UCSF Headache Center

Protocol

NCT03666663

Sphenopalatine Ganglion (SPG) Block Randomized Placebo Controlled Study

11/29/2018
Version 1.6

Nina Riggins, MD
Department of Neurology
UCSF Headache Center
2330 Post Street, Suite 610
San Francisco, CA 94115
415-353-8393
Nina.Riggins@ucsf.edu

CONFIDENTIAL

Table of Contents:

1. Introduction
    a. Project summary :

Chronic Migraine is a brain disorder with high prevalence. It is the 7th leading cause of disability worldwide according the WHO.

SPG block is a treatment for migraine that has been used for two decades. It can be done by needle injection of anesthetic to the region of the SPG. However, there are now multiple catheter devices that can be used to non-invasively administer anesthetic topically through the nasal cavity to the region of the SPG where the anesthetic is then absorbed through thin membranes covering the SPG.

Various anesthetic agents have been studied however currently, to our knowledge, there is no head to head comparison of the long versus short acting anesthetics. Studies of SPG blocks in the setting of chronic migraine are few as compared to the use of SPG as acute treatment for migraine.

With the use of an RCT, we aim to determine the overall efficacy of SPG blocks used at longer intervals than have been studied in the past as compared to placebo, as well as to examine the relative efficacy of the anesthetics used most commonly and studied for SPG blocks.

We will be using an FDA cleared device, the Sphenocath which was developed and registered with the FDA for this specific population and purpose. The study intervention is the standard practice in the UCSF Headache Center to perform SPG blocks for our patients with chronic migraine. The frequency we plan is less often than in previous studies of this intervention in this population. Patients will continue their usual headache care and treatments during the study.

i. Name and dosage of drugs

a. 2% lidocaine, 0.5cc each nostril
b. 0.25% bupivacaine, 0.5cc each nostril
c. 0.5% ropivacaine, 0.5cc each nostril
d. Placebo (normal saline), 0.5cc each nostril

ii. Pharmaceutical class of drugs

Anesthetics

iii. Structural formula of active drugs

a. lidocaine : $C_{14}H_{22}N_2O$
b. bupivacaine : $C_{18}H_{28}N_2O$
c. ropivacaine : $C_{17}H_{26}N_2O$

iv. Route of administration
1. Nasal application, via Sphenocath. This device is a small, flexible catheter which is a needle-less, topical applicator. It is FDA cleared for use to deliver anesthetic solution to the region of the SPG.

2. Research Plan and Procedures
a. Hypothesis

Use of SPG (sphenopalatine-ganglion) blocks approximately every 2-4 months for three treatments will be proven superior in migraine headache treatment as compared to placebo.

Using a placebo group and randomized control study design will control for the natural waxing and waning variation that can be expected to occur in migraine over the study duration.

Headache frequency and severity, as measured by daily standard headache diary, will improve with the use of repeated SPG Blocks every 2-4 months by the end of the study period.

One of the anesthetics will be found to be more efficacious than the other.

There will be an improvement in the effect and duration of the therapeutic benefit of the each of the repeated SPG blocks with anesthetics over time.

Patients receiving active treatment will require fewer acute treatments and emergency room visits than those receiving placebo.

b. Aims
i. To determine whether the use of SPG (sphenopalatine-ganglion) blocks less frequently than previously studied will still be effective in migraine headache prevention.
ii. To determine if there is a difference in efficacy between lidocaine and bupivacaine and ropivacaine
iii. To determine whether the repeated use of SPG blocks every 2-4 months for 3 treatments will have a cumulative effect with subsequent

treatments providing better and longer lasting effects on headache frequency and severity.

iv. To determine if repetitive SPG blocks can reduce the need and use of acute treatments and emergency room visits

c. Study Design

This will be a randomized, double blind, placebo controlled study of non-invasive SPG blocks in patients with chronic migraine using the Sphenocath device.

Approximately 120 patients will be randomized in a 1:1:1:1 ratio to receive SPG block using lidocaine, or bupivacaine or ropivacaine or normal saline every 2 to 4 months for three treatments. There will be approximately 30 subjects in each group.

The study period will run approximately 8 months.

During the study period participants will continue to use their usual headache medicines and treatments. Participation in this study will not change their other headache treatments.

d. Background and significance

The sphenopalatine ganglion is located in the pterygopalatine ganglia close to the sphenopalatine foramen and is located below the maxillary nerve as it crosses the fossa. The sphenopalatine ganglion has multiple connections to facial, trigeminal, parasympathetic and sympathetic systems which make it a promising target for migraine treatment. [1,2,3]

SPG blocks are widely used as an acute treatment of migraine[4-7,] ; and other headache disorders [8-10] although the preventive effects [11] have not been widely studied .

SPG blocks are quite commonly performed at the headache center to treat chronic migraine, and patients report significant relief. We would like to determine if the frequency and medications that we use as our standard of care prove to be significantly better than placebo and also to see if there is a difference in the anesthetics that we usually instill.

e. Preliminary studies

The use of SPG blocks for head pain goes back over a century. Sluder in 1908 was the first to describe injection of the sphenopalatine ganglion via the nasal approach and subsequently reported success with its use in headache, facial neuralgia, earache, and “lower-half headache”. (12)

Intranasal (IN) instillation of lidocaine has been studied as an acute treatment for migraine both in the emergency department and in the home setting. (13-16).

Maizels and Geiger (1999) in their placebo controlled study trained patients to self-administer the study solution intranasally (either 4% lidocaine vs placebo) (13). Fifty one subjects were instructed to treat every headache for 1 month. There were 95 headaches treated with IN lido and 108 headaches with placebo. Headache relief at 15 minutes was found to be markedly superior to placebo.

Benefit of SPG blocks with various anesthetics has been shown to be helpful in other head pain syndromes including reducing pain atypical face pain and cluster headache. (8-10)

In migraine specifically, SPG blocks have been studied in various populations including acute migraine, chronic migraine, chronic migraine with medication overuse, and status migrainosus. (4-7,11)

There are various methods for performing SPG blocks some of which are more invasive and risk prone that using catheter application.

Suprazygomatic injections to the region of the SPG was studied as an acute migraine treatment by Mehta et al (2018) in a cohort study (4). They injected a mixture of steroid (dexamethasone) and 0.5% ropivacaine through the skin above the zygomatic arch, to the region of the SPG. Eighty eight patients received a total of 252 injections to block the SPG. They reported no significant complications of the procedure. At 30 minutes following treatment, the overall reduction of pain among patients was statistically significant.

Cady et al (2015) investigated a less invasive, novel device (Tx360), to perform SPG blocks for chronic migraine. (7) They performed a double-blind, parallel-arm, placebo-controlled, randomized trial of 38 patients. They measured pain scores at baseline, 15 minutes, 30 minutes, and 24 hours post treatment. The active phase consisted of a series of 12 SPG blocks with 0.5% bupivacaine or saline which were provided 2 times

per week for 6 weeks. All side effects were mild to moderate, short in duration, and resolved spontaneously. No subject withdrew because of side effects which included mouth numbness (18%), lacrimation (29%), and bad taste (15%). Patients treated with bupivacaine showed a significant reduction in their pain scores from baseline at all intervals. Headache Impact Test-6 (HIT-6) scores were statistically significantly decreased in subjects receiving treatments with bupivacaine from before treatment to the final treatment, whereas no significant change was seen in the placebo group.

The authors went on to analyze the long term effect of these repetitive SPG blocks with bupivacaine in the second part of their study (11). They reassessed patients at 1 month and 6 months post active treatment and they found a sustained reduction of headache days along with an improvement in functional assessment in the treatment group.

Another catheter used to deliver medication topically to the region of the SPG is the Sphenocath. Binfalah et al (2018) reported on their open, uncontrolled, retrospective study of SPG blocks using Sphenocath for acute migraine (5). They enrolled 55 patients and delivered 2ml of 2% lidocaine to the region of the SPG bilaterally. Adverse events reported were mild, including transient throat numbness (100%), nausea (10.9%), dizziness (10.9%), vomiting (1.8%), nasal discomfort (18.2%), and worsening of preexisting headache (1.8%). These side effects were transient and lasted less than 24 hours. Headache freedom at 15 mins was 70.9%, at 2 hours was 78% and at 24 hours was 70.4%.

The Sphenocath is the device we have used in the UCSF Headache Center for more than 2 years with no significant side effect or complication experienced and with patients reporting relief. We routinely use all of the medications studied (lidocaine, bupivacaine and ropivacaine). The selection is usually based on provider preference or intuition since there is no evidence to guide the choice.

f. References

1. Goadsby PJ, Zagami AS, Lambert GA. Neural processing of craniovascular pain. Headache. 1991; 31:365-370
2. Piagkou M, Demesticha T, Troupis T, Vlasis K, Skandalakis P, Makri A, Mazarakis A, Lappas D, Piagkos G, Johnson EO. The pterygopalatine ganglion and its role in various pain syndromes: From anatomy to clinical practice. Pain Pract 2011; 12:399-412

3. Robbins MS, Robertson CE, Kaplan E, Ailani J, Charleston L, Kuruvilla D7, Blumenfeld A, Berliner R, Rosen NL, Duarte R, Vidwan J,Halker RB, Gill N, Ashkenazi A. The Sphenopalatine Ganglion: Anatomy, Pathophysiology, and Therapeutic Targeting in Headache. Headache. 2016 Feb;56(2):240-58.
4. Mehta D, Leary MC, et al. The Effect of Regional Anesthetic Sphenopalatine Ganglion Block on Self-Reported Pain in Patients With Status Migrainosus. Headache. 2018 Jul 25
5. Binfalah M, Alghawi E, Shosha E, Alhilly A, Bakhiet M. Sphenopalatine Ganglion Block for the Treatment of Acute Migraine Headache. Pain Res Treat. 2018 May 7;2018:2516953
6. Mojica J, Mo B, Ng A. Sphenopalatine Ganglion Block in the Management of Chronic Headaches. Curr Pain Headache Rep. 2017 Jun;21(6)
7. Cady R., Saper J., Dexter K., Manley H. R. A double-blind, placebo-controlled study of repetitive transnasal sphenopalatine ganglion blockade with Tx360® as acute treatment for chronic migraine. 2015;55(1)
8. Klein RN, Burk DT, Chase PF. Anatomically and physiologically based guidelines for use of the sphenopalatine ganglion block versus the stellate ganglion block to reduce atypical facial pain. Cranio. 2001;19:48–55.
9. Kittrelle JP, Grouse DS,Seybold ME. Cluster headache. Local anesthetic abortive agents. Arch Neurol.1985;42:496–498.
10. Candido K. D., Massey S. T., Sauer R., Darabad R. R., Knezevic N. N. A novel revision to the classical transnasal topical sphenopalatine ganglion block for the treatment of headache and facial pain. 2013;16(6):E769–E778.
11. Cady RK, Saper J, Dexter K, Cady RJ, Manley HR. Long-term efficacy of a double-blind, placebo-controlled, randomized study for repetitive sphenopalatine blockade with bupivacaine vs. saline with the Tx360 device for treatment of chronic migraine. Headache. 2015 Apr;55(4):529-42.
12. Sluder G. Lower half headache (neuralgic) of nasal origin. JAMA. 1922;79:1898–1899
13. Maizels M, Geiger AM. Intranasal lidocaine for migraine: a randomized trial and open-label follow-up. Headache 1999 Nov-Dec;39(10):764.
14. Blanda M, Rench T, Gerson LW, Weigand JV. Intranasal lidocaine for the treatment of migraine headache: a randomized, controlled trial. Acad Emerg Med. 2001 Apr;8(4):337-42.
15. Avcu N, Doğan NÖ, Pekdemir M, Yaka E, Yılmaz S, Alyeşil C, Akalın LE. Intranasal Lidocaine in Acute Treatment of Migraine: A Randomized Controlled Trial. Ann Emerg Med. 2017 Jun;69(6):743-751.

16. Kudrow L., Kudrow D. B., Sandweiss J. H. Rapid and Sustained Relief of Migraine Attacks With Intranasal Lidocaine: Preliminary Findings. 1995;35(2):79–82.

3. Procedure

UCSF Headache Center patients with chronic migraine who are identified by their treating physician to be a candidate for SPG block, and who meet inclusion criteria will offered enrollment in the study.

After the study risks have been explained and consent and HIPAA have been documented, the patient will be randomized to receive active drug or placebo using the FDA cleared medication delivery device, SphenoCath. This device is a needleless nasal topical applicator. The small flexible catheter is introduced through the nares and delivers medication non-invasively to the region of the SPG.

For those patients who wish to enroll, they will be randomized in 1:1:1:1 fashion in blocks to receive of the four study liquids given in three treatments spaced two to four months apart.

a. Study drugs : bilateral nasal applications via Sphenocath (each consisting of 0.5 cc of liquid per nostril) of the following:
    i. Lidocaine 2% OR
    ii. Bupivacaine 0.25% OR
    iii. Ropivacaine 0.5% OR
    iv. Normal Saline

b. Inclusion and exclusion criteria

Inclusion Criteria

1. Age 18 years or more at time of consent

2. Current patients in the UCSF Headache Center eligible to receive SPG blocks for migraine and would otherwise receive treatment clinically

3. Ability to provide consent for the research study

Exclusion Criteria

1. Pregnant or breast feeding within 4 weeks of enrollment

2. Inability to communicate with the study team

3. Patients who cannot read and understand English

4. Deemed unsuitable for enrollment in study by the investigator

5. Allergy to local anesthetics or saline

c. Recruitment and Consent

The patient will come to the UCSF Headache Center for their regular clinic appointment.

During this visit, the study team member will describe the research study and if they are interested in participating, the patient will have time to read through the consent form and clarify any questions that the patient may have regarding the study.

Once the patient reads and understands the Informed Consent From, eligibility will be determined by the study physician based on medical history and study criteria.

After signing the consent and HIPPA, they will be randomized to their study assignment.

d. Risks and Benefits

As part of the consent process, participants will be told that when topical anesthetics are used in the nose, mouth, or throat, it may cause decrease in local sensation for a few minutes. Participants will be told to be mindful when eating or drinking any foods or liquids in the hour after receiving treatment. They will be informed that they may experience short lasting dizziness or lightheadedness which is exceedingly rare in our experience but reported in previous studies.

The risk of allergies will be discussed, and all current medications and health conditions will be considered by the investigators before offering participation to patients.

Randomization and placebo risks will be described to the participant during the consent process.

e. Data collection

The data collected at each study visit will be the frequency and intensity of migraine headaches during the interval period. Data will be stored in HIPAA compliant fashion.

Chi square will be used to analyze to determine if there is a significant statistical difference among the groups.

After the next routine clinic visit post study period, we will compare mean number of headache days per month of mild, moderate and severe headache post treatment to the baseline collected prior to first SPG block.

f. Safety monitoring

Although there is safety data for the use of anesthetic nasal blocks, and a DSMB is not required, safety will be carefully monitored throughout this study.

There is no planned interim analysis. Participants may be removed from the study if it is in their best interest and it will be up to the determination of the PI, or participant.

Any serious adverse events will be communicated to the IRB, in accordance with their guidelines.

All serious and non-serious adverse events will be collected in an adverse event reporting form.

In accordance with the standard operating procedures and policies of the local Institutional Review Board (IRB), the site investigator will report SAEs to the IRB per UCSF IRB guidelines.

As part of the participant's visits, we will ask the patient about frequency and intensity of their headaches between visits (and review their standard clinic headache diary). Home medications along with any new medical problems will be reviewed with the participant before receiving the study treatment.