A randomized trial of CT fluoroscopy-guided targeted autologous blood and fibrin glue patching for treatment of cerebrospinal fluid leaks in spontaneous intracranial hypotension

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RESEARCH DESIGN AND METHODS (see Schema)

Patient Selection

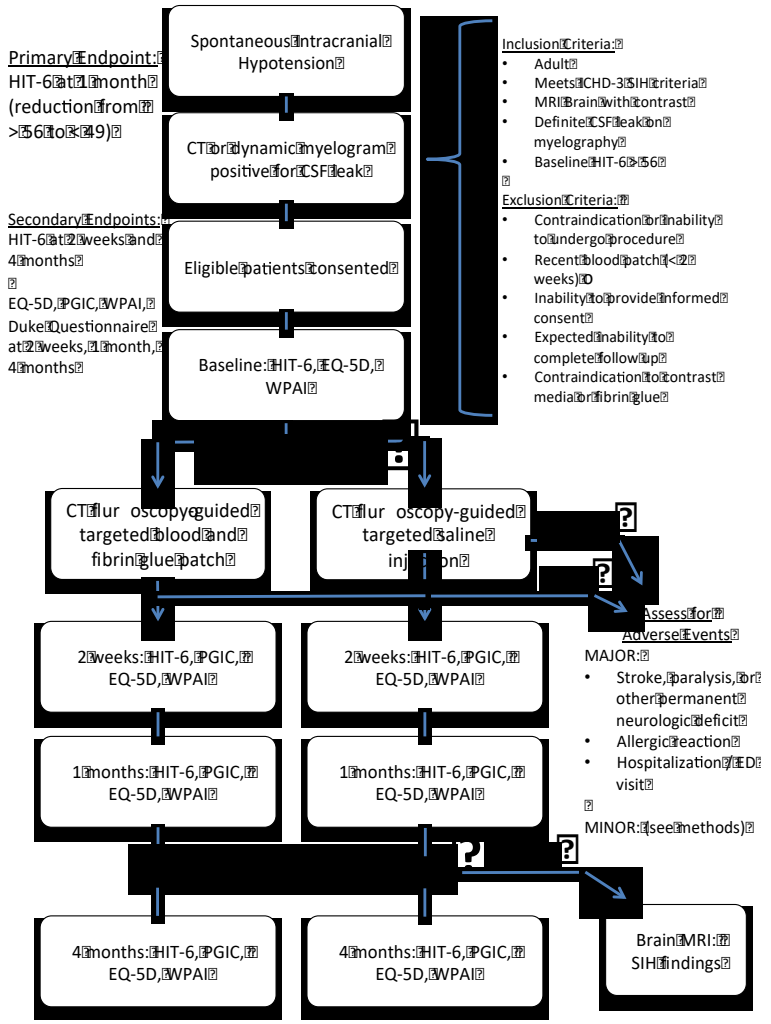
Table 1: ICHD-3 SIH Diagnostic Criteria
A) Any headache fulfilling criterion C
[redacted]
C) Headache has developed in temporal relation to the low CSF pressure or CSF leakage, or has led to its discovery
[redacted]

Inclusion Criteria: Adult patients meeting International Classification of Headache Disorders 3rd Edition (ICHD-3) criteria for a diagnosis of SIH (Table 1) who have had a contrast-enhanced brain MRI and a myelogram confirming the presence of a CSF leak will be recruited from the Duke Radiology spine intervention clinic [25].

Exclusion Criteria: (a) recent (i.e., < 2 weeks) blood patch, (b) contraindication or inability to undergo the procedure, (c) inability to provide informed consent, (d) expected inability to complete follow-up assessment, (e) a contraindication to receiving contrast material (precluding an epidurogram), or (f) contraindication to receiving fibrin glue (i.e., allergy). We aim to recruit 148 patients over 2 years. This number is based on the historical number of patients with SIH and confirmed CSF leaks treated at Duke, our sample size determination (*see Statistics*), and previously published studies.

CT Fluoroscopy-Guided Blood and Fibrin Glue Patching

We will employ a single-center, parallel, randomized, blinded, prospective design. Enrolled patients will be assigned to one of two treatment arms using a block randomization scheme: CT fluoroscopy-guided blood and fibrin glue patching targeted to the site of CSF leak or a simulated procedure without patching material. Baseline data will be collected including: (a) symptom profile and duration, (b) headache impact test (HIT-6), (c) EQ-5D (a measure of overall health status), and (d) work productivity and activity impairment (WPAI) (see *Outcomes*). All procedures will be performed under CT fluoroscopy on the same scanner (see *Resources*). The location of injection for patients in both arms will be targeted to the site of the CSF leak identified on prior imaging (e.g., CT or dynamic myelogram). All procedures will be performed by a board-certified radiologist with a CAQ in neuroradiology and at least six years of experience in CT fluoroscopy-guided spine injections.



Patients in both arms of the study will be placed supine on the CT gantry table. Intravenous (IV) access will be obtained and sterile autologous blood will be acquired for the purposes of possible patching. A planning CT scan (120 kVp, automatic tube current modulation: 100 – 400 mA, 2.5 mm section thickness, gantry rotation time 0.5 seconds) will be obtained with z-axis limited to the area of interest. Acquired images will be used to plan a needle trajectory and approach to the location of the CSF leak for targeted patching using previously described techniques for CT fluoroscopy-guided epidural patching (e.g. a lateral approach trajectory to the neuroforaminal epidural space, an oblique interlaminar trajectory to the dorsal spinal canal epidural space, or an approach traversing the neuroforamen to reach the ventral epidural space) [14, 26-29]. The skin surface will then be marked, sterilized, draped, and anesthetized with 2% lidocaine. At this point, a computer generated randomized treatment assignment will be delivered to the treating physician in an opaque sealed envelope, which will determine if the patient is treated with targeted blood and fibrin glue patching versus the simulated procedure. Patients and outcome assessors will remained blinded to the treatment assignment throughout the study. The treating physicians are unable to be blinded, as

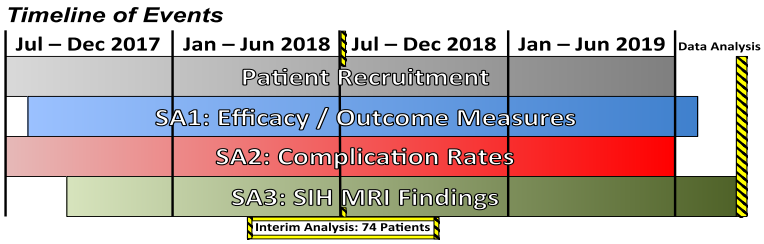
they will be aware of the type of patching material used. The effectiveness of patient blinding will be assessed using the Bang Blinding Index prior to discharge on the day of the procedure [30].

Targeted Patching of CSF Leaks with Blood and Fibrin Glue (Experimental Arm)

For patients randomized to targeted patching with blood and fibrin glue, a 22-gauge 3.5 or 5 inch Quincke tip spinal needle will be advanced under intermittent CT fluoroscopic-guidance to the epidural space at the target location. On reaching the target, gentle aspiration will confirm absence of blood return. Approximately 0.2 mL of contrast material (iopamidol 200 mgI/mL; Isovue-M 200, Bracco Diagnostics Inc., Princeton, NJ) will then be injected to assess needle tip position and potential future spread of patching material. Intravascular injection will be excluded using a "double-tap" technique (i.e., 2 sets of CT fluoroscopic images: an initial image immediately after injection and a second image acquired 2-3 seconds later to assess for contrast material washout), as previously described [31]. After visual confirmation of correct needle tip position, a mixture of autologous blood (~1 mL) and fibrin glue (~1-3 mL) will be slowly injected. This process will be repeated for all planned needle placements. The number of needle placements and total volume of blood and fibrin glue will be at the discretion of the treating radiologist, but will be based upon: (a) the extent of spread of patching material, (b) mass effect on the thecal sac and neural structures, and (c) patient symptoms. On completion of the procedure, the patient will be observed for 2 hours in the radiology post-procedural unit.

Simulated Patching Procedure (Control Arm)

Patients randomized to undergo the simulated patching procedure will have the same experience as the patients in the experimental arm, as described above. This includes placement of an IV, acquisition of sterile blood for potential autologous patching (which will be discarded rather than used), a planning CT, all of the same needle placements that would have been performed if the patient were randomized to the experimental arm, and contrast injection for the epidurogram. However, instead of injection of blood and fibrin glue patching material through the needles, an equivalent volume of preservative free sterile saline will be injected (buffered intrathecal electrolyte/dextrose injection; Elliots B Solution, Lukare Medical, Scotch Plains, NJ). On completion of the procedure, the patient will be observed for 2 hours in the post-procedural unit.



Adverse Events

Patients will be screened for adverse events immediately after the procedure as well as via phone call at one week post-procedure. While all adverse events will be recorded, the following will be considered major adverse events: stroke, paralysis, or other permanent neurologic deficit; allergic reaction; hospitalization or ED visit. Minor adverse events will include, but not be limited to: nausea and/or vomiting, symptomatic hypertension, vasovagal reaction, temporary weakness or sensory deficit, and urinary retention.

Patient Outcome Measures and Crossover

Headache Impact Test (HIT-6): A validated headache assessment tool with good internal consistency and test-retest reliability that is designed to provide a global measure of headache impact in six domains [32]. Scores range from 36 (asymptomatic) to 78 (severe headache). Score ranges: 36-49 (little or no headache impact), 50-55 (some impact), 56-59 (substantial impact), and >60 (severe impact) [33, 34]. Prior studies have determined that the minimally important clinical difference between groups is 1.5 points for the HIT-6 [35].
EQ-5D: A standardized measure of health status that provides a simple, generic measure of health for clinical appraisal [36]. It is well-validated for health status measurement [37] and for quality-of-life in headache [34].
Patient Global Impression of Change (PGIC): A validated 7-point Likert-type scale assessing a patient's overall impression of improvement after intervention [38, 39].
Work Productivity and Activity Impairment (WPAI): A validated instrument with good test-retest reliability used extensively in health research [40, 41] that quantifies impairment in daily activities and work productivity [42].
Crossover: Patients will be permitted to crossover to the other treatment arm two months after the procedure.

Statistics

Patient Outcome Analysis

The change in HIT-6 from a pre-procedural score of > 56 (substantial or severe impact on life) will be considered for each group at each time point. *Primary Endpoint (HIT-6 at 1 month):* We will apply a two-sample t test, or in the cases of low counts and non-parametric data a Wilcoxon Rank Sum test, to test the primary endpoint. *Secondary Endpoints:* The same analysis will be employed for all secondary endpoints at each time point.

Sample Size Determination

Based on previously acquired prospective outcomes data (unpublished), we will conservatively estimate a positive response rate of 50% in our experimental arm (see *Preliminary Studies*). In a meta-analysis examining sham procedures, our group found a maximum placebo response of 30% (Gu AP, unpublished). Therefore, to obtain a power of 0.8 (alpha 0.05) to detect superiority of the blood and fibrin glue patching group, assuming positive response rates of 50% for the patching group and 30% for the control group, we would need a total of 148 patients (74 patients in each arm).

Interim Data Analysis

An interim analysis will be performed of the first 74 patients by the biostatistician. All study participants and other personnel will remain blinded. Safety and efficacy will be evaluated using an O'Brien–Fleming stopping rule of $p < 0.001$ in order to evaluate for early evidence of treatment efficacy [43].

Crossover, Withdrawal, or Missing Data

We will employ an intention-to-treat (ITT) analysis for this trial [44]. Patients that crossover between study arms, withdraw from the study, or for whom there is missing data will all be handled in the same manner: we will conservatively assume that no further benefit will be gained from the initial treatment. As such, the most recent available outcomes data will be extrapolated to all later time points for which no data are available.

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