INTERVENTIONAL
RESEARCH PROTOCOL TEMPLATE
NCT# 03112720

Statistical Analysis Plan

TRIAL FULL TITLE	A Comparison of the Efficacy of Sphenopalatine Ganglion Block (SPGB) with 5% Lidocaine and Epidural Blood Patch (EBP) for the Treatment of Post-Dural Puncture Headache (PDPH)
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1 SAP Signatures

I give my approval for the attached SAP A Comparison of the Efficacy of Sphenopalatine Ganglion Block (SPGB) with 5% Lidocaine and Epidural Blood Patch (EBP) for the Treatment of Post-Dural Puncture Headache (PDPH) dated 10/5/2021

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Table of Contents

*Skip To Section: Hold **CTRL** + **Click (Below)** To Follow Link in **Blue***

1.0 Research Introduction

Title of Project

A Comparison of the Efficacy of Sphenopalatine Ganglion Block (SPGB) with 5% Lidocaine and Epidural Blood Patch (EBP) for the Treatment of Post-Dural Puncture Headache (PDPH)

NCT# 03112720

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1. Purpose

To compare the sphenopalatine ganglion block (SPGB), a local anesthetic technique that is facile to perform and carries fewer potential side effects, to the traditional, more invasive, epidural blood patch (EBP) for the treatment of post-dural puncture headache (PDPH). The SPGB is experimental while the EBP is considered to be the standard of care.

1.1. Objectives

1.1.1. To compare subjects who present with PDPH and are randomized into one of two treatment groups whether the SPGB technique is not inferior to the traditional EBP in treating their symptoms.

1.1.2. To follow subjects who initially present with PDPH to determine the efficacy of either technique in maintaining a symptom-free period.

1.1.3. To compare patients' experiences with the SPGB as compared to the EBP.

1.2. Hypotheses

1.2.1. There will be no appreciable difference in the amelioration of PDPH symptoms with the SPGB technique as compared to the EBP.

1.2.2. Both the SPGB and the EBP will maintain similar symptom-free periods.

1.2.3. The patients will experience less subjective discomfort with the SPGB as compared to the traditional EBP.

2. Background and Significance

Dural punctures may be intended or unintended following instrumentation of the spine when administering neuraxial anesthesia or performing diagnostic studies such as lumbar punctures and myelograms. As many as 40% of patients may complain of frontal and nuchal headache several hours after dural puncture (1). Furthermore, patients complain of diplopia, loss of hearing, nausea, and vomiting. Symptoms may be self-limited, though the time range varies. Significant morbidity can be observed during this interim as patients remain bed-ridden, missing time from work and enjoyment with their families. Conservative treatment measures include maintaining a supine posture, hydration with fluids, caffeine intake, and pain control

with traditional oral and parenteral medications (2) until the symptoms subside. When an unintentional dural puncture occurs during epidural catheter placement, the catheter can be left *in situ* with a low infusion of saline to ameliorate the symptoms partially.

Several theories exist to explain PDPH. Cerebral spinal fluid surrounds the brain and the spinal cord, all of which is surrounded by the dura mater. Traditionally, it was thought that following dural puncture, the leakage of cerebral spinal fluid (CSF) causes the brain that is usually suspended in this fluid to "sag", an action that exerts traction on the meninges, which in turn causes headache (3-5). Recent studies have questioned this as the sole mechanism since any leakage would be slow, and would not explain the stark difference in symptoms from the supine to orthostatic positions (6). Instead, these symptoms likely share an etiology with other so-called "neurovascular headaches". In the intact nervous system, CSF and the brain tissue exert pressure on the vasculature. This pressure is sufficient to cause collapse of the venous side of the circulation, a phenomenon known as "subdural venous collapse". Following dural puncture, CSF pressure, which is normally greater than atmospheric pressure, drops as it tends to equalize through this extradural communication. The decreasing CSF and tissue pressures release the subdural venous collapse, allowing vasodilation. Furthermore, since the dural puncture turns the usually closed system into an open one, CSF pressure becomes dependent on the patient's position, dropping significantly when sitting upright or standing. The dura is exquisitely sensitive to pain in the very areas surrounding blood vessels. The vasodilation triggers nociceptive nerve endings, which accounts for the exquisite pain from neurovascular headaches such as PDPH (6).

The EBP has traditionally been the definitive mode of treatment in patients with PDPH. This intervention involves the autologous transfusion of a patient's blood from a sterile peripheral site into the epidural space. Several studies have established the EBP as standard of care for PDPH. A randomized, controlled clinical trial has showed that EBPs resolve PDPHs after one week in 84% of patients compared to 14% with placebo (7). Another prospective, randomized, double-blinded trial compared EBP to conservative management (fluid replacement, non-steroidal anti-inflammatory drugs, and caffeine) for the treatment of PDPH. (8). These authors found that when treated conservatively patients with PDPH noted little to no change in headache, as reported on a visual analog scale (VAS). Their headaches rated 8.2 ± 1.4 both before and after treatment. In the group who received an EBP, patients reported a decrease in headache from 8.0 ± 1.6 to 0.7 ± 0.16. The authors further state that "The epidural blood patch represents the first choice treatment of PDPH no matter the etiology, being significantly superior to the conventional treatment which did not affect pain scores" (8). These studies have helped establish the EBP as a standard of care for PDPH. It now appears as a listed treatment for PDPH in common physician reference resources such as UpToDate® (Waltham, MA) (9).

Originally, the EBP was thought to act through a tamponade effect, plugging the dural defect and preventing the further leakage of CSF. As noted above, this is unlikely the true mechanism as patients often report immediate relief, which could not be explained by cessation of the minute flow of CSF. The more contemporary explanation is that the EBP does in fact plug the dural tear, but in doing so, it prevents the equilibration of CSF pressure with the atmospheric pressure. Injection of blood into the epidural space immediately raises

the CSF pressure within the closed spinal canal space and thus causes reflex cerebral vasoconstriction. Consequently, subdural venous collapse is restored and the headache subsides.

Although the EBP has been proven to be one effective treatment for PDPH, it is an invasive procedure and carries the same risks as those associated with the inciting event. Infections, subdural and epidural hematoma, needle trauma, and back pain have been described (10,11), in addition to a possible second dural puncture. Furthermore, the procedure requires the physician to be adept at the epidural injection technique, which usually limits treatment to anesthesiologists.

Given the purported neurovascular etiology of PDPHs, patients who suffer from this condition have been successfully treated with nerve blocks for immediate relief (12). We had proposed targeting the sphenopalatine ganglion based on the success of manipulating the trigeminal–autonomic arc for treating cluster headache, a type of neurovascular headache. Briefly, this reflex arc describes an afferent limb that includes trigeminal nerve fibers in the perivascular area of cerebral circulation. When stimulated, these neurons activate the efferent limb, the parasympathetic fibers within the greater superficial petrosal nerve, which in turn causes vasodilation (13). In neurovascular headaches, a triggering mechanism causes initial vasodilation which irritates the dura and stimulates the afferent limb of this arc. In PDPH, the equalization of pressure between the CSF and the atmosphere acts as a trigger. The parasympathetic efferent limb of this reflex causes vasodilation, which in this case is deleterious since it provides positive feedback to this reflex loop, causing continued headache. Blockade of the synaptic communication in the SPG would terminate this loop, and is the proposed pathophysiological mechanism by which neurovascular headaches are treated.

Our recent literature review has suggested that there are multiple techniques for performing the sphenopalatine ganglion block. A proven method for performing the block involves using a cotton tip applicator to place lidocaine gel in the middle posterior pharynx followed by administration of 1 mL of 4% lidocaine solution through the plastic channel of the applicator, all simply by placing the soft, flexible, cotton-tip applicator into the nares (14). This technique of transmucosal application of local anesthetics was proposed by Lebovits et al. (15) and others (16). The side effects associated with SPG blocks are minimal, often limited to the bitter taste of the anesthetic solution. The theoretical rare risks of anaphylaxis and severe epistaxis exist, but have not been described in the literature.

The SPGB has been described in the literature for the treatment of cluster headaches and is recognized as a treatment for this condition when other modalities fail (17-20). A study has investigated its use for the treatment of PDPH (21). Twenty-eight patients with PDPH were offered a SPG block prior to EBP. Nineteen of 28 patients noted relief and only 9 patients eventually needed an epidural blood patch after 1 week. Moreover, most patients (~93%) noted relief of headache at and beyond 72 hours following the procedure significantly decreasing morbidity during the otherwise symptomatic period. In this pilot study, approximately 68% of patients were saved from having to undergo the invasive EBP in favor of a more cost-effective and less invasive technique (21). This study has helped establish the

sphenopalatine ganglion block as a standard of care for the treatment of PDPH, especially when other modalities fail or are not preferred by the patient. The SPGB appears as a treatment in the common physician reference resource UpToDate® (Waltham, MA) for the treatment of adverse effects of neuraxial anesthesia (22).

3. Research Design and Methods

We propose to treat patients suffering from a severe and incapacitating headache resulting from dural puncture. Both the EBP and SPGB therapies have been shown to reduce the intensity of PDPH. The design of this study seeks to determine the duration of relief associated with both therapies and to compare the patient's satisfaction with both techniques.

3.1. Subject selection and enrollment considerations

3.1.1. Subject recruitment

Patients who suffer from headache following dural puncture may present following neuraxial procedures such as epidural anesthesia, diagnostic lumbar puncture, diagnostic radiographic studies to physicians in several departments (**Table 1**).

Table 1. Procedures that may result in PDPH and the respective departments to whom suffering patients may present

Recent procedure	Presenting department
Epidural or spinal anesthesia	Anesthesiology or Pain Medicine (division of Anesthesiology)
Epidural steroid injection	Pain Medicine
Diagnostic lumbar puncture	Medicine, Pediatrics, Neurology, Emergency Medicine (ER) RWJUH
Myelogram	Neurology

The members of the respective departments will be informed of this study for enrollment of patients. For the purposes of the initial referral, all patients meeting minimal criteria for PDPH (**Table 2)** will be considered. These criteria for referral will be published by electronic mail to the members of the aforementioned departments. Physicians who seek to make a referral will do so by contacting the Pain Medicine physician-on-call. This on-call physician is available continuously (24 hours per day, 7 days per week) by mobile telephone. The Pain Medicine physician-on-call will receive the demographic information of this patient in the hospital and inform the principle investigator or his designee for enrollment pursuant to criteria outlined in the next section.

Table 2. Minimum criteria for initial referral into study

Criterion
A neuraxial procedure within the past 7 days
Postural headache that improves with supine position
Absence of other more likely etiology of headache

3.1.2. Inclusion Criteria

We will include patients with a moderate or severe PDPH classification, modified from van Kooten et al. (7) Complete inclusion criteria follows (Tables 3–5)

Table 3. PDPH classification

Classification	Definition
Absent	no headache
Mild	postural headache with some restriction of daily activities but without confinement to bed and without associated symptoms
Moderate	postural headache with confinement to bed for at least part of the day **OR** postural headache with associated symptoms restricting daily activities
Severe	postural headache with confinement to bed for entire day with associated symptoms

Table 4. Symptoms associated with PDPH

Symptoms
Nausea and/or vomiting
Dizziness
Hearing loss, hyperacusis, or tinnitus
Photophobia, diplopia
Nuchal pain or stiffness

Table 5. Inclusion criteria

Criteria
Moderate to severe PDPH (Table 3) for greater than 24 hours, but not more than 7 days after the initial procedure
Men, women, and children ages 13–92
Consent to participate in this study

3.1.3. Exclusion criteria

Criteria to exclude patients are listed (**Table 6**). Urine pregnancy tests are standard of care for all women of child bearing age prior to any anesthesia procedures. We note that pregnancy is one of our exclusion criteria. Many of the patients we seek to enroll in this study will have received neuraxial anesthesia for childbirth. Since a urine pregnancy test is not reliable in post-partum women owing to residual circulating levels of the beta subunit of human chorionic gonadotropin hormone (β-hCG) leading to a false positive result (23), any woman who complains of PDPH within 7 days of delivery will be considered not pregnant and thus be eligible for our study. All other women of child bearing age will require a negative urine pregnancy test result within the last 7 days. If no pregnancy test was completed prior to referral to this study, the patient will be required to undergo one prior to randomization. Any patient who has a positive pregnancy test or refuses to undergo this test will be excluded from the study. The pregnancy test will be billed as part of the routine work up involved with the standard of care.

In patients receiving antithrombotic or thrombolytic therapy, we will use the most recent guidelines from the American Society of Regional Anesthesia Practice Advisory (24) to determine whether the patient may undergo neuraxial anesthesia. Any patient who would be unfit for epidural instrumentation will be excluded prior to randomization.

We will exclude non–English-speaking patients in this study. While both procedures could potentially be performed in patients regardless of language proficiency, this study will specifically assess the patients' symptoms such as pain, nausea, and discomfort among others as listed in (Table 8). These assessments would need to be made contemporaneously during the procedure, which can be difficult when using a telephone translator. There would be a delay in receiving a response; moreover, the patient would not be able to hold a telephone handset when assuming the correct posture and position for these sterile procedures.

Table 6. Exclusion criteria

Criteria
Age less than 13
Non–English-speaking
Pregnancy
Allergy to lidocaine or lidocaine-containing ointments or solutions
Heart disease with New York Heart Association (NYHA) Functional Classification II or greater
Current treatment with lidocaine patch or other topical or depot vehicle for chronic pain
Presence of a spinal cord stimulator, intrathecal pump, or other implanted device in the spine
Platelet count < 100,000/ μL
Sepsis
Skin or soft tissue infection overlying lumbar spine
Sinusitis requiring the current use of antibiotics
Nasal polyps
Nasal surgery within the past 7 days
Neurological event including stroke, intracranial hemorrhage, epidural hematoma, or other event causing a focal deficit within the past 30 days
Current anticoagulant therapy contraindicating epidural injection
Prior treatment with SPG block or EBP for this presenting condition

All inclusion criteria (table 5) and exclusion criteria (table 6) will be ascertained from the patient's medical chart.

All patients who are excluded due to one or more criteria listed above will be treated for their headache symptoms according to standard clinical practices, which may include EBP, SPGB or other block, or medical management as the clinical situation dictates. An anesthesiologist or a physician in another department may perform these procedures according to institutional practices. Exclusion from this study will not in any way prevent a patient with PDPH from receiving the treatment he or she would have otherwise received.

3.1.4. Consent Procedures

Once a patient is referred for enrollment for this study, only the anesthesiologists listed on this study (William Grubb, Shaul Cohen, Shruti Shah, Scott Mellender & Sagar Mungekar) will interview the patient to confirm that the minimum criteria listed in Table 2 are met. This interview will take place as soon as possible after the Pain Medicine physician-on-call refers the patient to the PI or SI. In all cases, this initial consultation will take place within 24 hours of the referral as is the standard practice for all consultation requests sent to the Pain Medicine physician-on-call. In the rare case that neither the PI nor any SI is available within this period,

the patient's PDPH will be treated according to standard practice. In no instance will treatment for PDPH be delayed because of failure of the PI or SI to interview the patient.

Only the anesthesiologists listed in this study will obtain informed consent (William Grubb, Shaul Cohen, Shruti Shah, Scott Mellender & Sagar Mungekar). The administrative assistant (Preet Patel) will not obtain informed consent. Resident anesthesiologists will not obtain informed consent. Each patient will be given the informed consent document to read and consider prior to agreeing to participate. The PI or SI will answer all the subjects' questions and ensure the subject has had adequate time to consider participation prior to signing the informed consent document. No study assessments, measurements, or interventions will occur prior to subject signing the informed consent document. In addition, at each new encounter with the subject, the investigator will ask the subject if he or she is agreeable to continued study participation.

We acknowledge that due to the intensity of the headache and any associated symptoms, the patient may not be able to give informed consent to participate in this study. If the PI or SI determines in such a case that the patient's overwhelming symptomatology prevents decision-making capacity regarding participating in this study or if the patient states that he or she cannot make a decision regarding participation in this study, then the patient will NOT be enrolled in this study. No surrogate decision maker will be allowed to give consent. As noted earlier, such patients will be treated for their headache symptoms according to standard clinical practices taking the patient's wishes into consideration. Failure to consent for participation in this study will not in any way prevent a patient with PDPH from receiving the treatment he or she would have otherwise received.

3.1.5. Subject Costs and Compensation

The subject will not incur additional costs outside of standard of care costs for medication and pregnancy testing that may be performed for routine standard of care. There will be no compensation for participation in this study.

3.1.6. Chart Review Selection

There will be no retrospective chart review. Below is the "Data Collection List" that will be used to gather data at every patient encounter as described previously.

Data collection sheet

(3.1.6 : there will be no retrospective chart review)

GROUP 1:Epidural Blood Patch					
Subject ID:					
	0 mins VAS	30 mins VAS	60 mins VAS	24 hrs VAS	48 hrs VAS
Orthostatic HA					
Supine HA					
Nuchal HA					
Nausea					
Auditory Disturbances					
Visual Distrubances					
Vomiting					
Pruritis					
Epistaxis					
Numbness					
Comfort with Procedure					
Blood Pressure					
Heart Rate					
Allergies					

GROUP 2: SPG Block							
Subject ID:							
	0 mins VAS	30 mins VAS	VAS not improved, SPG 2 at 30 mins	VAS not improved, SPG 3 at 30 mins	60 mins VAS	24 hrs VAS	48 hrs VAS
Orthostatic HA							
Supine HA							
Nuchal HA							
Nausea							
Auditory Disturbances							
Visual Disturbances							
Vomiting							
Pruritus							
Epistaxis							
Numbness							
Comfort with Procedure							
Blood Pressure							
Heart Rate							
Allergies							

3.2. Study Design

3.2.1. Type

This is a non-inferiority trial comparing the SPGB to the EBP for the treatment of PDPH. The study is not blinded to the subject or investigator. Due to the nature of the procedure and the anatomical site of intervention, both will know which method they are receiving or delivering. We acknowledge this as a limitation of our study but reiterate that blinding one or both parties is not feasible.

3.2.2. Randomization

Subjects suffering from PDPH shall be randomized to one of two groups (**Table 7**) by a random number generation spreadsheet (Excel, Microsoft, Redmond, Washington).

Table 7. Patients with PDPH to be treated for their symptoms are randomized to one of the two groups below

Group	Intervention
1, EBP (control)	EBP as described below
2, SPG block (treatment)	SPG block as described below

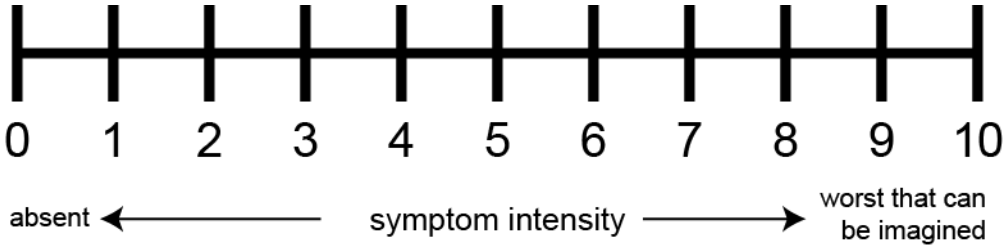
3.2.3. Symptoms assessment

After obtaining informed consent and inclusion in the study, the patient's symptoms will be assessed prior to the intervention. Four headache and associated symptoms will be assessed on a visual analog scale of 0 to 10 or in a binary manner (**Table 8** and Figure 1).

Table 8. Symptoms that will be assessed prior to and after interventions. VAS: (visual analog scale, 0–10, **Figure 1**)

Symptom	Description	Scoring System
orthostatic headache	headache that presents or worsens when changing from supine to sitting or standing position	VAS
supine headache	headache when supine	VAS
nuchal headache	pain in the back of the neck either when supine or sitting	VAS
nausea	nauseated with or without vomiting	VAS
auditory disturbances	tinnitus, hyperacusis, subjective loss or decrease in hearing, or worsening of any other symptoms with noise	VAS
visual disturbances	photophobia, diplopia, subjective loss or decrease in vision, or worsening of any other symptom with light	VAS
vomiting	vomiting that day since the past symptom assessment	binary (yes or no)
pruritus	itching in any part of the body	VAS
epistaxis	bleeding from either naris	
numbness	subjectively decreased sensation	VAS, location

Figure 1. Visual Analog Scale (VAS) used to grade severity of symptoms. 0 = symptom absent. 10 = symptom severity is the worst that can be imagined. Any integer between 0 and 10, inclusive, may be chosen by the patient.



For patients randomized to group 1 (EBP), the symptoms in Table 8 will be assessed and graded 30 and 60 min post-procedure in person by the anesthesiologist who performed the procedure. The same symptoms will be assessed 24 and 48 hours after the procedure, in person if the patient remains in the hospital or by telephone if the patient has since been discharged. In addition, at 30 min the patient's comfort level with the procedure will be assessed using the VAS (0 = no discomfort during procedure; 10 = as uncomfortable as could possibly be imagined during the procedure). Specifically, the investigator will ask the patient how comfortable they were with the procedure irrespective of headache relief.

For patients randomized to group 2 (SPGB), the symptoms in Table 8 will be assessed and graded at 30 min post-procedure. If this treatment does not decrease the patient's "orthostatic headache" severity past the pre-treatment score, then the SPGB will be performed for a second time. The symptoms will be graded again 30 min after the second block. If the "orthostatic headache" severity score is still unchanged, then a SPGB will be performed for a third time. If the "orthostatic headache" severity score remains unchanged at the 30 min mark following the third SPGB, the procedure will be considered a failure and conservative measures or an EBP will be offered to the patient.

If the first, second or third SPGB succeeds in decreasing the "orthostatic headache" severity score at 30 min post-procedure, the symptoms in Table 8 will be assessed and graded again at 60 min post-procedure. In all cases, the same symptoms will be assessed at 24 and 48 hours post-procedure in the manner noted above. If patients in any group on telephone interview note dissatisfaction with the alleviation of the symptoms or if the symptoms return, they will be given the option of arriving at the Pain Clinic at the New Jersey Pain Institute during normal clinic hours or to the emergency room (ER) after hours. At that time, they will be given the option of an EBP, SPGB or medical management. This is the same as what would be offered if a patient underwent treatment for a PDPH outside of this study and had symptoms return afterward.

3.3. Procedures

3.3.1. Location

Both procedures, the EBP and the SPGB will take place in the Regional Nerve Block Area, a section of the operating room holding (OR holding) suite specifically designed for the performance of regional nerve blocks. Patients who consent to this study will be transported to this area by the institution's patient transport personnel and any other personnel that the institutional policy dictates. This area is accessible by anesthesiologists and includes the requisite monitoring and procedure equipment. This private area is the same location used by anesthesiologists for other regional nerve blocks; however, only one patient will be in any one bed location area at any given time.

Only the anesthesiologists (William Grubb, Shaul Cohen, Shruti Shah, Scott Mellender & Sagar Mungekar) will perform these procedures. Administrative assistants (Preet Patel) and residents will not perform any procedures. Ancillary staff such as resident physicians, nurses and technicians may be required to assist in checking the patient into the area, monitoring, and positioning as institutional policy dictates. The pregnancy test is part of the exclusion criteria (section 3.1.3) and all details with respect to the pregnancy test can be found in that section. The pregnancy test is not a part of the procedures.

3.3.2. Monitoring

While either the EBP or SPG block are performed, the patient's vital signs will be monitored by continuous pulse oximetry and five-lead electrocardiography (EKG) and a non-invasive blood pressure cuff cycled at least every five minutes. After the randomized procedure is assigned, a time-out procedure will be performed according to institutional protocol.

3.3.3. EBP

Immediately after obtaining informed consent, inclusion in the study, transport to the OR holding suite, randomization to the control arm of this study, completion of the time-out procedure, and initial symptom assessment, the patient will receive an EBP. The EBP involves three separate procedures: epidural access, venipuncture, and autologous transfer. Vital-sign monitoring of the patient as described above will commence once the patient is checked into this area. Symptom assessment will be as described in section 3.2.3. In addition, the investigator will assess whether the patient has any adverse effects of this procedure. These are rare, but could include pain at the site, a new motor deficit, a new sensory deficit and continued bleeding from any puncture site.

3.3.3.1. Epidural Access

Epidural access will be performed by the anesthesiologist using the Perifix FX Epidural Anesthesia Kit (Braun, Bethlehem, Pennsylvania), the same kit that is currently used for epidural anesthesia. The subject will be

positioned in either the decubitus or sitting position. The anesthesiologist will wear sterile gown and gloves. The patients' skin over the lumbar area will be prepped with povidone-iodine three times and draped in a sterile fashion. The appropriate lumbar interspace, one or more interspaces above the presumed site of the initial dural puncture, will be identified by anatomical landmarks and palpation. Five mL of 2% lidocaine will be locally infiltrated with a 25-gauge needle. A 17-gauge Touhy needle will be placed into the epidural space using the loss-of-resistance to air technique. Once positioned, the sterile stylette will be replaced within the needle to maintain the sterility of the epidural space. All of the equipment described in this section is included in the aforementioned kit.

3.3.3.2. Venipuncture

A tourniquet will be applied to either upper extremity to identify a peripheral venous site. The intended area of venipuncture will be prepped with betadine or chlorhexidine gluconate and isopropyl alcohol 1-mL applicator (ChloraPrep, CareFusion, San Diego, California) according to the manufacturer's directions. Venipuncture will be performed with an 18-guage needle attached to a 20-mL syringe. Twenty mL of blood will be aspirated into this sterile system. The tourniquet will be released and the needle, removed. Hemostasis will be achieved with manual pressure followed by a sterile dressing.

3.3.3.3. Autologous Transfer

The stylette from the Touhy needle described above will be removed. Negative aspiration will confirm that the needle has not pierced the dura or vasculature. Using sterile technique, the autologous blood sample will be slowly injected into the epidural space through the Touhy needle. Following epidural needle removal, pressure dressings will be applied to achieve hemostasis. The patient will be returned to the supine position and will remain in this position for one hour.

3.3.4. SPG block

Immediately after obtaining informed consent, inclusion in the study, transport to the OR holding suite, randomization to the treatment arm of this study, completion of the time-out procedure and initial symptom assessment, the patient will receive an SPG block. Vital-sign monitoring of the patient as described above will commence once the patient is checked into this area.

The subject will be placed in the supine position with the neck extended to the extent that he or she can tolerate with the use of a shoulder roll and head-of-the-bed positioning as appropriate. One cm of 5% lidocaine ointment will be applied to the end of each of two sterile 6-inch hollow–plastic-shaft cotton-tip applicator (Cardinal Health, Dublin, Ohio). One so-treated applicator will be inserted each of the patient's two both nares, posteriorly directed toward the anatomic location of

the sphenopalatine ganglion. Correct positioning will evidenced by slight resistance at the appropriate depth. Four mL of 1% lidocaine solution will then be slowly injected into the hollow shaft of the applicator and allowed to anesthetize the ganglion topically by gravity flow for 30 minutes. The applicators will be removed from the nares and the subject will be returned to the supine position with a neutral neck position.

Symptom assessment, determination of treatment failure, and performance subsequent procedures will be as described in section 3.2.3. In addition, the investigator will assess whether the patient has any adverse effects of this procedure. These are rare, but could include pain in the nares, epistaxis, pharyngeal numbness and a bitter taste in the mouth.

3.4. Duration of Study

The study will last 8 years in duration.

3.5. Study Sites

This is a single-site clinical research study that will be conducted at Robert Wood Johnson University Hospital, New Brunswick, NJ 08901 by the PI and SIs of Rutgers Robert Wood Johnson Medical School, part of Rutgers, the State University of New Jersey.

3.6. Sample Size Justification

We derive data for calculation of the sample size from the prior studies noted above. In the control group (Table 7, Group 1, EBP) we predict a success rate of 84% as noted by van Kooten et al. (7). In the treatment group (Table 7, group 2, SPG block) we predict a success rate of 68% based on our pilot study (15). If therefore there is a true 16% (84% - 68%) in favor of the EBP group then 210 subjects are required to be 90% certain that the upper limit of a one-sided 95% confidence interval will exclude a difference in favor of the EBP group of more than 33%. This calculation was performed using the formula below (Table 9 and Equation) using an online calculator https://www.sealedenvelope.com/power/binary-noninferior/).

Our chosen non-inferiority limit *d* of 33% means that we believed saving 67% (100% – 33%) of patients from the invasive EBP in favor of the non-invasive, cost-effective SPG block would be clinically relevant.

Table 9. Values used for determination of sample size

Variable	Description	Value
n	sample size	210
$\boldsymbol{\phi^{-1}}$	cumulative distribution function of a standardized normal deviate	*n/a*
$\boldsymbol{\alpha}$	significance level, alpha	0.05
$\boldsymbol{\beta}$	false negative rate, beta, where power $(1-\boldsymbol{\beta}) = 0.90$	0.10
$\boldsymbol{\pi_s}$	success rate in control group	0.84
$\boldsymbol{\pi_e}$	success rate in treatment group	0.68
$\boldsymbol{d}$	non-inferiority limit	0.33

Equation. Sample size calculation for a binary outcome non-inferiority trial

$$\mathbf{n} = \left(\boldsymbol{\phi^{-1}}(\boldsymbol{\alpha}) + \boldsymbol{\phi^{-1}}(\boldsymbol{\beta})\right)^2 \times \frac{\boldsymbol{\pi_s} \times (\mathbf{100} - \boldsymbol{\pi_s}) + \boldsymbol{\pi_e} \times (\mathbf{100} - \boldsymbol{\pi_e})}{\boldsymbol{\pi_s} - \boldsymbol{\pi_e} - \boldsymbol{d^2}}$$

4. Study Variables

4.1. Independent Variables and Interventions

As described in Section 3.3 “Procedures”, above, the two interventions to be studied are the EBP and the SPG block. Though the EBP is the standard of care for definitive treatment for PDPH, both procedures are well documented in the literature. Furthermore, the SPG block has already been shown in our pilot study to decrease the symptom severity in patients with PDPH, thus patients in both arms of this study will receive a treatment modality.

4.1.1. Drug and device Intervention for EBP

The procedure for the EBP is described in Section 3.3.3 above. All of the drugs and equipment required are either part of the kit noted or readily available in the Regional Nerve Block area. No equipment or drug described is experimental or investigational. The Current Procedural Terminology (CPT®, American Medical Association, Chicago, Illinois) code for EBP is 62273, “Injection, epidural, of blood or clot patch”.

4.1.2. Drug and device Intervention for SPG block

The procedure for the SPG block is described in Section 3.3.4 above. All of the drugs and equipment required are readily available in the Regional Nerve Block area. No equipment or drug described is experimental or investigational. Though a CPT code exists for a SPG block involving an injection (64505), as the technique described herein is non-invasive and does not involve injection, and as a specific code does not exist for this technique, it will be included in the

appropriate level Evaluation and Management (E/M) code. (AMA Knowledgebase #5436).

4.2. Dependent Variables and Outcome Measures

Symptom assessment as described in section 3.2.3 will be by personal or telephone interview by the PI or SI using a questionnaire (Attachment 1). The laboratory tests noted in the exclusion criteria including the pregnancy test and platelet count (Table 6), and the medical history interview are not specific to this study, and would be part of standard practice if the patient sought intervention for a PDPH outside of this study. No specimens will be taken.

4.3. Risk of Harm

As noted earlier, both the EBP and the SPG block are well-established procedures with favorable safety profiles. The limited risks of the procedures themselves are listed in the procedure sections above, but these are not specific to inclusion in this study.

Subjects who are enrolled in this study will be randomized to either one of the treatment arms whereas patients would otherwise be given the choice of which one they prefer. There is a risk of psychological or emotional harm that is intrinsic to any such randomized treatment study; however, this risk is minimized since as stated earlier, all subjects retain the ability to be excluded from the study and undergo the procedure of their choice at any point in the study process.

This study aims to determine whether there is a difference in the symptom-free period. If the study ultimately finds that one treatment maintains a longer symptom-free period, the subject in the other arm of the study could face having to undergo a repeated or new procedure. Again, this harm is minimal, since symptom-assessment scheme is such that in the period that symptoms are likely to relapse after a failed treatment (1–24 hours), the patient will be repeatedly assessed.

The subject may encounter minor inconvenience after receiving two follow-up phone calls for symptom assessment instead of the standard one call. This would account for approximately 5 minutes of extra time out of the patient's day.

4.4. Potential for Benefit

All patients enrolled in this study will receive one type of treatment for a PDPH. Since we seek to enroll all patients who meet the minimum criteria for the diagnosis of PDPH (Table 2), all included subjects will potentially be spared pain medications that are often given during conservative treatment efforts as well as avoiding having to cope with these symptoms while medical management is attempted.

If one arm treatment is found to be better than the other, the subjects in that group may experience a quicker relief of symptoms, and improvement in the overall quality of life.

Following the conclusion of the study, the medical community will gain knowledge about the best method by which certain individuals may be treated for PDPH.

5. Data Handling and Statistical Analysis

5.1. Safeguarding Data

All data will be stored in a locked file in the office of the principal investigator with limited access. Once the subject is enrolled, he or she will be assigned a number that will both assign the subject to one of the arms as well as serve as the identification number for the storage of results. Since this study involves multiple contacts with the subject, one set of data will contain demographic information including the patient's name and telephone number, which is recognized as protected health information (PHI). The other set of data will only reference the assigned number and will contain the symptom assessment data. The link to the protected health information (PHI) will be stored separately from the study files and will be destroyed after all the data has been collected and analyzed. Up to 500 subjects may sign the informed consent for participating in this trial. This number is to ensure 210 subjects complete each study group below. Therefore, we will be replacing subjects that do not complete the study as designed.

5.2. Analysis

Nonparametric data such as those resulting from the VAS assessments from the two groups will be compared using the Mann–Whitney U test. The Student's *t*-test will be used to compare normally distributed continuous variables. A p value of less than or equal to 0.05 will be considered statistically significant.

6. Data and Safety Monitoring

All subjects enrolled in this study will receive at least one of two types of treatment for their PDPH. Both the EBP and SPG block are low-risk procedures that can be and are routinely performed in an office setting on outpatients in our pain clinic at the New Jersey Pain Institute. Furthermore, neither of these techniques are experimental; rather, their methods are well documented in literature and are common procedures in the pain medicine field.

Subjects who undergo the procedures within this study will have additional monitoring as opposed to patients who undergo the same procedures outside of this study. Patients in this study will receive two follow-up phone calls to assess their symptoms and to expedite the availability of any additional procedures that need to be performed. These telephone calls will also serve to inform the SIs and PI if the patients are experiencing any undue and unexpected harms as a result of this study. As all of the investigators in this study are in the department of anesthesia, they are the best equipped to identify potential side effects and treatment.

All subjects enrolled in this study will be given a contact sheet including phone numbers by which they may reach the PI, emergency room, the pain clinic, and the Pain Medicine

physician-on-call who, as previously stated, is available continuously by mobile telephone.

7. Reporting Results

7.1. Individual Results

The only laboratory tests that may be performed are a urine pregnancy test and a platelet count as part of the exclusion criteria (Table 6). Both of these tests are frequently performed on patients in the hospital. If this test was already performed before the patient was enrolled in the study, the physician who ordered the test will be responsible for notifying and counseling the patient. If the test is performed after enrollment in the study, in the case of an unexpected result, namely a positive pregnancy test or a low platelet count, the patient will be notified immediately after the PI or SI views the result. The patient will be excluded from the study and counselled about the ramifications of the results. These laboratory tests will be performed using the same equipment and methods that are used for all patients at Robert Wood Johnson University Hospital.

7.2. Aggregate Results

Aggregate results will be available after statistical analysis. Subjects may contact the PI to view or learn about the aggregate results after the study has been completed. Subjects may be provided with copies of abstracts or directions on how to retrieve the data resulting from this study. Any study data so released to the subjects will be anonymized such that no protected health information is traceable from those data.

7.3. Professional Reporting

The data gathered and conclusions reached from this study will be presented in several venues including departmental meetings, abstracts and posters at professional meetings, and a manuscript in a peer-reviewed pain medicine journal.

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