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Case Report

Management of Refractory Intracranial Hypotension Using Percutaneous Fibrin Sealant Patch – A Case Series and Review of the Literature

Kevin Wong, DO, Brian R. Monroe, MD, and S. Mark Poler, MD

Background: Intracranial hypotension (IH) among patients with persistent cerebrospinal fluid (CSF) leakage remains a challenging problem. The majority of these cases resolve spontaneously with conservative measures. The customary treatment for IH is epidural blood patch (EBP). In some cases, CSF leaks can persist for months or even years despite multiple trials of EBP. To date, there are only a limited number of published studies documenting the percutaneous injection of fibrin sealant for treatment of IH refractory to conservative measures and EBP.

Objective: Our objective was to perform a literature review and retrospective case series regarding patients who underwent percutaneous injection of fibrin sealant for treatment of refractory IH at our institution.

Study Design: This case series used a single-centered retrospective observational study design and literature review.

Setting: Patients in this case series were treated at a community-based tertiary care medical center.

Methods: Five consecutive patients with the diagnosis of IH refractory to conservative measures and EBP who underwent percutaneous patching with fibrin sealant were identified at our institution between January 1, 2000 and January 1, 2016. A retrospective chart review was performed and data including demographics, characteristics, interventions, clinical outcomes, and complications were collected. A critical review of the current literature regarding the percutaneous use of fibrin sealant for treatment of IH was conducted.

Results: Four of the 5 patients (80%) experienced no further symptoms of IH and no adverse events were noted. One patient (20%) ultimately required surgical duroplasty. Review of the current literature showed a total of 2 prospective case series, 4 retrospective case series, and 11 case reports. Our present case series and literature review demonstrated that fibrin sealants were well-tolerated by most patients and associated with low incidences of complications and recurrence.

Limitations: This study is limited by the small retrospective case series of 5 patients.

Conclusions: Percutaneous injection of fibrin sealant may be considered in refractory cases of IH when repeated trials of EBP have persistently failed. It appears to be a highly effective, safe, and easy-to-use alternative therapy for patients with refractory IH in an ambulatory setting. Our review of the literature revealed only studies with low quality of evidence, including case series and case reports. There is a substantial need for high-quality studies and clinical evidence to corroborate the efficacy and safety of this percutaneous technique. However, this ideal is very challenging because of the relative rarity and heterogeneous etiologies of cases.

Keywords: Fibrin sealant, intracranial hypotension, CSF leak, epidural blood patch, orthostatic headache, refractory, quality of life, percutaneous

From : Division of Anesthesiology, Geisinger Medical Center, Danville, Pennsylvania

Author for correspondence: Kevin Wong, DO
Address: Division of Anesthesiology, Geisinger Medical Center, 100 N. Academy Ave, Danville, PA 17821
E-mail: k6wong2003@hotmail.com

Intracranial hypotension (IH) is a neurological syndrome diagnosed in patients with orthostatic headache along with radiological evidence of low cerebrospinal fluid (CSF) pressure, CSF volume depletion, and/or the presence of a CSF leak (1). The annual incidence of low CSF pressure headache was estimated to be around 5 cases per 100,000, with the peak age group of around 40 years (2,3). Despite being attributed to diverse etiologies, IH is generally classified as either spontaneous (primary) or secondary (1). The latter is commonly iatrogenic from inadvertent dural puncture during neuraxial procedures, surgical dural violations, chiropractic manipulation, and degenerative spine disorders including osteophytic protrusion or herniated disc (1,4). In contrast, other identifiable traumatic etiologies or spontaneous IH are varied and speculative. Proposed etiologies include congenital weakness of the dural sac, pre-existing meningeal diverticula or cysts, dilated nerve root sleeves, heritable connective tissue disorders, or trivial trauma from mechanical stress (4).

The hallmark clinical manifestation of patients with IH is orthostatic headache, aggravated by upright posture and relieved with recumbency (1). The pathophysiology of orthostatic headache has had numerous hypothetical explanations. It was initially speculated to be caused by increased absorption of CSF, decreased CSF secretion, or both. With recent advances in imaging technology, CSF leakage through a dural breach has been widely demonstrated to be the major culprit of IH (2). Mechanisms postulated to account for the development of orthostatic headache include downward traction of pain-sensitive structures in the brain due to loss of CSF pressure, vasodilatation of cerebral veins and venous sinuses due to low CSF pressure or volume, and abnormal distribution of craniospinal elasticity (3,5). Other cardinal symptoms include nausea and vomiting, neck pain and stiffness, visual field defects, diplopia, tinnitus, hearing impairment, photophobia, phonophobia, vertigo, transient 3rd or 4th cranial nerve palsy, limb paresthesia, and, rarely, neurocognitive abnormalities including impaired mental processes, dementia-like presentation, ataxia, myelopathy, radiculopathy, parkinsonism, and coma (3,4,6).

The clinical diagnosis of IH is primarily made by performing focused history and physical examination. Radiographic evidence of CSF leakage or hypovolemia may be found (6,7). The hallmark magnetic resonance imaging (MRI) characteristics of IH include subdural fluid collections or hematomas, enhancement of the pachymeninges, engorgement of venous structures, pituitary hyperaemia, and sagging of the brain (1). Other radiographic modalities may be utilized to identify sites of CSF leakage including myelography, radioisotope cisternography, and digital subtraction myelography (8). These advanced imaging modalities occasionally allow clinicians to identify the exact locations of CSF leaks, especially for those that leak rapidly or locate in the ventral aspect of the epidural space (9). Despite increasing awareness and recognition of IH as a disease that affects potentially all age groups, IH remains frequently overlooked or misdiagnosed in differential diagnosis of headache (1,6). Failure to recognize and treat IH can substantially delay proper healing. This neurological syndrome may potentially develop into a chronic, debilitating disease that can significantly impair quality of life, resulting in functional decline, disability, and morbidity (10).

The treatment of both spontaneous and secondary IH usually begins with conservative measures including bed rest, hydration, caffeine, abdominal binders, and oral analgesics (1). Other pharmacologic therapies have also been studied clinically as alternatives including cosyntropin, hydrocortisone, methergine, gabapentin, and pregabalin (11). These conservative measures theoretically focus on increasing epidural pressure, inducing cerebral vasoconstriction, reducing sympathetic pain, and restoring the volume of CSF. Emerging therapies including acupuncture, occipital nerve blocks, and sphenopalatine nerve blocks have been introduced as alternatives for treatment. These techniques, however, were derived from low-quality evidence studies and creative innovation. Well-powered clinical trials would be needed to validate their efficacies.

The clinical course of this neurological syndrome is often benign and self-limited (12). Epidural blood patch (EBP) is frequently considered as the gold standard for IH treatment (3,4,6). The efficacy of EBP for postdural puncture headache (PDPH) have been reported to vary from 70% to 90% following the

first attempt but only 30% in spontaneous IH (1,3). Despite the proven efficacy of EBP, it remains unclear why a subset of patients persistently fails to benefit from these treatments. These patients may become chronically incapacitated for daily living activities and confined to bed, which substantially compromises their quality of life (10). In the recent years, there has been emerging interest in the percutaneous use of fibrin sealant as an alternative therapy for these patients. In this paper, we present the clinical outcomes of 5 consecutive patients with refractory IH who underwent percutaneous patching with fibrin sealant at our institution after failure of conventional EBP. The purpose of this report is to highlight the importance of percutaneous fibrin sealant patch as a simple and effective alternative for IH refractory to EBP prior to the consideration of surgical repair. We will also review the existing literature regarding this therapeutic approach for IH.

CASE SERIES

We conducted a retrospective, single-center case series to identify patients with refractory IH who underwent percutaneous patching with fibrin sealant at our institution between January 1, 2010 and January 1, 2016. Our Institutional Review Board (IRB) approved this review and did not consider it to be human subjects research. Demographic information and clinical data were obtained by performing comprehensive chart review of our electronic medical records while ensuring Health Insurance Portability and Accountability Act compliance. We initially identified 6 refractory cases of IH receiving fibrin sealant (EVICEL®, Ethicon, Inc., Somerville, NJ) for management in the past 6 years at our institution. One patient was excluded from this study. That patient underwent a reoperation for repair of the dural defect with direct suturing, fibrin sealant, and gelfoam due to persistent CSF leakage following implantation of an intrathecal pump despite 2 trials of EBP. No percutaneous injection of fibrin sealant was performed on this patient.

Patient 1

Patient 1 was a 62-year-old man, 162 cm, and 97 kg, with a history of hypertension, hyperlipidemia, bilateral carotid stenosis, chronic obstructive pulmonary disease, type 2 diabetes, degenerative lumbar spondylosis, and bladder tumor status post transurethral resection of a bladder tumor and instillation of intravesical chemotherapy. He underwent L4 through S1 fusion for his degenerative lumbar spondylosis. He later developed a positional headache due to suspected CSF leakage and pseudomeningocele. The headache caused a significant amount of distress and severely affected his quality of life. A caudal blood patch was performed and only provided relief lasting a few days. The decision was made to perform an EBP with fibrin sealant as an additive one month later.

The L2-3 level was identified fluoroscopically with hardware at L4. An 18-gauge Tuohy needle was introduced about 3 cm left of the midline. With the needle inserted about 3 cm into the soft tissue, a gush of clear fluid emerged from the needle enough to soak an area of the drape and quickly stopped flowing. The needle was then advanced fluoroscopically until loss of resistance was achieved. Injection of contrast demonstrated both cephalad and caudal spread with layering in the anterior epidural space. A mixture of 5 mL of autologous blood and 5 mL of the fibrinogen component of fibrin sealant was slowly injected after negative aspiration of blood and CSF. Thereafter, 5 mL of the thrombin component of fibrin sealant was injected slowly through the epidural needle followed by 15 mL of autologous blood. The epidural needle was removed and the patient remained neurologically intact in the postanesthesia care unit. The patient had immediate relief of his headache after the procedure. At his 2-year follow-up with the neurosurgery clinic, there had been no recurrence of his headache.

Patient 2

Patient 2 was a 47-year-old man, 180 cm and 89 kg, with a history of gastroesophageal reflux disease. He had been struck from behind in a motor vehicle accident about 9 months before arriving for diagnosis and treatment at our facility, having had no apparent injuries at the time of the accident. Several weeks following his accident, he developed a positional headache. The headache was diffuse and bilateral and originated from the base of the neck with radiation to the frontal area. The headache was rated 10 out of 10 on a visual analog scale. He was taking nonsteroidal anti-inflammatory drugs, acetaminophen, diazepam, and hydromorphone with some relief. The headache was exacerbated by bright light and activity, and associated with episodes of tinnitus, dizziness, jaw pain,

neck pain, polyuria, and night sweats. His occupational duties were adversely affected. MRI of the brain revealed bilateral subdural effusions with mild inferior displacement of the brain consistent with IH secondary to CSF leakage. MRI of the spine demonstrated fluid collection within the posterior epidural space from T3 to T8 (Fig. 1). Over the course of 4 months, the patient had 5 trials of EBP with relief of his headache lasting from 3 days to 3 weeks. The patient also had a trial of computed tomography (CT)-guided percutaneous patching with fibrin sealant at an outside hospital with myelography confirming a dura tear at the level of T4. Percutaneous injection of fibrin sealant via 4 needles placed with CT guidance provided him with a longer duration of relief than conventional EBP. About 5 days prior to his referral for surgical duroplasty, the positional headache recurred and became intolerable. The patient consented to a second trial of percutaneous patching with fibrin sealant at our institution.

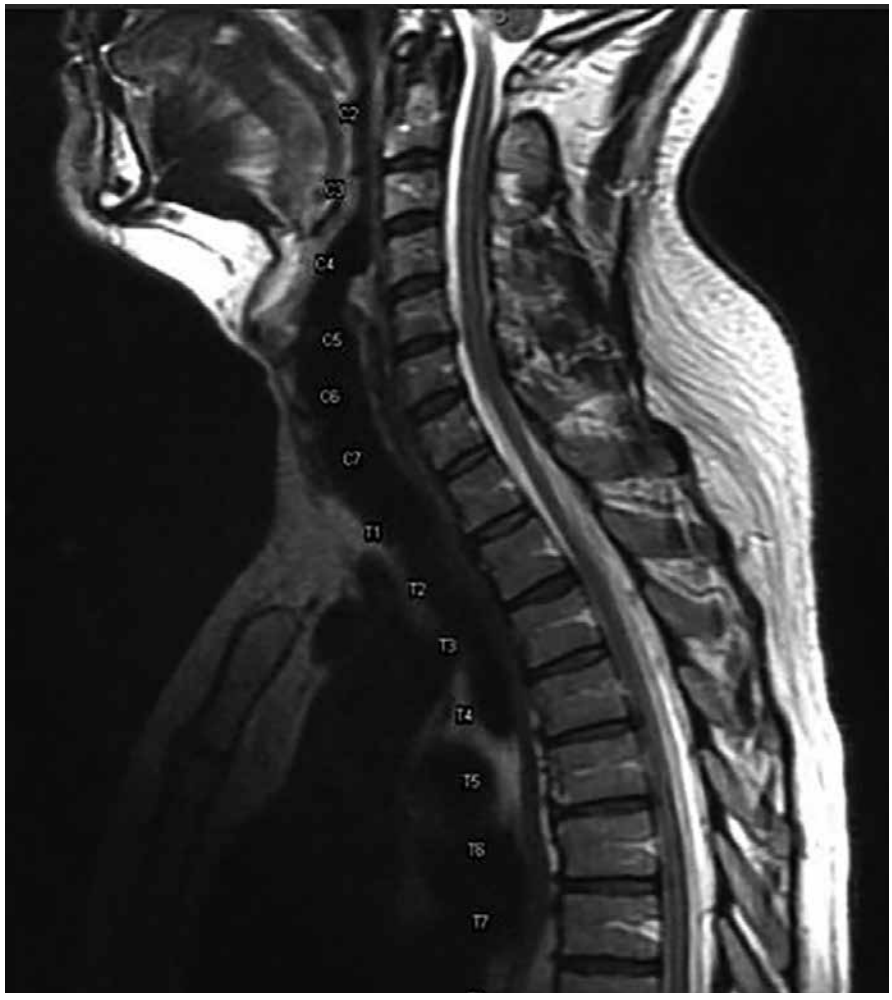

Fig. 1. Sagittal T2-weighted magnetic resonance imaging of the thoracic spine showing a collection of extradural fluid within the posterior epidural space that spanned from the level of T3 to T8.

With the patient in the right lateral decubitus position, the T3-4 and T4-5 interspaces were identified and an 18-gauge Tuohy needle was inserted via a left paramedian approach until loss of resistance was achieved. No aspiration of CSF or blood was appreciated. A volume of 10 mL of autologous venous blood was injected initially followed by a mixture of 5 mL of fibrinogen and thrombin into the epidural space. Only 5 mL of the fibrin sealant was injected as its increasing viscosity prevented further injection. After aspirating the Tuohy needle to clear the clot, an additional 20 mL of autologous blood was injected. The patient was subsequently discharged home in stable condition with partial relief of his headache. Because none of the 13 percutaneous interventions produced more than 3 weeks of respite, the patient was referred to an outside hospital for surgical repair of his dural defect. At that hospital, multiple imaging procedures were employed over several days that were only able to determine the segment of the thoracic spine where the leak was located. During surgery, an anterior

elliptical dural hole with a long-axis diameter greater than 10 mm was repaired. He continued to experience relief from headaches 3 years following the surgery. Repeat MRI of the thoracic spine 2 years after surgery showed postsurgical changes at the levels of T2 and T3 with no evidence of CSF leakage. Of note, however, he continues to suffer considerable disability and physical limitation due to chronic back pain, ability to lift only light-weight objects, and difficulty sitting at his desk job. Such limitations after thoracic laminectomy are apparently well known in patient mutual support communities, but seldom reported in the literature.

Patient 3

Patient 3 was a 39-year-old woman, 170 cm and 106 kg, with a history of glaucoma and dyslipidemia, who presented to the emergency department due to worsening headache over the previous week. The patient was diagnosed with spontaneous IH about a month prior by her neurologist. The headache was described as sharp, throbbing, positional, frontal, and occipital with radiation to the posterior aspect of the neck. It was associated with symptoms of nausea, diaphoresis, photophobia, and phonophobia. The patient denied any history of dural puncture. She worked as a housekeeper and her work frequently involved heavy lifting and physical exertion such as scrubbing the floors and lifting water buckets. MRI of the brain revealed findings consistent with IH including sagging brainstem, venous engorgement, prominence of the pituitary gland, dural thickening and enhancement, and minimal bilateral subdural hygroma. CT-myelogram and MRI of the spine demonstrated contrast extravasation in the dorsal epidural space extending from C8 to T6, compatible with CSF leakage (Fig. 2). However, the precise location of the dural defect was not clearly demonstrated. Conservative measures including bed rest, hydration, steroid taper, gabapentin, and analgesics had all failed to provide any relief. The patient had 2 trials of EBP with transient relief lasting 3 and 14 days, respectively, and a trial of epidural infusion of normal saline with no significant relief. Repeat MRI of the spine demonstrated similar findings of abnormal fluid signal within the dorsal epidural space from the C8 to T6 levels. The patient agreed to proceed with a trial of percutaneous patching with fibrin sealant.

An epidural was performed at the T9-10 level using the loss-of-resistance technique followed by a gradual injection of 6 mL of the fibrinogen component diluted with 6 mL of normal saline through a 17-gauge Tuohy needle.

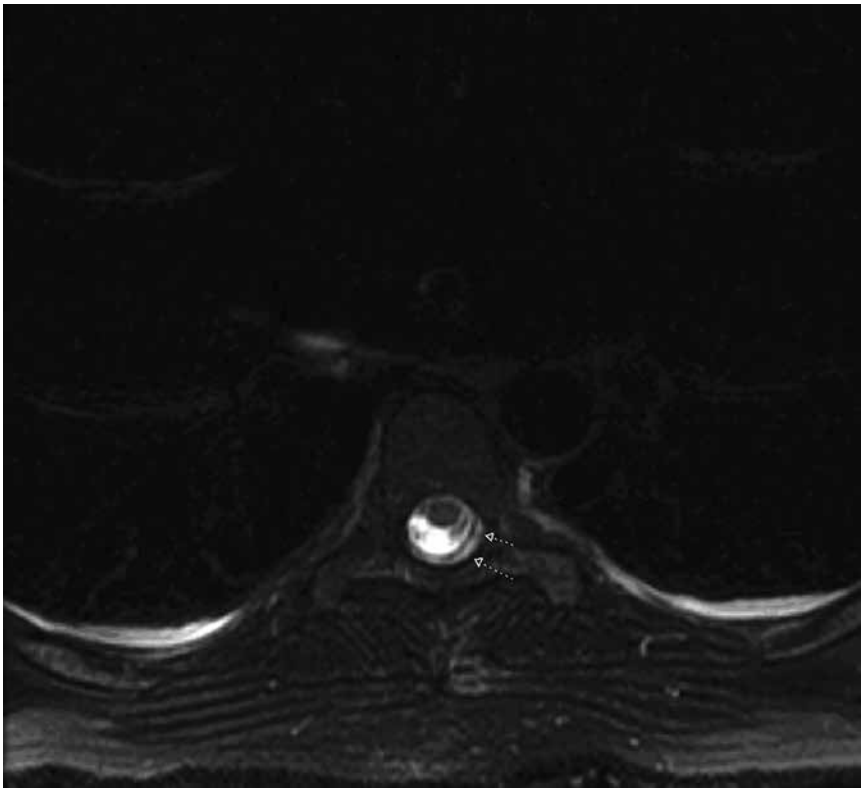

Fig. 2. Transverse T2-weight magnetic resonance imaging of the thoracic spine showing a small amount of abnormal extradural fluid signal intensity along the dorsal epidural space at the level of T6 with no discrete dural defect identified.

The thrombin component was not injected due to the development of significant back pressure. Despite multiple attempts at different thoracic levels using the midline or paramedian approach, correct placement of the needle in the epidural space was uncertain because only subtle loss of resistance was felt and fluoroscopy was unavailable for guidance. The headache only resolved transiently after the procedure and remained persistent for the following 2 days. A second trial of percutaneous patching with fibrin sealant was repeated at the level of L2-3 under fluoroscopic guidance. The thoracic level was avoided due to the significant challenges during the last trial. Upon successful localization of the 17-gauge Tuohy needle in the epidural space using fluoroscopy, injection of contrast dye could be seen layering in the anterior spinal canal at levels T8 to L3. Equal volumes of 5 mL of blood and fibrinogen were injected first, and then equal volumes of 5 mL of blood and thrombin were injected. An additional 30 mL of autologous blood was injected gradually and stopped due to bilateral aching in her hips and legs. The patient was evaluated in the recovery unit with complete resolution of her headache about 5 hours after the procedure. She was subsequently discharged home in stable condition. At her 2- and 4-week follow-up appointments, she reported that her headache had significantly improved despite intermittent episodes of transient frontal or occipital headache upon standing and lifting objects. She could return to work and had no recurrent headache at her 18-month follow-up phone call.

Patient 4

Patient 4 was a 27-year-old woman, 162 cm and 55 kg, with a history of recurrent meningitis, coil embolization of a right maxillofacial arteriovenous malformation about a month prior to presentation, and cystic hygroma. She also had a remote history of pseudotumor cerebri that was successfully treated with acetazolamide. She recently had a lumbar puncture and was subsequently diagnosed with aseptic meningitis at an outside hospital. During her hospital stay, her condition improved with intravenous methylprednisolone. A 5-day course of oral prednisone taper was prescribed upon her discharge from the hospital. On postlumbar puncture day 6, she developed severe unremitting positional headache in the occipital region. The headache was progressively worsening and associated with nausea, vomiting, neck stiffness, photophobia, and intermittent tinnitus in her left ear. It was throbbing in nature with retrobulbar pressure sensation. Her nausea and vomiting became so severe that she was not able to tolerate oral intake. Prochlorperazine, diphenhydramine, and ondansetron provided no relief. She denied any fever, chills, rigors, sick contacts, and other neurological deficits. MRI of her head revealed signs of IH, including mild downward slumping of the midbrain and partial effacement of the basilar cisterns (Fig. 3). Conservative measures including caffeine, aggressive hydration, and low-dose opioids had failed. The patient underwent 2 trials of EBP with headache relief only lasting 2 days. She was admitted to our institution due to rapid progression and worsening of her headache. Upon bedside evaluation, the patient only had mild relief of her headache with 10 to 15 degrees of bed elevation. Despite her atypical symptoms of CSF leakage, MRI and CT imaging of her head showed evidence of CSF extravasation and sagging brain. She also had complete but transient resolution of her symptoms after her previous trials of EBP. The diagnosis of IH remained reasonably convincing to us based on radiographic evidence and her clinical course. The decision was made to augment the EBP with fibrin sealant.

An 18-gauge Tuohy needle was inserted midline at the T12-L1 level. Loss of resistance was achieved and 5 mL of contrast was injected to confirm proper placement of the needle in the epidural space. A total of 5 mL of the fibrinogen component of fibrin sealant was first injected. The needle was flushed with 5 mL of saline followed by 5 mL of the thrombin component of fibrin sealant. An additional 5 mL of saline was injected to flush the needle followed by gradual injection of autologous venous blood. Only 7 mL of blood was injected due to the onset of bilateral leg pain. The patient already had significant relief midway through the procedure and her headache had nearly resolved upon completion. Two days post procedure, she had no headache upon ambulating and standing for a 20-minute shower. However, she was complaining of sinus pressure with blood-tinged nasal drainage. Given the change in the characteristics of her headache, a new onset of sinus congestion was suspected. She was discharged 2 days later. On a follow-up phone call, she reported that her headache

was resolved about 2 months later with no recurrence in the following 2 years.

Patient 5

Patient 5 was a 58-year-old woman, 157 cm and 70 kg, with a history of lumbar fusion for spondylolisthesis followed by the implantation of an intrathecal hydromorphone pump for failed back surgery syndrome. She had a dural puncture during a trial placement of a spinal cord stimulator at the spinal level of L1-2 at an outside hospital. Since then, she developed severe positional headache with pain localizing in the frontal and occipital regions. The headache was described as constant, throbbing, cramping, and stabbing. Other cardinal symptoms included unilateral hearing loss, weakness, intermittent spells of confusion, insomnia, nausea, and vomiting. The headache was exacerbated with upright position and relieved by lying flat. MRI of her spine demonstrated postoperative changes from her previous lumbar surgery. Conservative measures including bed rest, hydration, and opioid had failed. Prior to presentation, she had 3 trials of EBP in the past 10 months with only 50% of headache relief each time lasting several days. She also required central venous catheterization during her third EBP due to difficult intravenous access. The headache confined her to bed for most of the day and negatively impaired her quality of life. The decision was made to proceed with a trial of percutaneous patching with fibrin sealant due to recurrent failures of EBP and the likelihood of difficult intravenous access.

With the patient in a prone position, an 18-gauge Tuohy needle was introduced into the epidural space at the L1-2 level using the loss-of-resistance technique. Contrast dye was injected to confirm proper placement under fluoroscopic guidance. A total of 5 mL of fibrinogen solution was administered into the epidural space. A volume of 1 mL of normal saline was used to flush the needle followed by an injection of 5 mL of thrombin into the epidural space. Upon completion of the procedure, the patient had immediate relief of her headache. A second trial of fibrin sealant was repeated due to recurrent headache about 2 months later. Again, she had complete relief of her headache after the procedure. The patient returned to our clinic 14 months after her second percutaneous patching with fibrin sealant with recurrence of her headache. Percutaneous injection of fibrin sealant was performed for the third time. The patient did not seek further treatment for the following 4 months and remained asymptomatic since the third trial of percutaneous patching with fibrin sealant. This case was recently published as a single case report in a peer-reviewed journal (13).

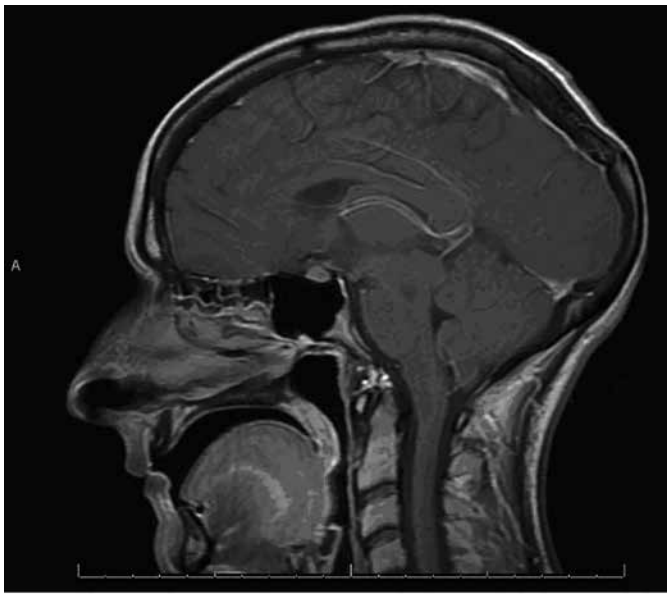

Fig. 3. Sagittal T1-weighted magnetic resonance imaging of the brain demonstrating mild downward slumping of the midbrain consistent with intracranial hypotension.

RESULTS

Five consecutive patients with refractory IH who underwent percutaneous injection of fibrin sealant were identified through our retrospective chart review. All of them had failed conservative measures including conventional EBP. Characteristics of our patients are summarized in Table 1. All patients were Caucasian. Their ages ranged from 27 to 62 years, with a median age of 47 years. There were 2 men and 3 women, for a male-to-female ratio of 1:1.5. Three patients had secondary IH: one from unrecognized durotomy during a lumbar laminectomy and 2 from a postlumbar puncture injury of the dura. The other

Table 1. Demographics, patient characteristics, indications, clinical outcomes, and complications.

Pt No.	Age (yrs)/ Gender	Height (cm)	Weight (kg)	Body Mass Index (kg/m^2)	No. of Epidural Blood or Saline Patches Prior	Etiology of Dural Tear	Duration of Headache (mos)	Volume of Blood-Fibrin Sealant Patch (mL)	Spinal Level of Epidural	Site of CSF Seak	No. of Repeat Trials of Fibrin Sealant	Complications	Follow-up interval (months)	Comments
1	62/M	172	92	31.8	1	Post-laminectomy CSF leak	2	30	L2-3	L4-S1	0	None	24	Excellent result with no recurrence
2	47/M	180	89	27.4	6	Spontaneous IH from mechanical trauma after MVA	5	35	T4-5	T3-8	1	None	23	Poor result and required surgical duroplasty
3	39/F	108	106	37.2	2	Spontaneous IH likely from trivial trauma	1	12-40	T9-10	T8	1	None	18	Excellent result with near complete resolution of symptoms
4	27/F	163	55	20.9	2	PDPH	0.25	27	T12-L1	Lumbar	0	None	15	Excellent result with no recurrence
5	58/F	157	70	27.7	3	PDPH after spinal cord stimulator implantation	10	10	L1-2	L1-2	2	None	19	Good result with recurrence twice requiring repeat fibrin sealant patching

2 patients had spontaneous IH likely related to trivial trauma. The volume of epidural injectate ranged from 10 to 40 mL, with a mean of 25.7 mL. Four of the 5 patients (80%) were successfully treated with percutaneous fibrin sealant patch. Of these 4 patients, one patient (25%) had recurrent headache within one year but was successfully treated with repeat percutaneous fibrin sealant patch. One patient (20%) with spontaneous IH ultimately required surgical duroplasty for definitive repair. The nonsurgical patients were available for follow-up at 15- to 24-months post procedure, with a mean of 20 months. Of the 4 patients with complete recovery of their symptoms, one patient had intermittent, transient episodes of orthostatic headache from straining activities such as coughing, sneezing, and heavy lifting. None of the 5 patients had any adverse events from percutaneous fibrin sealant patch.

LITERATURE REVIEW RESULTS

We performed a literature search to identify relevant articles on the PubMed/MEDLINE database since inception. We also reviewed the reference list of these publications carefully to identify additional studies. The following keywords and their respective combinations were used in this search: “percutaneous,” “epidural,” “headache,” “fibrin glue,” “fibrin sealant,” “CSF leak,” and “intracranial hypotension.” The inclusion criteria used were all studies including abstracts, case reports, review articles, case series, and controlled trials. Publications that were excluded from this review included those that were not written in English or did not specifically

address the epidural use of fibrin sealant for the treatment of IH. We ultimately reviewed a total of 16 peer-reviewed publications, one abstract, one in vitro study, and 2 in vivo studies for clinically relevant information.

DISCUSSION

Although the frequency of refractory IH remains relatively low, as the majority of IH cases resolve spontaneously, persistent CSF leakage can pose considerable morbidity, especially when early diagnosis and proper treatment are delayed (1). IH is treated conservatively in a stepwise fashion with increasing invasiveness. When conservative measures have failed, EBP can be performed with a relatively high degree of success (1,3,4). Despite these measures, IH may remain refractory in a small subset of patients. Managing patients with IH refractory to conservative measures including EBP can be challenging due to the paucity of alternative nonsurgical therapies. If left untreated, persistent CSF leakage can lead to fistula formation, resulting in potentially life-threatening complications such as cortical venous thrombosis and subdural hematomas (4,14). Early suspicion, correct diagnosis, and immediate treatment of IH are essential. Avoidance of surgical procedures with possible associated residual complications is desirable when possible.

Fibrin sealant has been extensively studied in a variety of neurosurgical, otolaryngology and facial plastic procedures for its safety profile and efficacy in hemostatic, adhesive, and sealing capabilities (15,16). It is a sterile, commercially available product manufactured from pooled human plasma consisting of 2 components that are serologically tested to ensure viral clearance (14). The first solution contains mainly a sterile concentrate of human fibrinogen dissolved in sterile water with pH levels ranging from 6.7 to 7.2 (17). The second solution contains human thrombin that dissolves in calcium chloride with a pH of 6.8 to 7.2. Both vials need to be thawed and used within 30 days if refrigerated or 24 hours if stored at room temperature. Upon mixing individual solutions of the 2 components, the formation of a pastry-like layer will adhere to the tissue surface by undergoing the last step of the coagulation cascade, in which thrombin cleaves fibrinogen to generate a fibrin clot (18). Meta-analysis of surgical outcomes after the use of fibrin sealant has demonstrated improved outcomes by reducing perioperative blood loss and the subsequent need for allogenic blood transfusion with no increase in the incidence of infection, hematoma formation, or death (19). Literature review also supports the benefits of fibrin sealant in creating a watertight dural seal (20). As demonstrated in a swine model, an injection of 1.4 mL of fibrin sealant was effective against a CSF pressure of 24.5 cm H_2O (21). Likewise, fibrin sealant could resist a pressure of 25 to 35 cm H_2O in an in vitro model simulating a continuous CSF leak secondary to dural puncture with a 17-gauge Tuohy needle (22). Fibrin sealant also has an acceptable safety profile with few adverse effects reported since 1987, most of which were speculative rather than conclusive in nature (20,23).

Of the 5 patients with refractory IH in our case series, all of them had failed conservative measures including EBP. Four of the 5 patients (80%) were successfully treated with percutaneous injection of fibrin sealant. One of these 4 patients (25%) had recurrent headache requiring repeat trials of percutaneous fibrin sealant patch. Patient 2 remained symptomatic despite 2 trials of percutaneous patching with fibrin sealant. He eventually underwent surgery for dural closure at an outside hospital. Intraoperatively, the dural defect was found to have a size of greater than 10 mm. With such a large size of dural defect, it was not surprising to us that our percutaneous approach had failed. Mihlon et al reported a retrospective case series of 9 patients with the diagnosis of postsurgical durotomy who underwent CT-guided percutaneous patching with blood. He found that the percutaneous approach was unlikely to be effective in those patients with dural defects of greater than 5 mm and the presence of pseudomeningocele (24). CSF from a small leak was believed to be more easily absorbed, while marked outflows of CSF through a large dural defect could increase likelihood of developing a pseudomeningocele, complicating the ability to repair with a blood patch (25). Interestingly, patient 1 in our case series had a positive outcome despite the presence of pseudomeningocele. This apparently contradictory finding might be attributed to the use of fibrin sealant and the large volume of injectate in our patients. Clinical reports of successful use of fibrin sealant to seal CSF leaks following

percutaneous aspiration of pseudomeningocele for similar indications have also been demonstrated in the recent literature (26-28). We believe that the ability of fibrin sealant to withstand high hydrostatic pressure might be worthy of consideration in cases with dural defects greater than 5 mm, but less than 10 mm, and the presence of pseudomeningocele (25). Our case series supports the idea that percutaneous injection of fibrin sealant should be attempted in the presence of a large dural defect and pseudomeningocele with the understanding that fibrin sealant is generally thought to be superior in tensile strength and clotting ability than a natural blood clot. Further scientifically rigorous studies would be warranted, though difficult, to validate this hypothesis.

Notably, we were not able to follow precisely the protocol in the studies performed by Franzini et al in 2010 and 2013, in which the fibrinogen and thrombin components of fibrin sealant were mixed immediately before injection. Injecting this highly viscous mixture through an 18-gauge Tuohy needle proved to be extremely challenging for us. As demonstrated in patient 2 of our case series, we were only able to inject 5 mL of the fibrin sealant through the Tuohy needle due to the rapid congealing of the coagulum after mixing of the fibrinogen and thrombin. Rapid fibrin cross-linking permitted only a small injected volume before injection was halted by high resistance. We thereby administered fibrinogen first, followed by a small bolus of saline to flush the needle prior to injection of thrombin to prevent formation of an occlusive clot in the needle.

There is a paucity of high-quality studies in the current literature on percutaneous fibrin sealant patching for IH. A comprehensive review of the literature revealed a total of 2 prospective case series, 4 retrospective case series with one in abstract format, and 11 case reports, as shown in Table 2 (7,13,16,18,27-38). There were no randomized controlled trials, only lower-quality studies including case reports and case series. An analysis of the available data showed a total of 209 patients with 86 men and 123 women, for a male-to-female ratio of 1:1.4. The mean patient age was 46.9 years (range, 15 to 74 years). There were a total of 162 reported cases of spontaneous IH associated with trivial trauma, meningeal diverticulum, connective tissues disorder, or unknown etiology; and 39 cases of secondary IH associated with postsurgical durotomy, accidental dural puncture from neuraxial procedures, and intrathecal catheterization for drug delivery systems. Of the 8 remaining patients from a study conducted by Elwood et al, 2 patients had spontaneous IH and the other 6 patients only had a reported diagnosis of "intracranial hypotension headache" (38). We were not able to differentiate whether these cases were spontaneous or secondary IH. The most common site for percutaneous injection of fibrin sealant was the lumbar epidural space. This finding was skewed because all patients in the 2 largest studies consisting of 28 and 80 patients by Franzini et al in 2010 and 2013, respectively, underwent percutaneous intervention at the lumbar level regardless of the actual site of CSF leakage (7,36). The authors abandoned attempts to localize CSF leaks by imaging, treating symptoms empirically.

Upon review of the data in the current literature, the reported success rates of percutaneous fibrin sealant patch for IH varied from 12.5% to 100% (7,13,16,18,27-38). By analyzing the available data in the literature, we found that refractory cases of spontaneous IH responded less favorably than those of secondary IH. In one retrospective study consisting of 45 patients with spontaneous IH refractory to conservative measures and EBP, the efficacy of percutaneous fibrin sealant injection was found to be 30% (35). Among these 15 patients with favorable responses, 9 of them had excellent outcomes with minimal to no symptoms and 6 of them had mild improvement of symptoms. None of them required any surgical interventions. However, the efficacy would have been 20% (9 of 45) if it were computed based on complete resolution of symptoms rather than the need for operative repair, suggesting potential bias. Two other small case series conducted by Schievink et al also reported only 25% and 50% success rates in subgroups of 8 pediatric and 4 adult patients, respectively, having spontaneous IH refractory to conservative measures and EBP (31,39). In contrast, 2 large case series of 28 and 80 patients with spontaneous IH conducted by Franzini et al in 2010 and 2013 reported success rates of 70.4% and 87% at 3-month follow-up assessments, respectively (7,36). Not surprisingly, the reported higher success rate from these 2 studies might be related

Table 2. Previous case series and case reports from literature review including summary of patient characteristics, type of study, intervention, clinical outcomes, complications, and overall success rate of epidural fibrin sealant patch in patients with intracranial hypotension.

Author, Yr	Patient Population and Indication	Etiology	Technique	Spinal Level(s)	Source of Fibrin Sealant	Outcome Measures	Results	Complications	Comments	Success rate	Type of Study
Patel et al, 1996 (27)	6 consecutive pts with CSF leaks after spinal surgery	Secondary	A total of 4 to 18 mL of equal volumes of autologous/ homologous cryoprecipitate mixed with thrombin-calcium chloride-iopamidol was injected	Lumbar	Not specified	Relief of symptoms	50% of pts with either resolution or marked reduction of symptoms at follow-up visits ranging from 3 to 12 mos	1/6 pt with suspected aseptic meningitis	50% of patients with no relief of symptoms and required surgical repair of dural tear	50%	Retrospective case series
Gerritse et al, 1997 (29)	3 advanced cancer pts with persistent CSF leak during long-term intrathecal catheterization	Secondary	3 to 4 mL of fibrin sealant was injected	Lumbar	Tisseel	Assessment of neurological symptoms and signs of CSF leak	No increase in neurological impairment of all 3 pts	None	2/3 patients' death reported in 2 to 3 weeks following the procedure due to natural progression of their advanced cancer and 1/3 patient had no recurrent CSF leak at 10-months follow-up	100%	Case report
Crul et al, 1999 (30)	1 pt with persistent PDPH after lumbar puncture despite 3 trials of EBP	Secondary	3 mL of fibrin sealant was injected	L3-4	Not specified	Overall improvement	No recurrent headache at 7-mo follow-up	None	-	100%	Case report
Kamada et al, 2000 (26)	1 pt with IH headache due to persistent CSF leak at the level of C2 despite 2 trials of EBP	Spontaneous	2.8 mL of fibrin sealant followed by 0.5 mL of normal saline flush	C2	Beriplast P	Improvement of neurological symptoms and repeat MRI and CT myelography	No recurrent symptoms at 1-mo follow-up	None	No major difficulty injecting fibrin glue through the epidural catheter	100%	Case report
Patel et al, 2000 (28)	23 pts with CSF leak after spinal surgery treated with percutaneous placement of fibrin sealant	Secondary	Equal volume of autologous/ homologous cryoprecipitate mixed with thrombin-calcium chloride-iopamidol solution was injected ranging from 4 to 24 mL in total volume	Not specified	Not specified	Relief of symptoms	65% of pts with symptoms either decreased or resolved markedly after procedure	22% of pts had aseptic meningitis	Aseptic meningitis was resolved following 2-3 days of conservative therapy including bed rest and analgesics	65%	Retrospective case series

Table 2 (cont.). Previous case series and case reports from literature review including summary of patient characteristics, type of study, intervention, clinical outcomes, complications, and overall success rate of epidural fibrin sealant patch in patients with intracranial hypotension.

Author, Yr	Patient Population and Indication	Etiology	Technique	Spinal Level(s)	Source of Fibrin Sealant	Outcome Measures	Results	Complications	Comments	Success rate	Type of Study
Schievink et al, 2004 (31)	4 pts with confirmed diagnosis of spontaneous IH who failed conservative treatment and the placement of at least 3 EBP	Spontaneous	4 to 20 mL of fibrin sealant was injected through a transforaminal approach either unilaterally or bilaterally depending on the site of CSF leaks	C4-5, C5-6, C6-7, T12-L1	Tisseel	Resolution of symptoms	Two of 4 pts became asymptomatic within 24 to 48 hrs of procedure with no recurrence at 6-mo and 12-mo follow-up	None	50% of patients avoided surgery in this small group of patients	50%	Case report
Gladstone et al, 2005 (32)	1 pt with 3-mo history of chronic exertional headache with orthostatic features due to spontaneous CSF leak who had 2 unsuccessful trials of EBP	Spontaneous	3.5 to 4 mL of fibrin sealant was injected into the epidural space surrounding the T2 and T3 nerve root and theca	T2 and T3	Tisseel	Overall improvement	Remained free from headache at 6-mo follow-up	None	-	100%	Case report
Schievink et al, 2007 (33)	1 pt with spontaneous IH due to CSF leak associated with a thoracic meningeal diverticulum	Spontaneous	2 mL of fibrin sealant was injected	Thoracic	Tisseel	Level of consciousness, GCS score, and ability to ambulate	Headache free at 6-mo follow-up	None	-	100%	Case report
Trentman et al, 2008 (34)	1 pt with refractory postural headache due to multilevel thoracic CSF leaks despite 2 trials of EBP	Spontaneous	3.5 to 5 mL of fibrin sealant was injected into the right T4 neural foramen and left T11-12 via a transforaminal approach	T4, T11-12	Tisseel	NRS-11, overall improvement, repeat MRI of the cervicothoracic spine	Headache remains refractory despite 7 EBP and 2 CT-guided fibrin glue injections	None	The patient never achieved complete pain relief	0%	Case report
Ospina J et al, 2009 (35)	45 pts with diagnosis of spontaneous IH unresponsive to conservative therapy	Spontaneous	Not specified	Not specified	Not specified	Improvement of symptoms and if surgery is required	30% of pts showed significant improvement with minimal to no symptoms and no surgery was required	None	-	30%	Retrospective case series

Table 2 (cont.). Previous case series and case reports from literature review including summary of patient characteristics, type of study, intervention, clinical outcomes, complications, and overall success rate of epidural fibrin sealant patch in patients with intracranial hypotension.

Author, Yr	Patient Population and Indication	Etiology	Technique	Spinal Level(s)	Source of Fibrin Sealant	Outcome Measures	Results	Complications	Comments	Success rate	Type of Study
Fanzini et al, 2010 (36)	28 pts with diagnosis of spontaneous IH resistant to conservative measures	Spontaneous	5 mL of fibrin sealant mixed with 5 mL of homologous blood and 3 mL of hydrosoluble contrast medium	L1-2	Not specified	Relief of clinical symptoms and MRI findings	At 3-mo follow-up, 70.4% (19/27) remained asymptomatic. At 1-yr follow-up, 81.8% (18/22) remained asymptomatic. At 3-yr follow-up, 83.3% (10/11) had complete resolution of symptoms; 8.3% complained of sporadic orthostatic headaches	None	8.4% of patients failed to follow up with them at 3-years follow-up	70.4% at 3-months follow-up, 81.8% at 1-year follow up; 83.3% at 3 years follow-up	Retrospective case series
Fontaine et al, 2012 (37)	1 pt with spontaneous IH	Spontaneous	Not specified	T12	Tisseel	Regression of all symptoms and radiological abnormalities	Not specified	None	A case of severe spontaneous IH with atypical symptoms mimicking Ménière's disease	100%	Case report
Freeman et al, 2013 (16)	3 pts with PDPH secondary to CSF leak from implantation or removal of intrathecal drug systems	Secondary	Case 1: 3 mL of fibrin sealant was injected; case 2: a mix of 10 mL of fibrin sealant and 2 mL of blood was injected; case 3: 7 mL of fibrin sealant was injected	Case 1 and 2: L2-3; case 3: L1-2	Not specified	Overall improvement	Case 1 and 2: headache free at 2-yr follow-up; case 3: headache free at 1-yr follow-up	None	-	100%	Case report
Franzini et al, 2013 (7)	80 pts with spontaneous IH resistant to conservative treatments for at least 2 mos	Spontaneous	5 mL of fibrin sealant mixed with 5 mL of homologous blood and 3 mL of hydrosoluble contrast medium	L1-2 or lower levels	Not specified	Overall improvement	87% of pts had complete regression of symptoms within 3 mos; 13% of pts required a second treatment, reaching a global success rate of 90%	None	25% of patients had recurrence of the disease within 2-8 years after the procedure, requiring a repeat blood patch	87% at 3-month follow up	Prospective case series

Table 2 (cont.). Previous case series and case reports from literature review including summary of patient characteristics, type of study, intervention, clinical outcomes, complications, and overall success rate of epidural fibrin sealant patch in patients with intracranial hypotension.

Author, Yr	Patient Population and Indication	Etiology	Technique	Spinal Level(s)	Source of Fibrin Sealant	Outcome Measures	Results	Complications	Comments	Success rate	Type of Study
Mammis et al, 2014 (18)	2 pts with PDPH: Case 1 had poor venous access and developed PDPH after implantation of intrathecal pump; case 2 had persistent PDPH despite 3 trials of EBP after a trial of spinal cord stimulator placement	Secondary	5 mL of fibrin sealant was injected in case 1 but terminated due to development of low back pain.	Case 1: L2-3; case 2: L1-2	Tisseel	Overall pain relief	Case 1: resolution of headache postoperatively; case 2: resolution of headache at 2-wk follow-up	None	-	100%	Case report
Elwood et al, 2016 (38)	8 pts with refractory IH headache	Either spontaneous or secondary	Up to 10 mL of fibrin sealant was injected until sensation of paresthesia. Less than 1 mL of autologous blood was used to flush the needle. Once paresthesia had resolved, the mix of 10 mL of autologous blood and 3 mL of contrast was injected until pressure paresthesia recurred. Saline or 1% lidocaine was used to flush the epidural needle before withdrawal.	L1-2	Tisseel	NRS-11, duration of relief, functional improvement, and patient satisfaction	Decreased pain scores at 3-mo follow-up among 4/8 pts	None	-	12.5% with complete resolution of symptoms; 37.5% with partial relief of symptoms	Prospective case series
Wong & Monroe, 2016 (13)	1 pt with persistent PDPH despite 3 trials of EBP after a trial of spinal cord stimulator placement	Secondary	5 mL of fibrinogen followed by 1 mL of normal saline and 5 mL of thrombin	L1-2	Evicel	Overall pain relief	Resolution of PDPH for the following 2 mos	None	Required repeat trial of fibrin glue followed by complete resolution of PDPH for the following 6 months	100%	Case report

to the selection of patients who failed conservative measures, but not conventional EBP. The authors performed untargeted EBP on all patients to support their hypothesis that spontaneous IH could be treated simply by increasing the epidural pressure to achieve equilibrium between the epidural and spinal pressure, regardless of the actual site of the CSF leak. Despite the lower success rate of untargeted EBP compared to targeted EBP in patients with spontaneous IH from other studies (40-42), encouraging outcomes from the studies of Franzini et al implied that the addition of fibrin sealant to the blood patch might contribute to a higher success rate by enhancing the adhesive and sealing effect on a dural breach. A recent small prospective case series enrolled a total of 8 patients with refractory IH, and they found a 12.5% (1 of 8) and 37.5% (3 of 8) rate of excellent and good outcomes, respectively, for an overall favorable response of 50% at the 3-month follow-up (38). These findings, however, were not consistent with those reported by Franzini et al. Such discrepancy might be related to 2 factors. First, the sample size was much smaller in this prospective case series. Second, the author enrolled patients with IH refractory to both conservative measures and at least one trial of EBP, instead of those resistant to conservative measures only.

Despite variations among different studies, patients with spontaneous IH refractory to measures including EBP consistently reported less favorable responses to percutaneous fibrin sealant patch (31,35,39). These patients often presented with unidentifiable, multi-level, and/or ventral CSF leaks, resulting in lower response rates than those with secondary IH (43,44). Despite the small size of our case series, our finding of a lower success rate in patients with spontaneous IH was consistent with the analysis of the current data in the literature.

On the other hand, favorable results ranging from 50% to 100% had been reported in refractory cases of secondary IH (13,16,18,27-30). Two retrospective case series of 6 and 23 patients with persistent CSF leaks after spinal surgery found success rates of 50% and 65%, respectively (27,28). Of the 29 patients in these 2 studies, a total of 6 patients (20%) may have incurred aseptic meningitis from inadvertent injection of fibrin sealant into the subarachnoid space. All 6 patients fully recovered after a few days of conservative measures including bed rest and oral analgesics. Less encouraging results from these 2 studies might be related to the use of autologous and homologous cryoprecipitate. Indeed, commercial fibrin sealant has been shown to be more efficacious than that harvested from cell saver or other forms of preparations in rat models (45). Two important distinctions between the noncommercial and commercially-available fibrin sealants were the viral inactivation step of commercial fibrin sealant and the use of bovine thrombin in noncommercial fibrin sealant (46). These characteristics might explain the observation of 6 cases of aseptic meningitis from these 2 studies. Exposure to bovine thrombin was also found to be associated with acquired Factor V deficiency (46). Commercial fibrin sealants have several advantages. They contain a very concentrated level of clotting factors and produce more predictable outcomes given the consistency in their manufacturing processes (47). In noncommercial fibrin sealant, the level of clotting factors is less predictable and concentrated. Depending on the functional levels of clotting factors and reconstitution process, the formulations of noncommercial fibrin sealant could vary significantly, producing inconsistent outcomes (47). Despite the relatively low rate of success from these 2 studies, all reported cases from other studies achieved complete recovery of their symptoms after 2 or fewer trials of percutaneous fibrin sealant patch (13,16,18,29,30). The majority of these cases highlighted the long-term benefits of percutaneous fibrin sealant patch in refractory cases of IH, regardless of spontaneous or secondary etiology.

In our case series, we performed percutaneous patching by injecting a mix of fibrin sealant and autologous venous blood in a volume of 10 to 40 mL, with a mean of 25.7 mL. Review of the current literature found that patching volumes varied widely from 2.8 to 20 mL (7,13,16,18,26-34,36,38,39). The optimal volume for fibrin sealant remains to be determined. We believed that the optimal volume should be determined clinically, based on the specific leak type and location. As demonstrated in our present case series, we favor the use of a larger volume including fibrin sealant, compared to other studies in the literature. One previous case report and a small retrospective case series implied that a large-volume blood patch might be useful in cases of spontane-

ous IH (44,48). We intended to use a large volume based on the understanding of the pathophysiology of spontaneous IH proposed by Franzini et al in 2010 (36). Hypothetically, percutaneous patching with blood products underwent a 2-step process (1,3,4). First, the injection of blood products into the epidural space would have increased intrathecal pressure by direct compression of the dura. Second, the injectate would have sealed the dural defect from further CSF leakage by formation of a clot. In some cases, a small volume of injectate would have been adequate for treatment, particularly in the setting of secondary IH. Positive outcomes with small injected volumes were reported in several refractory cases of secondary IH, where definite sites of CSF leakage were known (13,16,18,29,30).

On the contrary, a small volume of injectate might be inadequate to treat spontaneous IH. The sites of CSF leakage in patients with spontaneous IH were often difficult to identify, such as in those with rapid and ventral CSF leaks (43,44). These patients often present with multiple sites of leakage possibly due to intrinsically fragile or diffusely fenestrated dura (7,44). In our case series, we added autologous venous blood to fibrin sealant to enhance the volume of injectate in the epidural space. Using a larger volume of injectate would have allowed fibrin sealant to spread more diffusely throughout the epidural space, augmented by autologous clotting factors in the blood. Hypothetically, a large volume of injectate could have reached undiscerned sites of CSF leakage in these patients. The complete filling of the epidural space with injectate would have distributed the forces of increased epidural pressure more evenly throughout the epidural space. Upon reversal of the transdural pressure gradient, the balance of CSF dynamics between the intrathecal and epidural spaces might have been achieved and CSF would have ceased to drain into the epidural venous system (7,36). By combining fibrin sealant with blood as an adjunct to generate a large volume injectate, we believed the regenerative and therapeutic effect on dural defects in patients with spontaneous IH could be substantially enhanced. We chose whole blood as an additive to the fibrin sealant because only these 2 injectates showed efficacy in maintaining a sustained CSF pressure upon administration into the epidural space over a 240-minute period using a rat model (49). Other injectates such as dextran 40, hetastarch, and normal saline bolus only provided a transient effect on maintaining CSF pressure, suggesting relatively rapid absorption or diffusion of these compounds from the epidural space (49). Currently, there is no clear evidence to indicate that a large volume of percutaneous fibrin sealant patch exhibits greater therapeutic efficacy than small-volume injectate in patients with IH. Further studies should be considered to evaluate the effect of larger-volume fibrin sealant patch on patients with refractory IH.

After more than 40 years of clinical use in surgical patients for hemostatic and adhesive capabilities, there were anecdotal reports of adverse effects associated with the use of fibrin sealant near dura mater. The most commonly encountered adverse reaction was aseptic meningitis, with a total of 9 suspected cases (23,27,28,50). Other adverse events – including 4 cases of allergic reactions or anaphylactic shock possibly related to the use of aprotinin, one case of meningitis with a fatal outcome, one case of venous air embolism using a spray applicator, one case of adhesive arachnoiditis, and one case of epidural hematoma due to obstruction of the epidural drain – were also reported in a variety of neurosurgical cases (20,51,52). Infectious disease transmission has long been a potential safety concern with the use of fibrin sealant (18). This homologous commercial product was extracted from pooled human plasma, although no such adverse event had been documented (18). These complications were postulated to be caused by inadvertent injection or migration of fibrin sealant into the intravascular or subarachnoid space (27). Most of these adverse events remained merely speculative. Patients in our case series did not develop any clinically significant adverse events within an average follow-up duration of 20 months. It is important to always consider these potentially life-threatening complications when discussing the use of fibrin sealant as a therapeutic option with patients.

Our case series was mainly limited by the small number of patients and its retrospective nature. Although our institutional chart review sought patients over a period of 6 years, all of the patients in our present case series underwent the percutaneous patching with fibrin sealant during the last 3 years reviewed, limiting the follow-up interval of our patients. Review of the current literature found no randomized controlled trials for the efficacy of percutaneous

patching with fibrin sealant in patients with refractory IH, consistent with its low prevalence in the general population.

CONCLUSION

The present case series demonstrated positive results in a small set of patients, with 80% experiencing substantial relief or complete resolution of IH symptoms. Our extensive literature search identified only studies of low-quality evidence, including case series and case reports, which do not support drawing definitive conclusions regarding the efficacy of percutaneous fibrin sealant patch for the treatment of refractory IH. Despite the lack of high-quality studies, our present case series and review of the literature suggest that percutaneous patching with fibrin sealant is a well-tolerated therapeutic option with promising outcomes for refractory cases of IH headache. The risk of infectious complications and other reported adverse events has been low. Until now, it is unfortunate that the available data on the efficacy and safety of percutaneous patching with fibrin sealant has been derived mostly from lower-evidence retrospective case series with the potential of bias. With the growing interest in seeking alternatives for treatment of refractory IH to avoid required surgical intervention, there is a substantial need for high-quality, evidence-based studies. Given the low prevalence of refractory IH, a controlled randomized prospective trial may not be feasible. A well-designed prospective cohort study would be an acceptable alternative to validate the effectiveness of this approach.

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Author Contributions

BRM designed the original study. KW performed the chart review, literature review, and writing of the manuscript. SMP and BRM reviewed and edited the manuscript. All authors reported no conflicts of interest and approved the final version of this manuscript.

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