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TESI DI LAUREA

Assessing Epidural Blood Patch clinical outcome in Spontaneous Intracranial Hypotension: A Multicenter study

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ABSTRACT

Background and Purpose: Spontaneous Intracranial Hypotension (SIH) is characterized by reduced cerebrospinal fluid (CSF) pressure, typically resulting in orthostatic headaches and various neurologic symptoms which significantly impacts patients' quality of life. This study aims to evaluate the efficacy of epidural blood patching (EBP) in alleviating symptoms of SIH and assesses patient overall satisfaction post-procedure.

Methods: This multicenter retrospective study is based on a cohort of 52 SIH patients. After a screening process, 30 patients meeting the inclusion criteria were considered (mean age 46.8 years, 67% females). The study analyzed clinical records, the impact of headaches on daily living (HIT-6 score), and overall patient satisfaction (OS) post-EBP. Follow-up durations ranged from 6 to 36 months.

Results: Among the 30 patients, 73% received non-targeted EBP, 13% targeted EBP, and 13% underwent both. The mean number of EBPs performed was 1.7. Follow-up revealed that one patient (3%) developed rebound intracranial hypertension, managed with acetazolamide. HIT-6 scores varied widely, with a median of 48, indicating a moderate impact on daily activities. Overall satisfaction median was 5 out of 10, with 33% reporting high satisfaction (OS $\geq$8). Despite EBP, 45% of patients experienced residual symptoms affecting their quality of life.

Discussion: The demographic profile aligned with existing literature, showing a higher prevalence in females and a mean age of diagnosis in the mid-40s. The study highlights the variability in EBP efficacy, with many patients requiring multiple treatments and some experiencing persistent symptoms. Patient satisfaction was moderate, emphasizing the need for comprehensive management strategies that address both physiological and psychological aspects of SIH.

Conclusions: EBP is a key treatment for SIH but demonstrates variable efficacy, necessitating individualized treatment plans and multidisciplinary approaches. Future research should focus on conducting long-term follow-up to enhance patient outcomes and quality of life.

1. INTRODUCTION

1.1 Definition and Discovery

Spontaneous Intracranial Hypotension (SIH) represents a fascinating yet underexplored frontier in neurology, primarily characterized by low cerebrospinal fluid (CSF) pressure with no apparent cause.

Spontaneous intracranial hypotension was first described in 1938 by Georges Schaltenbrand, a neurologist in Würzburg, member of the Nazi Medical Association. He investigated a special subtype of headaches which were often associated with changes in posture, suggesting a positional component to their symptoms. This observation led him to hypothesize that changes in cerebrospinal fluid (CSF) pressure might be involved in the genesis of these headaches, hence the name "hypoliquorrhea"[1].

1.2 Epidemiology

According to the first community-based study on the topic, the estimated incidence of spontaneous intracranial hypotension is around four cases per 100000 person-years[2], with a female to male ratio of approximately 2:1. Although this is considered a rare disease, growing recognition among health-care practitioners and increased sensitivity of diagnostic tests points to a higher true incidence[3].

1.3 Etiology

The etiology of SIH is predominantly attributed to spinal CSF leaks. Although CSF leaks can also arise from the skull base, these types of leaks do not typically cause orthostatic headache, are more commonly associated with high (rather than low) CSF pressure, and do not cause brain imaging manifestations of SIH[4]. Patients with genetic connective tissue disorders, such as Marfan syndrome or Ehlers-Danlos syndrome, are at higher risk of spontaneous spinal CSF leaks than the general population[5, 6], because of the structural weakness of the dural membranes which might render them more susceptible to CSF leakage.

1.4 Pathogenesis

According to the root cause, three types of spinal CSF leak have been described (**Figure 1**).

Type 1 leaks are typically ventrally located dural slits caused by an osteodiscogenic microspur (eg, a calcified disc protrusion or osteophyte penetrating the thecal sac. They account for approximately one-quarter of cases of SIH and are most commonly found in the in the thoracic or lower cervical spine, where calcified disks are most common[7]. Leaks due to ventral tears are often rapid, resulting in extensive epidural CSF collections. The spur may protrude into the tear, preventing healing, and necessitating a surgical resection of the spur for dural closure[8].

Type 2 leaks are leaking spinal nerve root diverticula. On surgical exploration, they have been found to represent areas of dural dehiscence that permit protrusion of the leptomeninges though the dural defect, creating a fragile outpouching prone to rupture[9]. They are found most commonly in the thoracic or upper lumbar spine, either along a nerve root sleeve or at the nerve root axilla where it joins the thecal sac. Some diverticula involve large meningeal tears that allow rapid egress of CSF, whereas others produce slow weeping of CSF with the Valsalva maneuver[10]. On imaging, leaking diverticula can mimic perineural cysts found in normal patients; however, the presence of a broad base along the thecal sac or location at the axilla of the nerve root in the context of SIH should suggest a pathologic diverticulum. Other imaging features, such as the number, size, or complexity of any given perineural cystic structure have not been shown to distinguish normal perineural cysts from leaking diverticula[11]. The presence of perineural cysts alone in the absence of leaked epidural fluid is not sufficient to establish a diagnosis of SIH because such cysts are found commonly in normal patients[11]. As an example, sacral perineural cysts (or Tarlov cysts), a commonly encountered incidental finding of which the global prevalence is estimated to be around 4% [12] are not usually associated with spontaneous CSF leakage[13].

Type 3 leaks are direct CSF-venous fistulas (CVF) between the subarachnoid space and spinal epidural veins[7]. CSF is normally reabsorbed at the level of spinal nerve roots, with transport of CSF across the wall of arachnoid villi regulated by vacuoles[14]. In contrast, CSF volume loss due to CVFs is unregulated, resulting in CSF volume depletion and intracranial hypotension. The fistula is often located along the nerve root sleeve and is associated with a perineural diverticulum in approximately 80% of cases[15]. Flow across the fistula is unidirectional because CSF pressure is physiologically maintained at a greater pressure than venous pressure[16]. CVF is a more recently recognized cause of SIH, firstly defined in 2014 thanks to direct visualization using digital subtraction myelography (DSM)[17]. Once escaped into the epidural space, CSF is rapidly absorbed by the spinal epidural venous plexus, which is often maximally dilated in the setting of SIH. Due to high CVF flow velocity, conventional imaging such as MRI and CT myelography are unable to detect the presence of contrast in epidural veins, demonstrating the diagnostic pitfall. Despite the lack of direct visualization, indirect evidence for rapid venous absorption such as contrast in the renal collection system on CT myelography or early activity of tracer in the bladder on nuclear cisternography is common[18].

While Type 1 and 2 leaks typically lead to CSF effusion from the intrathecal space to the epidural compartment, resulting in a spinal longitudinal extradural CSF collection (SLEC)[19], whereas type 3 leaks typically do not result in SLEC[7].

Figure 1. Causes of SIH. The most common causes of spontaneous spinal CSF leaks include: A) Fragile meningeal diverticula, usually associated with nerve root sleeves; B) Ventral dural tears, often causes by calcified disk protrusion or osteophytes; C) CSF venous fistula, abnormal connection between a meningeal diverticulum and segmental spinal vein

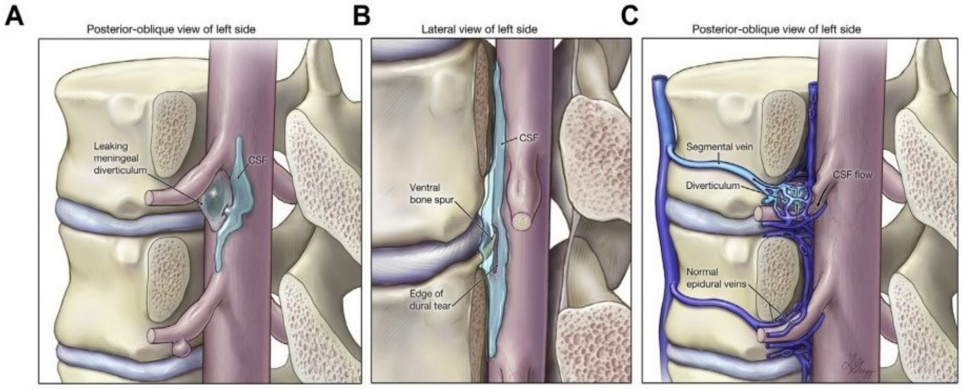


Image from: Spontaneous Intracranial Hypotension Pathogenesis, Diagnosis, and Treatment [20].

1.5 Clinical Presentation

Most patients with spontaneous intracranial hypotension present acutely with typical orthostatic headache. The headache intensifies in the upright position and diminishes after lying down[7, 21]. Patients who present with orthostatic headache can have many potential differential diagnoses. First, if patients have a recent history of lumbar puncture, peridural anaesthesia, or spinal or cranial surgery, traumatic CSF leak should be assessed. Common conditions such as sinusitis, cervicogenic headache and migraine could cause positional symptoms as well[21]. Therefore, it is important to focus on key clinical clues that can help the clinician to make a correct diagnosis.

The clinical manifestations of spontaneous intracranial hypotension are thought to result from increased efflux of CSF in the upright position, leading to traction on pain-sensitive fibres within the dura mater. Neurologic symptoms such as diplopia, dysgeusia, and vestibulocochlear disturbances are instead related to brain sagging and traction on the cranial nerves[21]. Alternatively, vestibulocochlear disturbances can result from negative intracranial pressure transmitted through the patent cochlear aqueduct and perilymph, leading to endolymphatic hydrops and Ménière’s disease[22].

Additionally, enlargement of the pituitary gland or the pituitary venous plexus, hyperprolactinaemia, galactorrhoea, and other endocrine disorders have been reported in patients with spontaneous intracranial hypotension[23].

The orthostatic characteristic can become less apparent over time, and more than a third of patients with a longer duration of illness will have non-orthostatic headache and non-headache complaints, making correct diagnosis more challenging[24]. Non-orthostatic forms of headache include thunderclap, non-positional, exertional, cough-related, and second half of the-day types[25]. It is therefore essential to evaluate the characteristics of the initial headache type and an unexplained chronic headache should be investigated further for potential spontaneous intracranial hypotension.

1.6 Diagnosis

Knowledge about spontaneous intracranial hypotension has substantially increased over the past decade, and the underlying pathological mechanisms of this disorder have been elucidated[21]. Nonetheless, diagnostic criteria for spontaneous intracranial hypotension, and the optimal assessments to use, remain topics for debate and despite advancements in diagnostic imaging, many cases are likely underdiagnosed or misdiagnosed[21]. Spontaneous intracranial hypotension was misdiagnosed in up to 94% of individuals, most commonly as migraine, meningitis, psychological disorder, or even malingering[18].

Patients presenting with orthostatic headache should have a brain MRI. A nine-point brain MRI-based score has been proposed for diagnosis of spontaneous intracranial hypotension. This score stratifies the likelihood of finding a spinal CSF leak in patients with clinically suspected spontaneous intracranial hypotension[26, 27]. The score comprises three major and three minor signs reported in **Figure 2** with a predicted value reported in **Figure 3**. The major signs (scoring two points each) are pachymeningeal enhancement, engorgement of venous sinus, and effacement of the suprasellar cistern (≤4,0 mm). The minor signs (scoring one point each) are subdural fluid collection, effacement of the prepontine cistern (≤5,0 mm), and reduced mamillo-pontine distance (≤6,5 mm). The

SIH score helps to establish if more spine imaging is warranted, because not every patient with orthostatic headache should be subjected to multiple myelograms.

To further investigate the precise CSF localisation, three dynamic myelography techniques have been described: conventional dynamic myelography, digital subtraction myelography, and dynamic CT myelography[28]. With all of these myelographic techniques, iodinated contrast media is injected into the intrathecal compartment by lumbar puncture. Patient positioning can be adapted according to the findings of previous spine MRI. As an example, suspected ventral osteodiscogenic microspur should be placed in prone decubitus while suspected rupture of a spinal nerve root cyst should be instead placed in lateral decubitus. With each of these methods, the moment that the contrast first exits the intrathecal space and enters the epidural compartment, forming a double contour, must be captured to confidently localise the vertebral level of the leakage[21]. If the initial examination did not identify the precise site of CSF leakage, during a repeat examination, the region of the presumed leakage could be narrowed.

A postmyelography CT restricted to the level of leakage should be done immediately after conventional dynamic myelography or digital subtraction myelography to identify underlying osseous pathology, such as bony spurs of the vertebral endplates or calcified disc protrusions. Because of the time required to transfer a patient from a myelogram table to a CT scanner, the temporal resolution of postmyelography CT is poor and does not generally allow for precise leak localisation[21]. Nonethless, postmyelography CT can also provide indirect evidence of CSF leakage. Some studies have shown renal pelvic opacification on postmyelography CT in patients with a CSF leak compared with patients without spontaneous intracranial hypotension[29, 30]. When postmyelography CT shows leakage of contrast but the site of the leakage cannot be localised with conventional dynamic myelography or digital subtraction myelography, dynamic CT myelography is an important technique and should be considered for leak localisation[31, 32], especially at the cervicothoracic junction, where superimposition of bony structures reduces image quality on conventional dynamic myelography or digital subtraction myelography[21].

Example of diagnostic work-up for CSF leak detection are reported in: **Figure 4** for type 1 leak; **Figure 5** for type 2 leak; **Figure 6** for type 3 leak.

Figure 2. A) Coronal T2-weighted magnetic resonance imaging (MRI) with subdural effusion (white arrowhead 1). B) Coronal T1-weighted MRI after gadolinium injection of the same patient, with dural enhancement (white arrowhead 2) and venous engorgement (white arrowhead 3). C) Sagittal T2-weighted MRI with effaced suprasellar cistern (black arrowhead 4; pathologic ≤4 mm), decreased mamillopontine distance (black arrowhead 5; pathologic ≤6.5 mm), and effaced prepontine cistern (black arrowhead 6; pathologic ≤5 mm)

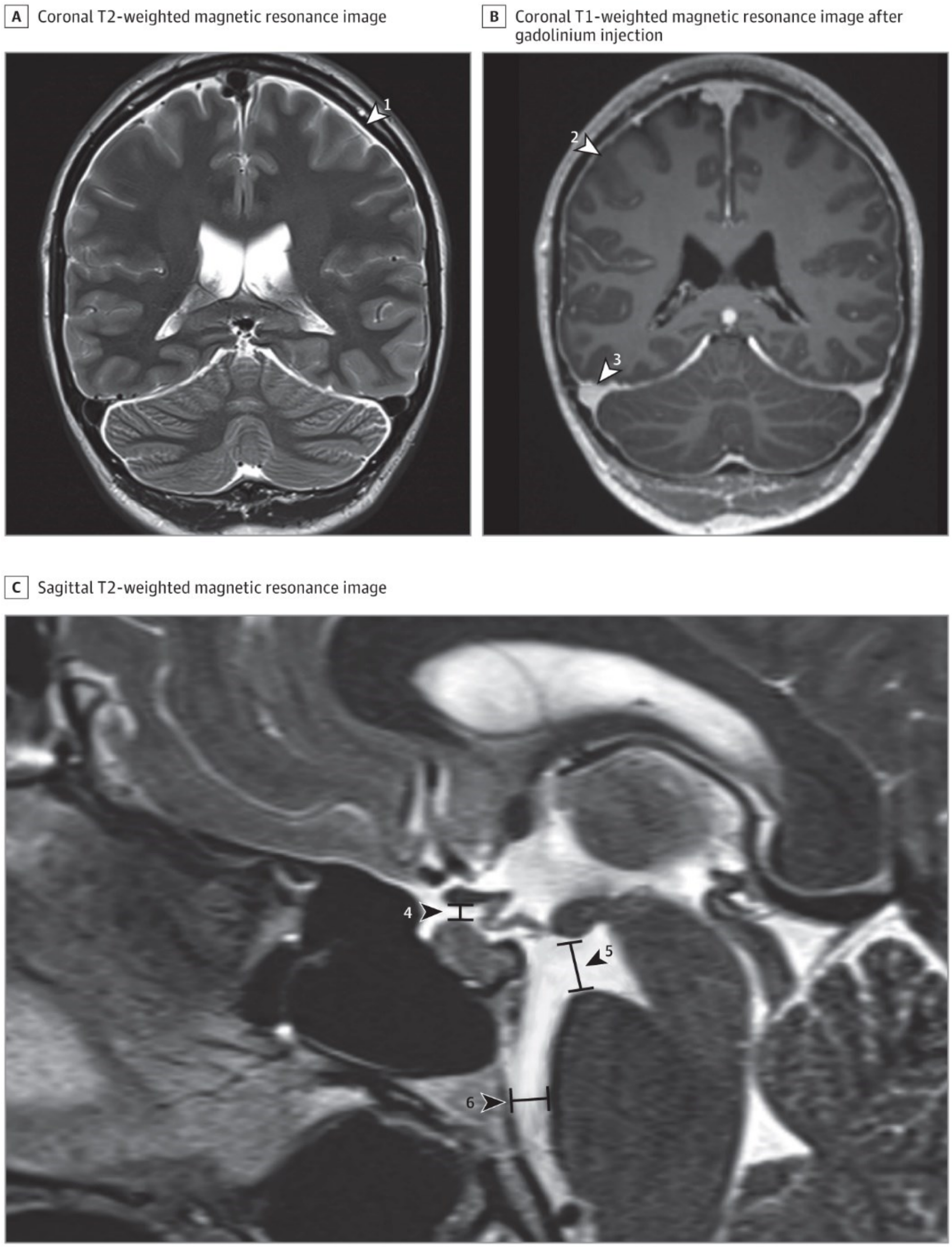


Figure 3. Six imaging signs an the relative Odds Ratio (OR) identified by Dobrocky et al [27] in predicting the final diagnostic score and the need for additional spinal imaging

Characteristic	Coefficient (95% CI)	Odds Ratio (95% CI)	*P* Value	Score Points
Engorgement venous sinus	2.95 (1.18-4.72)	19.12 (3.26-112.30)	.001	2
Pachymeningeal enhancement	4.04 (2.50-5.59)	57.01 (12.18-266.78)	<.001	2
Subdural fluid collection	1.54 (−0.10 to 3.17)	4.65 (0.90-23.92)	.07	1
Suprasellar cistern[a]	3.48 (2.36-4.60)	32.32 (10.55-99.02)	<.001	2
Prepontine cistern[b]	1.47 (0.41-2.52)	4.34 (1.51-12.47)	.007	1
Mamillopontine distance[c]	1.13 (0.07-2.19)	3.08 (1.07-8.90)	.04	1

[a] ≤4 mm.
[b] ≤5 mm.
[c] ≤6.5 mm.

Figure 4. Type 1 CSF leak A) Prone myelography showing a regular ventral profile of the dural sac (arrows) with anterior extravasation at C5–C6 into the epidural space (arrows with dot). B, C) Sagittal and axial planes Myelo-CT shows the presence of a C5–C6 disc herniation, with an osteophyte of the upper somatic margin of C6 (arrows), in the right paramedian site, probable cause of the dural tear. D) Myelo-CT also shows the presence of contrast in the epidural space (arrow with dot), anterior to the dural sac (arrow)

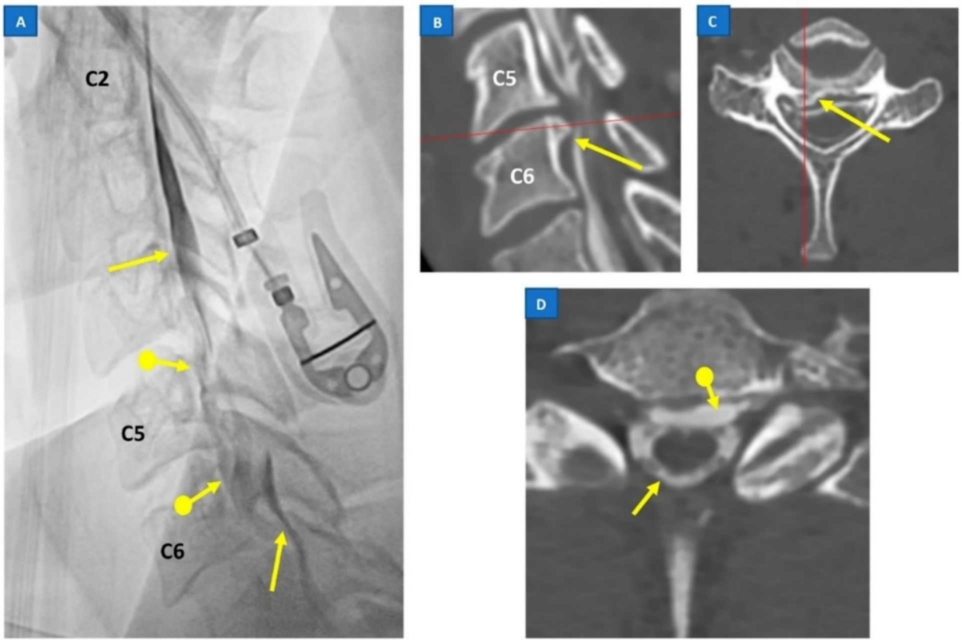


Image from: Overview of Spontaneous Intracranial Hypotension and Differential Diagnosis with Chiari I Malformation [33].

Figure 5. Type 2 CSF leak A) Schematic depiction of a proximal nerve root sleeve tear bridging the epidural and neural foraminal compartments. B-G) Images from a single patient. B) Sagittal T1WI of the brain shows the

engorged pituitary gland (open white arrow) and dural thickening on the clivus (short white arrows). C) Sagittal T1WI of the brain shows a “positive venous distension sign” with a convex undersurface of the middle third of the dominant transverse sinus (short black arrow). D) T2-weighted axial MR image of the thoracic spine shows SLEC+ (white arrows) external to the dura (white arrowhead). E) Subtracted image from a prone thoracic DSM shows a posterolateral collection of contrast (black arrow). F, G) Subtracted and nonsubtracted images from a repeat right lateral decubitus DSM show contrast leaking into the extradural space (black arrows) from a tear along the proximal aspect of the right T11 root sleeve (long white arrow). Note the BB (nipple marker) placed on the skin for landmarking (dashed white arrow)

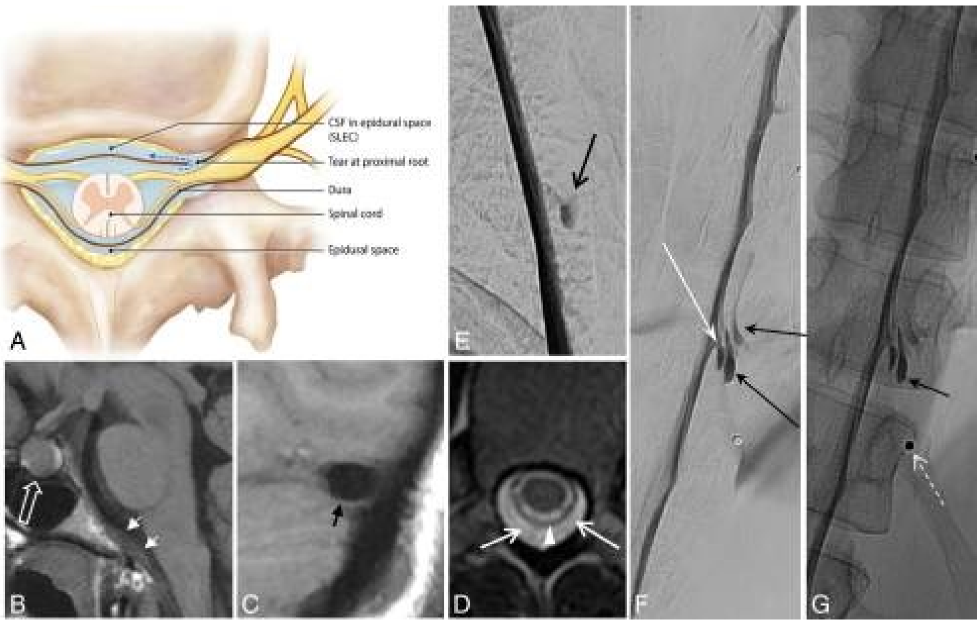
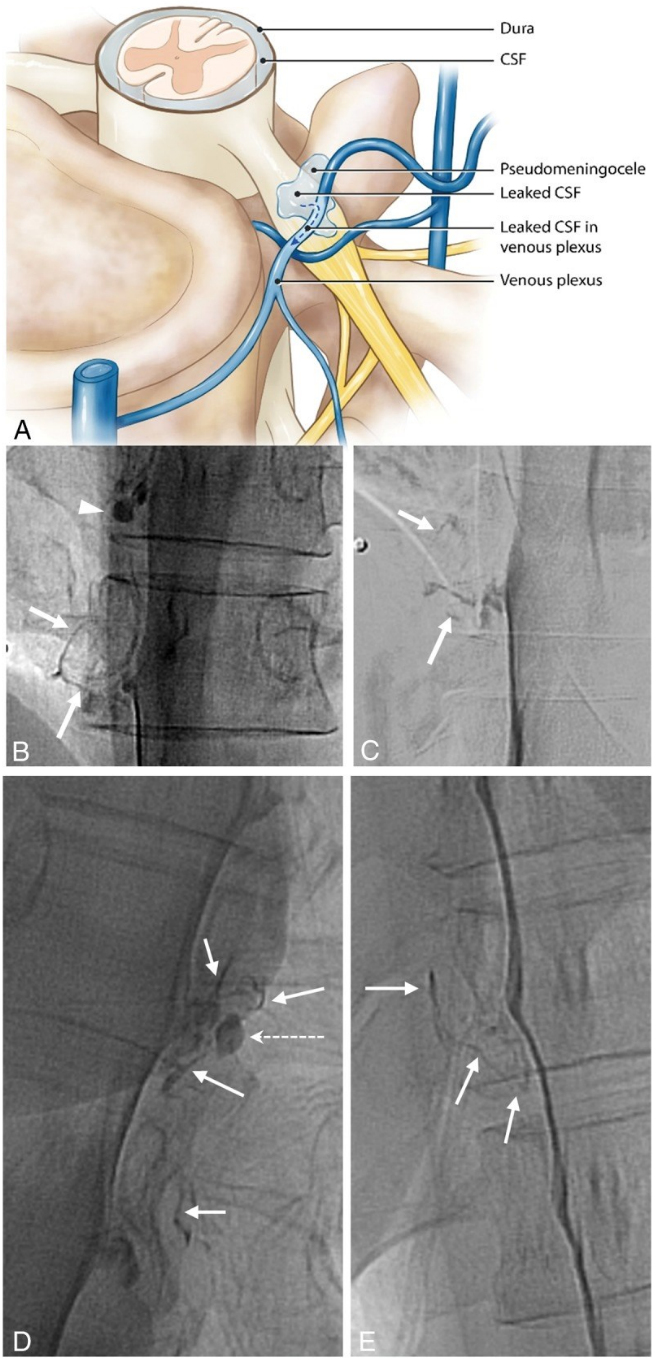


Image from: Spontaneous Intracranial Hypotension: A Systematic Imaging Approach for CSF Leak Localization and Management Based on MRI and Digital Subtraction Myelography [19].

Figure 6. Type 3 CSF leak



A) Schematic depiction of a CSF-to-venous fistula arising from a dural tear along the nerve root sleeve beyond the epidural compartment. B) Nonsubtracted and magnified image from a left-side down SLEC- patient with SIH. C) Subtracted and magnified image from left-side-down DSM in the same patient. A small vascular structure, in keeping with a tortuous vein of a CVF, can be seen coursing away from the root sleeve (arrows). An incidental normal diverticulum is also noted at the level above (arrowhead). D, E) Nonsubtracted images of decubitus DSMs of two other similarly presenting patients with SLEC- demonstrating CVFs. Globular collections of contrast (dashed arrow) are commonly seen near the expected zone of origin of the vein, possibly representing a focal extravasation (pseudomeningocele) of contrast or a diverticulum from which the vein appears to arise.

Image from: Spontaneous Intracranial Hypotension: A Systematic Imaging Approach for CSF Leak Localization and Management Based on MRI and Digital Subtraction Myelography [19].

1.7 Treatment

First-line treatment is conservative. Anecdotally, bed rest, oral hydration, theophylline, and oral caffeine administration have been proposed for non-invasive treatment of spontaneous intracranial hypotension[34, 35]. In contrast, no headache medications have yet been reported to be widely effective in treating SIH[20]. It is often stated in the literature that most cases of SIH have a benign course and resolve with conservative measure although few studies systematically address this assumption and forced bed rest is detrimental for social and economic impact. Additionally, long term follow-up in these patients prove that conservative measure fail to completely solve the headache. Nearly two-third still have mild to moderate headache at 6 months and half of them still had headache symptoms at 2 years[36].

Percutaneous therapy with epidural patching is done frequently and could be considered the standard of care in spontaneous intracranial hypotension[21]. Its mechanism of action is thought to be direct tamponade of the leak or by decreasing the compliance of the thecal sac, which shifts the CSF pressure gradient cranially[20]. It is mainly performed as non-targeted patch at the lumbar spine or at the thoracolumbar junction[20]. Although some studies claim to have used a targeted approach for epidural blood patching, the method of localising the level of spinal leakage is not always reliable because of the low accuracy for CSF leak localisation on any static spine imaging, including MRI or postmyelogram CT. This diminished accuracy is mainly due to: Poor temporal resolution; encounter of multiple suspicious lesions when the actual leak almost exclusively occurs in a single location[37]; the presence of extensive CSF collection in the epidural compartment represent a false localising sign[21]. EBP is usually performed with autologous blood. Fibrin sealant, a biological product developed to facilitate dural repair during surgery, has been injected (an off-label use) in addition to or in place of blood[38]. Estimates of the efficacy of EBP vary significantly between investigations, with response rates to initial EBP ranging from 36% to 90%[39-43]. Treatment with EBP usually needs to be repeated, as only 1/3 of the patients respond well after the first EBP and up to half of the patients who receive three or more EBPs respond well[41]. Additionally, EBP is less effective for patients with CSF-venous fistulas than it is for people with other types of CSF leak. In one series, only three of 22 patients with a CSF-venous fistulas reported symptomatic relief from a combination of autologous blood and fibrin glue patching at the level of the fistula[15]. In a larger series of 40 patients with CSF-venous fistulas who underwent blood or fibrin patching, only one had a durable response[44].

Surgery is generally reserved for patients with well-localized CSF leaks who fail EBP. Leaks associated with nerve root sleeve diverticula are typically easier to access than ventral leaks and may be treated via primary dural repair, clipping of the leaking root sleeve, or epidural packing[9, 45]. Ventral leaks are less accessible and harder to expose surgically, especially when approached extradurally. Posterior transdural approaches that open the thecal sac posteriorly can allow for direct visualization of the ventral dural tears and permit resection of any associated osteophyte[8]. Surgical ligation of the CSF-venous fistula, in contrast to EBP, has been reported to provide immediate symptom relief[46].

Brinjikji and colleagues[47] described a novel transvenous approach for CSF-venous fistula treatment to avoid the surgical invasiveness. Selective catheterisation of the periradicular vein draining the CSF-venous fistulas, previously identified on digital subtraction myelography, was done via the azygos or hemiazygos vein. The draining vein is subsequently occluded with a liquid embolic material.

1.8 Prognosis

The evolving landscape of SIH research highlights the complexity of its management Despite not typically being considered a life-threatening disorder, spontaneous intracranial hypotension can cause considerable morbidity and mortality[20, 48, 49]. SIH is associated with profound headache which slowly alienates the patients from the usual life, depicting higher rates of depression, anxiety, and physical disability over time, ultimately affecting basic activities of daily living[50].

According to the literature, patients often have severe impairment of quality of life and psychological distress and might have been referred to several clinicians before receiving an accurate diagnosis and effective treatment to alleviate symptoms and prevent long-term complications such as subdural hematomas and permanent neurological deficits.

Even in cases where there is a significant delay in diagnosis, offering treatment showed a trend for a better outcome and symptomatic improvement based on quality-of-life questionnaires[51]. Based on recent studies, the long-term prognosis is good in most patients although significant long-term recurrence rate may occurs[41]. It is therefore essential to increase SIH awareness and plan a long-term follow-up.

1.9 Purpose

This study seeks to evaluate the long-term efficacy of EBP with HIT-6 questionnaire, elucidating how different approaches and clinical characteristics could be valuable for the patient long-term outcome and overall quality of life.

2. MATERIAL AND METHODS

2.1 Study design

In this study, a retrospective review of the medical records of patients suspected of having SIH was conducted in two distinct Neuroradiological department: The first at the AOPD of the University of Padova and the second at the AO Federico II of the University of Napoli.

The first center performed a database search on the electronic Regulatory Information System (eRIS), searching for the keywords 'epidural blood patch' and 'myelography' from January 2015 to February 2024. Medical records from 34 potential candidates were collected. The second center included consecutive patients presenting with symptoms concerning for intracranial hypotension from 2021 to 2023. Medical records from 18 patients were collected. Patients were screened for SIH independently by two authors and interviewed telephonically with the Headache Impact Test (HIT-6) questionnaire to evaluate the headache burden and the quality of life after EBP. The study was approved by the Regional Ethics Committee and consent to share medical records was obtained telephonically during interview.

2.2 Inclusion Criteria

Of scheduled epidural blood patch and myelography in our centers, we included only patients with confirmed SIH who provided sufficient data on outpatient or telephone follow-up. Patients were included if medical charts contained data on headache characteristics at onset, frequency, and intensity; MR imaging; treatment with EBP; and sufficient data on headache characteristics at follow-up. A minimum follow-up period of at least 6 months after establishing the diagnosis was essential for the purpose of the HIT-6 questionnaire validity.

2.3 Exclusion Criteria

Patients with recent (<6 months) head or spinal trauma, lumbar punctures, and/or spinal anesthesia were excluded from the study. Exclusion was then applied to absence of direct or indirect signs of CSF leak by neuroimaging modalities (MRI, CT/MR angiography). Additionally, patients who did not performed at least one EBP nor received a follow-up telephone call to assess the HIT-6 questionnaire were also excluded.

2.4 Data Collection

The following data were collected and analyzed: demographic variables; Symtomatic onset and diagnosis delay; precipitating factors at onset; Neuroimaging findings (brain MRI, spine MRI, CT, and myelography); type, location and number of EBPs performed; relapse rate and time to relapse; follow-up period. Headache frequency and intensity at onset and follow-up was first collected at follow-up appointments and ultimately during the telephonic interview. In order to reflect the clinical daily practice, we obtained all the initial imaging descriptions by experienced neuroradiologists. In case of doubt or unclear descriptions, the co-relator reassessed the images.

2.5 Diagnostic and Treatment workflow

At our centers, when SIH was suspected, the initial diagnostic assessment warranted contrast-enhanced cerebral MRI to rule-out common causes such as colloid cyst of the third ventricle, intracranial neoplasm, sinusitis, and cerebral venous thrombosis and investigate sign of cerebral hypotension. Non-contrast spinal MRI followed to investigate for potential leaks. All patients were first treated with nontargeted EBP in the lumbar region followed by additional non-targeted/targeted EBP if no clinical or radiological improvement was found at 3 months follow-up. The EBP was performed as follows: the patient was placed lying in the left lateral position. A standard epidural kit and an 18-gauge or 20-gauge angiocatheter was used to draw autologous blood in a sterile fashion. The epidural space was identified in the standard fashion using loss-of-resistance to air or saline. Once the placement of the needle tip of the epidural needle was confirmed, approximately 20-40 mL of autologous blood was injected slowly (30 to 60 seconds) into the patient's epidural space to create the blood patch. Patients who failed to improve after the repeated procedure or experienced a relapse of symptoms were studied with dynamic CT myelography to investigate the source of the spinal leak. Patients with confirmed type 1 or 2 CSF leak undergone additional EBP while patients with confirmed type 3 CSF leak were treated with surgery or, more recently, with spinal embolization according to Brinjinki approach[47].

More recently, diagnostic and treatment workflow aligned with recent studies[21]. Spine MRI included a heavily T2-weighted, fat-suppressed, high-resolution, 3D sequences to visualise the dura and screen for the presence of SLEC versus no SLEC, which guided further diagnostic steps. A type 1 or 2 leak was suspected in patients with SLEC, and a CSF-venous fistula in patients without SLEC. SLEC+ patients were treated promptly with non-targeted procedures while SLEC- patients undergone dynamic CT myelography for CVF detection.

2.6 Patient-reported outcome measures

Telephonic interview was made to assess the 6-item Headache Impact Test (HIT-6) with the goal to evaluate EBP outcome and overall quality of life after the procedure. A sample of HIT-6 questionnaire is provided on **Figure 7**. Possible HIT-6 scores varies between 36 and 78 points[52]. HIT-6 scores below 50 points indicate no or little impact of headache in daily life[52, 53]. Headache impact score on activities of daily living (ADL) was evaluate as follows: ≤49: little or no impact; 50–55: some impact; 56–59: substantial impact; ≥60: severe impact. After completing the questionnaire, all patients were asked whether undergoing spinal EBP has restored prior psychological and physiological status. Based on these given responses, the patients were then asked to express on a scale 1-10 the overall satisfaction (OS) of choosing to undergo the EBP. Satisfaction was then evaluated as follows: ≥8: high satisfaction; 6-7: moderate satisfaction; ≤5: low satisfaction.

Figure 7. HIT-6 questionnaire sample

Headache Impact Test (HIT-6)

Headache Impact Test (HIT-6) questionnaire was designed to help you describe and communicate the way you feel and what you cannot do because of headaches.

To complete, please circle one answer for each question.

1. When you have headaches, how often is the pain severe?
   never rarely sometimes very often always

2. How often do headaches limit your ability to do usual daily activities including household work, work, school or social activities?
   never rarely sometimes very often always

3. When you have a headache, how often do you wish you could lie down?
   never rarely sometimes very often always

4. In the past four weeks, how often have you felt too tired to do work or daily activities because of your headaches?
   never rarely sometimes very often always

5. In the past four weeks, how often have you felt fed up or irritated because of your headaches?
   never rarely sometimes very often always

6. In the past four weeks, how often did headaches limit your ability to concentrate on work or daily activities?
   never rarely sometimes very often always

	+		+		+		+	
NEVER 6 points each		RARELY 8 points each		SOMETIMES 10 points each		VERY OFTEN 11 points each		ALWAYS 13 points each

To score, add points for answers in each severity rating.

You should share your results with your doctor. Headaches that stop you from enjoying the important things in life, like family, work, school or social activities could be migraine.

Higher scores indicate a greater impact on your life

Score range 36-78

TOTAL SCORE

Reference:

Yang M, Rendas-Baum R, Varon SF, Kosinski M. Validation of the Headache Impact Test (HIT-6™) across episodic and chronic migraine. *Cephalalgia*. 2011;31(3):357-367. doi:10.1177/0333102410379890.

3. RESULTS

3.1 Patient population

52 patients were initially selected as candidates from both hospitals, exclusion criteria were applied as follows: four patients were excluded due to recent history of trauma or spinal interventions; six patients did not show clear signs of either type 1/2 nor type 3 CSF leak; two patients were excluded due to symptomatic improvement and rejection of scheduled EBP; two patients were managed surgically without EBP trial; two were excluded due to EBP scheduled but not yet performed; six patients were not reached telephonically to conduct the HIT-6 interview. 30 patients were included and clinical records were collected and reported in **Table I**. A clinical presentation extracted from this cohort is reported on **Figure 8**. The mean age at diagnosis was 46.8 with a female prevalence of 67% (20/30). Only 7% (2/30) received the diagnosis more than a year after the initial presentation. 90% (27/30) demonstrate signs of SLEC on spinal MRI. Of them, 11% (3/27) were diagnosed with type 1 leak whereas 30% (8/27) were found to have a type 2 leak; equivocal findings were found in the remaining 59% (16/27) of patients. 3 patients (10%) did not demonstrate signs of SLEC and the source of leak was attributed to CVF.

The EBP was targeted to the previously identified leak in four patients (13%), non-targeted at the lumbar spine in twenty-two patients (73%); a trial of non-targeted followed by targeted procedure in four patients (13%). Autologous blood injection was pursued until unbearable pain or headache presentation. The mean quantity of injected blood was 38 ml on the first EBP, 28 ml for eventual EBP repetition. The mean number of EBP performed among the cohort was 1.73; only three patients (10%) received more than 2 EBP. After EBP, all patients were followed-up either clinically or radiologically for at least 6 months. Fifteen of them were lost on subsequent follow-up while the remaining fifteen were followed-up on a long-term regular basis (minimum of 12 months, maximum of 36 months). During follow-up time, one patient (3%) developed rebound intracranial hypertension and was treated with 500mg acetazolamide daily until the condition resolved.

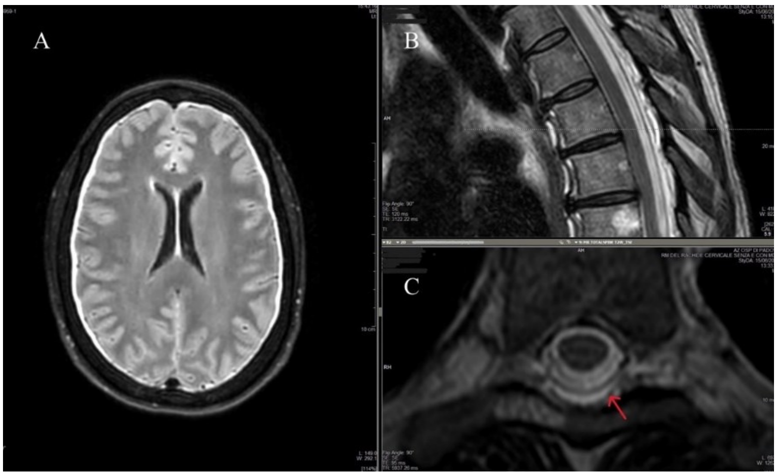
Table I. Clinical characteristics of included patients

Subject number	Age at diagnosis	Sex	Diagnosis delay	Type of leak	EBP (type)	EBP (n)	Follow-up (months)
1	23	F	<1 year	½	Non-targeted	2*	>12
2	49	F	<1 year	1	Non-targeted	2	>12
3	35	F	<1 year	½	Non-targeted	3*	>12
4	53	F	<1 year	½	Non-targeted	2*	>12
5	56	M	<1 year	½	Non-targeted	1	>12
6	61	F	<1 year	½	Non-targeted	1	>12
7	61	M	<1 year	½	Non-targeted	1	>12
8	55	M	<1 year	½	Targeted	1	>12
9	53	M	<1 year	½	Non-targeted	2	>12
10	42	F	<1 year	½	Non-targeted	2	>12
11	54	M	>1 year	3	Non-targeted/targeted	5	>12
12	49	F	>1 year	1	Non-targeted/targeted	7	>12
13	70	F	<1 year	½	Non-targeted	1	<12
14	27	F	<1 year	2	Non-targeted	1	<12
15	44	F	<1 year	½	Non-targeted	1	<12
16	33	F	<1 year	½	Non-targeted	1	<12
17	50	F	<1 year	½	Non-targeted	2	<12
18	37	M	<1 year	1	Non-targeted	1	>12
19	25	F	<1 year	½	Non-targeted	2	<12
20	39	M	<1 year	½	Non-targeted	1	<12

21	50	F	<1 year	2	Non-targeted/targeted	2	>12
22	73	F	<1 year	2	Non-targeted/targeted	2	>12
23	53	M	<1 year	2	Non-targeted	1	<12
24	36	M	<1 year	3	Non-targeted	1	<12
25	72	M	<1 year	2	Non-targeted	1	<12
26	42	F	<1 year	2	Targeted	1	<12
27	15	F	<1 year	2	Targeted	1	<12
28	47	F	<1 year	2	Targeted	1	<12
29	33	F	<1 year	3	Non-targeted	1	<12
30	66	F	<1 year	½	Non-targeted	2	<12

*Last EBP within 3 months from telephonic interview

Figure 8. A 49-year-old woman (patient #2) presented at the Padova center complaining worsening orthostatic headache for the past month. A) Brain MRI FLAIR shows bilateral subtle subdural collections; dural venous system dilation and decreased intra-ventricular volume. B) Spinal MRI T2 midsagittal image shows a posterior spinal longitudinal extradural CSF collection (SLEC) extending from D2-D10; a large vertebral hemangioma with T2 hyperintense signal is also present at D5. C) Spinal MRI T2 axial image shows the differentiation between the hypointense meningeal layer and the hyperintense SLEC (red arrow) at D3



3.2 Patient reported outcome

DL questionnaire results are reported in **Table II**. Except for three patients who received the telephonic interview within 3 months of last EBP, the remaining 90% were interviewed in a temporal window from at least 6 months to 5 years after the procedure/s. The total score ranged from 36 to 66 with 48 as the median. The first quartile (25%) was 36 while the third (75%) was 59; the interquartile range (IQR) was 23.

The median expressed satisfaction was 5/10; the first quartile (25%) was 2 while the third (75%) was 8; the interquartile range (IQR) was 3.

Ten patients reported an OS ≥8, consistent with a lower score on HIT-6. While two patients reported a moderate satisfaction rate (OS 6-7), eighteen patients reported a low satisfaction (OS ≤5) with a variable score on HIT-6 regarding the impact of ADL. Specifically, seven patients (35%) had a substantial headache impact, consistent with treatment failure; nine patients (50%) had some impact or little to no impact on ADL consistent with treatment success; four patients (22%) were found to have a CVF (type 3 CSF leak) which was subsequently treated either radiologically or surgically according to the individual leak characteristics and patient decision. Surgical closure yielded a partial improvement compared to the EBP while radiological embolization procedure yielded a successful outcome compared to the EBP (OS ≥8).

Of the six patients with HIT-6 total score ≤55 after the EBP who expressed an OS ≤5, three of them reported little improvement in SIH symptoms but a rising acceptance of headache which became less bothersome over time; two patients had chronic headache before SIH which remained constant in frequency but became more bothersome after the EBP and included additional symptoms such as tinnitus, vertigo, lightheadedness; three patients were unable to fully engage in physical activities without experiencing headache so had to modify their routine and behaviours; one patient improved the headache but had a persistent tinnitus which became bothersome in quiet environments and forces him to fall asleep with musical background.

Table II. HIT-6 individual score report and Overall Satisfaction after Epidural Blood Patching

Subject number	Item #1	Item #2	Item #3	Item #4	Item #5	Item #6	Total score	Overall Satisfiction (OS)
1	6	8	8	6	8	6	42	4/10
2	8	8	10	6	8	8	48	5/10
3	6	10	8	6	6	6	42	5/10
4	6	11	13	11	10	11	60	2/10
5	11	11	11	11	11	11	66	2/10
6	6	6	6	6	6	6	36	10/10
7	6	6	6	6	6	6	36	10/10
8	10	8	8	6	6	8	46	7/10
9	6	6	6	6	6	6	36	10/10
10	11	10	10	11	11	10	63	5/10
11	11	11	11	11	11	11	66	1/10*
12	10	10	10	10	13	10	59	2/10**
13	6	6	6	6	6	6	36	10/10
14	6	6	6	6	6	6	36	10/10
15	6	6	6	6	6	6	36	10/10
16	6	6	6	6	6	6	36	5/10
17	6	6	6	6	6	6	36	8/10
18	6	6	6	6	6	6	36	8/10
19	6	6	6	6	6	6	36	8/10
20	6	6	6	6	6	6	36	10/10
21	11	11	13	8	8	8	59	5/10
22	10	10	10	6	6	6	48	7/10
23	10	11	11	8	6	10	56	5/10
24	11	11	11	10	10	10	63	2/10*
25	10	10	10	10	8	10	58	2/10
26	11	10	11	6	6	6	50	5/10
27	11	11	11	8	8	8	53	5/10
28	11	11	11	8	6	8	55	5/10

29	11	13	11	10	10	11	66	2/10*
30	11	11	11	11	11	11	66	1/10

*After failing single or multiple EBP, patient #11 and #24 underwent single or multiple spinal embolization procedures to close the spinal CSF-venous fistula were performed with successful outcome (≥8/10).

**After failing single or multiple EBP, patient #12 underwent spinal surgical closure of the dural breach with moderate successful outcome (6-7/10).

4. DISCUSSION

4.1 Patient Demographics and Clinical Characteristics

This study aimed to characterize the demographic and clinical profile of a cohort of patients with SIH undergoing EBP and to investigate the outcome after the procedure using a combination of the HIT-6 questionnaire and patient-perceived overall satisfaction. The study cohort aligns with existing literature, with a higher prevalence of SIH in females, with a mean age at diagnosis of approximately 46 years. The delay in diagnosis in patients with SIH is common but our study did not suffer any significant diagnostic nor therapeutic delay. Commitment in early recognition of SIH is strongly emphasized across the literature and increased awareness among healthcare professionals is essential to further progress in effective management.

4.2 EBP Efficacy and Patient Outcomes

The majority of patients in this study received non-targeted EBP, with a smaller subset undergoing targeted procedures based on identified leak sites. The mean number of EBPs performed was nearly 2 indicating that multiple treatments are often necessary to achieve symptomatic relief. This finding is consistent with other studies that report varying success rates (29-90%)[39-41, 43] on initial EBP treatments and highlights the need for repeated procedures in many cases[21, 36, 43].
The evaluation of the effectiveness of treatments in patients with SIH is complex. Evaluating EBP outcomes with radiological findings would not guarantee a comprehensive view of the patient and has already failed in determining a clinical-radiological effective comparison[21]. Since radiological evaluation is not reliable, it is necessary to implement other assessment tools.

The HIT-6 questionnaire implemented here revealed a wide range of impacts on daily living, with scores varying from 36 to 66. Notably, the median HIT-6 score of 48 (IQR 23) suggests a moderate impact of headache on daily activities post-EBP and point towards a significative clinical improvement. The relatively large interquartile range further illustrates the variability in patient experiences, with some patients achieving significant improvement while others continue to experience substantial headache-related impairment. This finding aligns with other studies conducted on EBP leak closure[21, 43] and it is comparable to surgical leak closure as showed in a study where the median HIT-6 total score shifted significantly from 65.5 (IQR 61.8–69.3) prior to treatment to 51.5 (IQR 40.0–61.0) after 6 months [51]. This data seems to suggest that a considerable number of patients improves after the procedure, but the results also indicate an incomplete recovery from the SIH burden. In addition, considering the headache component alone is a limitation and a poor indicator of the full spectrum of SIH manifestations. Patients performing poorly at HIT-6 could be relieved from the disease burden in different aspects other than headache alone. As an example, one recent study employed multiple scoring systems to evaluate the EBP outcome[54]. Sixty-nine patient who did not meet the International Classification of Headache Disorders 3rd edition committee (ICHD-3) criteria for SIH but showed symptoms coherent with spinal hypotension were assessed an average of 377 days after the last EBP. Of the outcome indicators employed, it is interesting to note the clinically meaningful response rate[55, 56] difference between HIT-6 and PROMIS Global Physical Health. For the headache indicator, a clinically meaningful improvement was reached by thirty (45%) patients; for the PROMIS Global Physical Health indicator the same outcome was reached by thirty-seven (54%) patients. Combining the indicators together, it appeared that forty-four (64%) of patients reached a clinically meaningful response.

Therefore, it is crucial to avoid relying on a single indicator. In this study we evaluated the OS as an additional indicator to evaluate how patients define the treatment effect in terms of recovery, return to usual activities, and relief from the psychological or physiological burden of the disease.

4.3 Satisfaction and Quality of Life

Patient satisfaction, as measured by the overall satisfaction (OS) scale, averaged 5 out of 10. While ten patients reported high satisfaction (OS ≥8), indicating successful treatment outcomes, the majority of patients expressed low satisfaction (OS ≤5). This discrepancy highlights the multifaceted nature of SIH management, where even successful EBP can leave residual symptoms or lead to new challenges such as modified daily routines to avoid symptoms despite leak control. Individual patient sensitivity and perception of the disease make it difficult to find a single explanation for this behaviour. For instance, some patients chose to limit physical exertion and avoid activities that exacerbate their symptoms, while others modified their daily routines to incorporate more rest periods. Most patients had a common tendency to adjust and adapt their usual activities to the disease rather than engage in those activities as before. This finding aligns with a recent study on 106 patients with suspected or confirmed SIH who performed poorly across various quality of life measures (SF-36, PHQ-9, GAD-7, FACIT-12-Sp, HIT-6, and C-SSRS)[50]. Specifically, compared with the general population, participants performed significantly worse across all physical domains of the Short Form Health Survey (SF-36). Mean scores for role limitations because of physical health and pain were more than 30 points lower, and physical functioning and energy/fatigue were more than 20 points lower. Additionally, in contrast with this study, almost three-quarters of participants fell into the most severe headache impact category (HIT-6), with higher median HIT-6 score[50]. A cross-sectional study on 64 patients with confirmed SIH reported that after treatment more than half of patients still amended their work duties due to SIH and more than a quarter lost their job with significant impact in financial health[57].

The dissatisfaction among some patients, despite undergoing EBP, underscores the need for comprehensive management strategies that address both the physiological and psychological aspects of SIH.

4.4 Clinical Implications of Poor Outcome and Patient Satisfaction

In our study, out of 30 included patients, eight patients (27%) reported an OS ≤2 with a corresponding mean score on HIT-6 of 63. Out of these, three patients (38%) underwent additional procedures which included either spinal closure or percutaneous embolization of an identified CSF-venous fistula, with successful outcome. This highlights the importance of recognizing EBP-non responders as they could need more advanced and invasive diagnostic and therapeutic options. Recognising EBP- non responders can be difficult and requires broad evaluation with multiple indicators, but physician-patient communication remains the key aspect for proper management. Due to spinal imaging detection limitations, identification of CSF-venous fistula can be challenging. It entails highly specific diagnostic examinations performed by experienced Neuroradiologists. These previously considered rare entities are now estimated to account for up to half of SIH cases [58-60]. It is therefore essential to conduct in-depth diagnostic investigations driven by both EBP-failure and CSF-venous fistula prevalence awareness.

4.5 Future Directions

The findings of this study emphasize the variability in EBP success rates in SIH and consequent patient satisfaction. Multiple aspects of the disease need to be evaluated to consider the treatment as effective. Relying solely on the improvement of key symptoms or features could represent a poor indicator of good outcome in the broad spectrum of SIH. The value of accurate EBP outcome evaluation and the potential benefits of advanced imaging techniques for CSF-venous fistulas detection and management represent pursuable future directions which could implement SIH long-term prognosis. Future research should also focus on refining imaging protocols to improve leak localization accuracy. Long-term follow-up studies are crucial to understanding the nature of SIH and the effectiveness of different therapeutic approaches over extended periods.

4.6 Limitations

This study suffered significant limitations. The retrospective nature of this study represented a biased prone system, especially during the questionnaire distribution when recall bias could become substantial. The lack of validated diagnostic criteria could have created selection bias. Similarly, the absence of standardised criteria to establish the efficacy of treatments could lead to heterogeneous evaluations. Nevertheless, this study could give an insight into the complexity of SIH and pave the way for a crucial systematic patient centered approach.

5. CONCLUSIONS

This study highlights the significant impact of SIH on patients' quality of life and the variable efficacy of EBP in treating this condition. While EBP remains the gold standard first line treatment of SIH, the mixed outcomes observed in this cohort highlight the need for individualized evaluation and comprehensive patient care strategies. Better awareness amongst professionals and general practitioners, enhanced diagnostic protocols and a multidisciplinary approach to treatment, incorporating both conservative and interventional techniques, are essential to improving patient's quality of life. Continued research aimed to increase SIH awareness and understanding are imperative to address its nuances and to develop more effective and personalized interventions.

5.1 Personal considerations and interpretations

When interviewing patients, the psychological aspect of SIH sometimes seemed to prevail over symptoms. Patient were frequently told to rest and adapt their habits to cope with symptoms. Even after treatment, patients were afraid to regain their life back because they feared that symptoms would recur. For some patients even experiencing tension headache or migraine was not tolerable, as any kind of pain was perceived as SIH recurrence. I personally encouraged some of them to slowly engage in previously enjoyed activities to develop a positive reinforcement rather than a negative one. I believe it is therefore important to properly communicate with patients, understand their frustrations and focus on regaining a quality of life. SIH is an idiopathic condition for most patients and, although we know how different leak types arise, we do not know what triggers the condition for most patients and why the symptoms present only at a certain and non-specific point in life.

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