improvement with resolution of pulsatile tinnitus and headaches (no papilledema). One patient did not have a recent pretreatment LP but did have papilledema that resolved. Finally, five patients had not reached the 3 month mark by the time of the analysis and their follow-up LP was still pending.

The VSS procedural details have been described in previous publications from our group. A minimum CSF-OP of 25 cm H₂O before the procedure was necessary for VSS. Briefly, the VSS procedure requires dual antiplatelet therapy with aspirin and clopidogrel, initiated 1 week before the procedure and continuing for 1 month post-procedure, with continued aspirin monotherapy for 5 more months. Thus, at the time of post-stenting LP the patients were on aspirin only. A catheter venogram under local anesthesia was performed to obtain venous sinus pressure measurements through a microcatheter positioned in the superior sagittal, transverse, and sigmoid sinuses and the jugular bulb. A trans-stenotic gradient of ≥8 mm Hg was a prerequisite for stenting. The stent placement was performed under general anesthesia.
Clinical neurology

Data collection
All data were prospectively collected and included patient demographics, weight (kg), body mass index (BMI), acetazolamide daily dosage (mg), procedural details, complications, venous sinus pressures (mm Hg), trans-stenotic pressure gradient (mm Hg), transverse sinus symmetry, and type of venous sinus stenosis.

CSF-OP
The CSF-OP was measured via a fluoroscopy-guided LP. The majority of the LP procedures (82/100) were performed in the left lateral decubitus position, whereas the remainder were performed in the prone position. The pretreatment CSF-OP was measured within 3 months before VSS. The post-treatment assessment took place 3 months after VSS and included a contrast-enhanced MR venogram (MRV) followed by LP with CSF-OP. The daily dosage of acetazolamide (mg) was documented at the time of pre- and post-treatment LP. Following VSS, the acetazolamide dosage was decreased when there was evidence of improvement in papilledema, visual dysfunction, and presenting symptoms. Body weight (kg) and BMI were also collected at the time of pre- and post-stenting LP.

Type of cerebral venous sinus stenosis
The type of venous sinus stenosis was documented with pretreatment MRV and catheter venography. Extrinsic stenosis was defined as a long segment stenosis with obtuse margins, whereas intrinsic stenosis was defined as a short segment stenosis with acute margins and focal filling defect in the venous sinus lumen.

Transverse sinus symmetry
The pattern of venous outflow from the superior sagittal sinus to the transverse sinuses was documented using pretreatment MRV and catheter venogram at the time of stenting. As reported in a previous publication from our group, a co-dominant system was considered when the transverse sinuses were symmetric with <3 mm difference in maximal diameter on MRV. A unilateral dominant system was considered when there was absence of one transverse sinus (ie, aplastic) or asymmetric transverse sinuses with >3 mm difference in maximal diameter (hypoplastic).

Procedural parameters
During catheter venography and with the patient under local anesthetic only, the following parameters were recorded: pressure in the superior sagittal sinus and trans-stenotic gradient (difference between the proximal transverse and distal sigmoid sinus.

Statistical analysis
Descriptive statistics were made for all variables of interest in the statistical analysis. Q–Q plots were used to plot residuals for the three variables (weight, CSF-OP, and acetazolamide usage) before and after treatment as a test of normality. A paired t-test was used to examine significant differences before and after treatment in these three variables. To assess statistical correlation between superior sagittal sinus pressure, trans-stenotic gradient, and pre-stenting CSF-OP, Pearson correlation coefficients were calculated and P value obtained. The change in CSF-OP (ie, difference in CSF-OP before and after stenting) was measured as an absolute change, relative change (%), and as a binary indicator by assessing whether or not the post-treatment CSF-OP was <25 mm H2O. The Pearson correlation test was used for assessing the statistical correlation between the absolute and relative changes of CSF-OP with superior sagittal sinus pressure and trans-stenotic gradient. An unpaired t-test was conducted to investigate statistical differences between absolute and relative changes of CSF-OP against the pattern of venous outflow (co-dominant versus unilateral) and type of stenosis (intrinsic versus extrinsic). Fisher’s exact test was used to investigate the association between the categorical indication of post-treatment CSF-OP <25 cm H2O and the pattern of venous outflow (co-dominant versus unilateral) and type of stenosis (intrinsic versus extrinsic). An unpaired t-test was used to investigate statistically significant differences between the categorical indication of post-treatment CSF-OP <25 mm H2O with the parameters superior sagittal sinus pressure and trans-stenotic gradient. To assess whether acetazolamide usage was decreased in both intrinsic and extrinsic types of stenosis, the paired non-parametric Mann–Whitney U test was used separately for both groups. An unpaired Mann–Whitney U test was conducted to investigate differences in acetazolamide requirement post-treatment between intrinsic and extrinsic types of stenosis. Similarly, to assess differences in usage before and after VSS between co-dominant and unilateral groups, a paired Mann–Whitney U test was used separately for both groups. Also, to find differences in post acetazolamide usage between co-dominant and unilateral groups, an unpaired Mann–Whitney U test was conducted.

RESULTS
We report the results from 50 patients with IHI who underwent VSS and had CSF-OP measurements before and 3 months after treatment (47 women and 3 men; age range 7–59 years). Twenty-nine patients (58%) had extrinsic stenosis and 21 had intrinsic stenosis (42%). The stent was placed in the right lateral (transverse and sigmoid) sinus in 37 patients and the left lateral sinus in 13 patients (74% and 26%, respectively). No patient was treated with bilateral lateral sinus stenting. Although there were no neurological complications, one patient developed a retroperitoneal hematoma from the femoral artery puncture site that was managed with observation, without any need for transfusion or surgery. Another patient had a ruptured ovarian cyst 4 days post-stenting that may have been related to the dual antiplatelet therapy. There was no occurrence of in-stent stenosis or thrombosis. No patient required alternative surgical treatment (VSS, CSF shunt, or therapeutic LP) up to the 3-month follow-up mark.

CSF-OP
The average pretreatment CSF-OP was 37 cm H2O (range 25–77) and the average post-treatment CSF-OP was 20.2 cm H2O (range 10–36), with an average reduction of 16.8 cm H2O (P<0.01) Table 1. The post-treatment CSF-OP was <25 cm H2O in 40/50 patients. The most significant change was 50 cm H2O (27 cm H2O after treatment from 77 cm H2O before treatment), which was documented in a patient with fulminant presentation and severe papilledema that resolved after stenting. Three out of the 50 patients in our series did not show any reduction in CSF-OP. One patient who experienced initial improvement in symptoms and resolution of papilledema returned the week before the 3-month LP with recurrent headaches; the CSF-OP had slightly increased (29 cm H2O from 28 cm H2O) and MRV demonstrated a new stenosis adjacent to the stent. The patient was subsequently treated with a second VSS procedure and had significant reduction of CSF-OP at follow-up (21 cm H2O). The second patient had the same CSF-OP before and after VSS and did not experience symptomatic improvement. The third patient had the same CSF-OP before and after VSS but at the time of...
follow-up was off acetazolamide; this patient required serial large volume spinal taps and 1 g acetazolamide daily prior to venous stenting.

Acetazolamide
The average acetazolamide daily dose decreased from 950 mg to 300 mg at the time of 3-month follow-up (P < 0.01). No patient required an increase in acetazolamide dose 3 months after VSS. Thirty-five of the 50 patients (70%) had discontinued acetazolamide by the time of the 3-month follow-up assessment.

Weight loss
The average weight before treatment was 95.4 kg with an average BMI of 35.41. There was an average increase in body weight of 1.1 kg at the 3-month follow-up with an average increase in BMI of 0.35 (P = 0.03). Twenty-one patients (42%) had weight gain >1 kg (range 1–13.6 kg), whereas 10 patients (20%) had a body weight loss of >1 kg (range 1–5.9 kg) and 19 patients (38%) maintained the same body weight (within 1 kg).

Procedural parameters
There was a statistically significant linear correlation between the pressure in the superior sagittal sinus and the trans-stenotic gradient with the pretreatment CSF-OP (P < 0.001 and Pearson correlation coefficient 0.46 and 0.49, respectively). There was no statistically significant correlation between the pressure in the superior sagittal sinus and the absolute or relative changes in post-stenting CSF-OP or the categorical indicator (<25 cm H_{2}O). There was no statistically significant correlation between the trans-stenotic gradients and the absolute and relative changes in post-stenting CSF-OP or the categorical indicator (<25 cm H_{2}O).

Extrinsic versus intrinsic stenosis
There were 29 patients (58%) with extrinsic stenosis and 21 patients (42%) with intrinsic stenosis. At the 3-month follow-up assessment, the patients with extrinsic stenosis showed a 44% mean reduction in CSF-OP (from 37.34 to 20.93 cm H_{2}O) whereas the patients with intrinsic stenosis showed a 47% reduction of ICP (from 36.48 to 19.29 cm H_{2}O). The mean absolute change and percent change in CSF-OP did not differ between the extrinsic and intrinsic groups, nor was the rate of improvement to <25 cm H_{2}O.

At the 3-month follow-up there was a 62% decrease in the daily dosage of acetazolamide among patients with extrinsic stenosis compared with an 81% decrease in daily dosage of the medication among patients with intrinsic stenosis. Similarly, 62% of patients with extrinsic stenosis and 80% of patients with intrinsic stenosis did not require any acetazolamide at 3 months. Both intrinsic (P < 0.01) and extrinsic (P < 0.01) groups showed a statistically significant decrease in acetazolamide usage (paired Mann–Whitney U test). However, acetazolamide usage after treatment failed to show a statistically significant difference between the intrinsic and extrinsic types of stenosis (P = 0.13).

Unilateral dominant versus co-dominant transverse venous sinuses
There were 31 patients with a unilateral dominant pattern (62%) and 19 patients with a co-dominant system (38%). There was no statistically significant difference in the degree of absolute, percent, or categorical change (CSF-OP <25 cm H_{2}O) between the unilateral dominant and co-dominant groups. Both the unilateral dominant (P < 0.01) and co-dominant (P < 0.01) groups showed a statistically significant decrease in acetazolamide usage. Acetazolamide usage after treatment, on the other hand, failed to show a statistically significant difference between unilateral dominant and co-dominant groups (P = 0.67).

DISCUSSION
While VSS has become increasingly popular as a minimally invasive surgical treatment for IIH, high quality and objective data are necessary to validate its efficacy. As patients with IIH are often poly-symptomatic with a psychological component, we wanted to report objective reproducible data and explore whether the reduction in CSF-OP could be related to other confounding factors such as acetazolamide usage and/or weight loss. In what is to our knowledge the largest series of IIH patients with CSF-OP measurements before and after VSS, we demonstrate a statistically significant 45% mean reduction in ICP 3 months after VSS, despite a statistically significant reduction in acetazolamide usage and an increase in BMI in the majority of patients.

Our results corroborate those published in prior series showing a meaningful reduction of CSF-OP after VSS and support the role of VSS as an effective surgical treatment for CVSS. Donnet et al showed a mean reduction in CSF-OP of 24.2 cm H_{2}O 3 months after VSS in 10 patients. In a previous publication from our group, we demonstrated a 20 cm H_{2}O reduction 3 months after VSS in 13 patients (these patients were also included in the present analysis). The differences in mean reduction of CSF-OP are most likely related to the number of patients included in the earlier reports, to the average pretreatment ICP, and the degree of acetazolamide usage post-treatment.

Others have shown an immediate reduction of ICP using ICP monitors implanted at the time of stenting. Liu et al demonstrated an immediate reduction of 27 cm H_{2}O at the time of stenting in 10 patients, with an additional reduction of 10.8 cm H_{2}O overnight. Similarly, Matloob et al showed an immediate decrease in ICP post-stenting in 9/10 patients, with a mean reduction of 7.8 cm H_{2}O that was sustained for at least 24 hours. Although complications of ICP monitors following stenting have not been reported in the literature, we felt that implanting an ICP monitor at the time of stenting could result in hemorrhage in the setting of antiplatelet agents and intraprocedural anticoagulation.

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### Table 1

<table>
<thead>
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<th>CSF-OP (cm H_{2}O)</th>
<th>Acetazolamide (mg)</th>
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<tbody>
<tr>
<td></td>
<td>Pre VSS</td>
<td>Post VSS</td>
</tr>
<tr>
<td>All (n=50)</td>
<td>36.98</td>
<td>20.24</td>
</tr>
<tr>
<td>Ex (n=29)</td>
<td>37.34</td>
<td>20.93</td>
</tr>
<tr>
<td>In (n=21)</td>
<td>36.48</td>
<td>19.29</td>
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Ex, extrinsic venous sinus stenosis; In, intrinsic venous sinus stenosis.

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Intrinsic stenoses are anatomically fixed narrowed regions of the sinus, and in some cases may act as a primary mediator of the pathophysiology of IIH. Conversely, extrinsic stenoses improve with ICP reduction and are therefore not felt to be an isolated cause of IIH. It has been hypothesized, however, that an initial elevation in ICP due to other factors such as recent weight gain compresses the sinus at a vulnerable location, leading to secondary venous hypertension and ultimately an even greater elevation in ICP, since the CSF drains into the sinuses through the arachnoid granulations. The additional increase in ICP results in further venous sinus stenosis and a positive feedback loop ensues, ultimately resulting in a more severe disease presentation. With this difference in mind, we hypothesized that VSS of an intrinsic stenosis would lead to a greater reduction in ICP than extrinsic stenosis. Indeed, in a previous report from our group we observed a trend (non-statistically significant) in ICP than extrinsic stenosis. Indeed, in a previous report from our group we observed a trend (non-statistically significant) towards a greater reduction of ICP in the intrinsic stenosis group. This observation was not confirmed in this larger series, likely reflecting the fact that CVSS—which it is extrinsic or intrinsic—is probably just one factor that interacts with others to result in IIH. Indeed, since intrinsic stenoses are often the result of longstanding anomalies, the advent of IIH at a given time of life must reflect the addition of some new contributing factor such as weight gain.

We did find that the need for acetazolamide was reduced in the intrinsic stenosis group, both in terms of absolute daily dosage and of the proportion of patients who stopped the medication completely within 3 months after treatment, but these differences were not statistically significant. Perhaps the number of patients is still not adequate to achieve statistical significance.

We also looked at differences in outcome between patients with unilateral dominant versus co-dominant cerebral venous outflow patterns. Despite a significant reduction in CSF-OP and acetazolamide usage after stenting in both groups, there was no difference in outcomes between the two groups. In a prior publication we have shown that, in cases of co-dominant pattern, the majority of the venous outflow after stenting is via the stented side (path of least resistance). Therefore, after stenting, both groups functionally behave in the same fashion, which explains the similar outcomes.

Limitations of the study
Our study was limited by the timing of the follow-up CSF-OP measurement at 3 months after stenting. Our results do not tell us about the speed of ICP reduction during those 3 months, which is an important factor in ensuring that papilledema resolves before permanent vision loss ensues. Since it has already been demonstrated that the ICP decreases immediately after VSS using ICP monitors, and since we could not perform LP within the first 5 weeks while clopidogrel was still in effect, we opted to perform the LP at 3 months to evaluate whether the immediate reduction in ICP was sustained.

Another potential limitation of our study is the use of LP as a means to assess ICP. Measurements derived this way might be spurious owing to patient’s body habitus, anxiety, and position. The alternative would be to use an ICP monitor before and after stenting and document ICP changes over a longer period of time and with positional changes and various activities. A recent comparison of ICP monitoring and LP measurements performed within the previous 6 months showed that only 2/17 patients had high ICP when the ICP monitoring was utilized, whereas all 17 had high ICP by LP. In another study ICP monitoring did not show high ICP in 7/8 patients with high ICP by LP. The authors did not report the time interval between LP and ICP monitoring. From our review, there is no available study in the literature comparing LP and ICP monitoring performed at the same time, or at least a very close time interval. According to current guidelines, the diagnosis of IIH requires demonstration of high ICP by LP. There is definitely a role for ICP monitoring in complex cases, but the reality is that LP is widely accepted for the diagnosis and management of IIH. In our study we used LP under fluoroscopy before and after treatment, and we feel that any errors of ICP measurements inherent to LP did not affect the outcomes of this study.

Lastly, in the vast majority of patients the LP was performed in the left lateral decubitus position, with only a few performed in the prone position. A prospective study of 52 patients evaluated for IIH showed no significant differences when CSF-OP was measured in the prone versus the lateral decubitus position while undergoing a fluoroscopy-guided LP, and we do not feel that this change in positioning would have had a significant effect on our results.

CONCLUSION
We have provided evidence that there is significant decrease in CSF-OP in patients with IIH 3 months after VSS, independent of acetazolamide usage or weight loss. As a high CSF-OP is a sine qua non for the diagnosis of IIH, and normalization of ICP is an established treatment endpoint, the data we present in this report are fundamental in supporting the beneficial role of VSS as a therapeutic option in carefully selected patients with proven IIH.

REFERENCES