Study Title: A Phase II Randomized Controlled Double-Blind Clinical Trial of Sphenopalatine Ganglion Block for Headache after Concussion

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1. Project Summary

While advancements have been made in the understanding of practices to optimize recovery from concussion, the current standard of care remains largely based around the management of physical and cognitive activity levels, as well as physical therapy modalities.[1] Despite optimal use of these measures, some patients do not recovery from concussion a timely manner, leading to prolonged symptomatic period and associated medical costs.[2] There is a lack of direct interventions to improve the recovery from concussion, and so there is a need for further research on potential treatments for concussion.

Headache is among the most common symptoms following concussion,[3] but there are no established treatment guidelines for post-traumatic headache.[4] Sphenopalatine ganglion (SPG) blocks have been used for other headache disorders, with previous studies showing benefit in primary headache disorders including migraine[5] and cluster headache.[6] Anecdotal reports have suggested similar benefit from SPG blocks in chronic post-traumatic headache,[7] but there have been no formal studies establishing this benefit, nor has this been studied in the earlier period of recovery after concussion. Given the high frequency of headache after concussion, and potential physiologic similarities between post-traumatic headache and other headache disorders such as migraine, the SPG block has potential as treatment for post-traumatic headache that may improve recovery from concussion.

2. Objective

The objective of this study is to determine if a SPG block performed after concussion is associated with improvements in post-traumatic headache. The primary outcome will be measured by a reduction in headache severity score of 50% or more in the 48 hours following the procedure compared to the 48 hours prior to the procedure. Secondary objectives will be measured by a reduction in Patient Global Impression of Change rating, number of headache occurrences, days with headache, hours per day with headache, and as-needed headache medication uses. Exploratory objectives are to evaluate if a SPG block improves other non-headache concussion symptoms, as measured by Sport Concussion Assessment Tool version 5 (SCAT5) symptom numbers and severity scores at baseline prior to the procedure and following the procedure; and to evaluate if a SPG block results in improvement in physiologic changes related to potential autonomic nervous system dysfunction due to concussion, as measured by comparisons in orthostatic heart rates and resting heart rate variability recorded prior to and after the procedure.

3. Specific Aims/Hypothesis:

Specific Aim #1: To evaluate the effects of a SPG block on headache severity after concussion. We hypothesize that a greater reduction in mean headache severity score in patients who receive a SPG block with lidocaine in the 48 hours after the SPG block compared to the 48 hours before the SPG block. We also hypothesize that patients who receive a SPG block with lidocaine will report lower mean Patient Global Impression of Change (PGIC) scores at two hours and 24 hours post-SPG block compared to those who receive placebo.

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Specific Aim #2: To evaluate the effects of a SPG block on headache frequency and duration after concussion. We hypothesize that patients who receive a SPG block with lidocaine will report less headache days, less headache episodes, and a lower mean number of hours with headache per day than the patients who receive a placebo SPG block in the one week after the SPG block compared to the one week before the SPG block.

Specific Aim #3: To evaluate the effects of a SPG block on as-needed headache treatments after concussion. We hypothesize that patients who receive a SPG block with lidocaine will report a lower mean number of doses of as-needed headache treatments per day than the patients who receive a placebo SPG block in the 48 hours and one week after the SPG block compared to the 48 hours and one week before the SPG block.

Exploratory Aim #1: To evaluate the effects of a SPG block on non-headache concussion symptoms. We hypothesize that patients who receive a SPG block with lidocaine will report lower symptom scores for nausea or vomiting, dizziness, blurred vision, sensitivity to light, and sensitivity to noise than those who receive a placebo SPG block in the 24 hours, 48 hours and one week after the SPG block compared to the 24 hours, 48 hours, and one week before the SPG block.

Exploratory Aim #2: To explore the potential effects of a SPG block on heart rate measurements. We hypothesize those receiving a SPG block with lidocaine will have lower rates of abnormal orthostatic heart rate elevations on standing and higher RMSSD (root-mean square differences of successive R-R intervals) than those who receive a placebo SPG block at 15 minutes following the SPG block compared to before the SPG block.

4. Background

The sphenopalatine ganglion (SPG) is a collection of neurons in the pterygopalatine fossa with parasympathetic, sympathetic, and sensory components that have been implicated in neurologic conditions causing headache and facial pain.[8] Blockade of the SPG has been performed using different methods, including introduction of a local anesthetic (e.g. lidocaine) into the nasal passage using a soft catheter.[9] There is evidence of sustained relief from SPG blockade in primary headache disorders, including chronic migraine[5] and cluster headache.[6] Additionally, there is a case report showing benefit in post-concussion syndrome.[7] However, there have been no studies evaluating the use of SPG blocks for post-traumatic headache in the early symptomatic period after concussion.

Autonomic nervous system dysfunction that has been demonstrated following concussion is believed to play a role in symptom generation.[10] As the SPG is an important relay center for autonomic nervous system transmission, and the benefits of SPG blocks may be related to modulation of autonomic function,[8] it is anticipated that using SPG blocks in symptomatic concussion patients may improve their recovery. The current standard of care in managing sport-related concussion is largely based

around management of physical and cognitive activity levels, as well as over-the-counter medications for symptom management and physical therapy modalities.[1] However, despite optimal use of these measures, for some patients symptoms of concussions do not resolve in a timely manner, leading to prolonged symptomatic period and associated medical costs.[2] Therefore, this proposed trial has potential to fill the need for additional treatments to optimize recovery from concussion.

5. Study Device

The SpenoCath device is a soft, flexible catheter that is indicated to deliver fluid (such as medication) into the nasal passage, which can facilitate the direction of fluid to the pterygopalatine fossa where the sphenopalatine ganglion resides. The device is a disposable, single use catheter that is attached to a syringe which contains medications (such as local anesthetics) used in procedures such as SPG blocks. The user inserts the device into the nares of the patient and advances a soft, angled tip that directs the medication to the target area within the nasal passage. It is designed to be used by trained medical professionals.

6. Methodology

6.1 Study Sites:

This is a single-center study that will be completed at the University of Michigan (UM). Subjects will be enrolled from concussion clinics at UM. Research visits will be completed either at the conclusion of a scheduled clinic follow-up visit, or as a separate research visit in the clinic space or an approved research space at UM.

6.2 Study Duration:

The anticipated enrollment period will be approximately nine months. Enrollment will begin following IRB approval and completion of other necessary regulatory approvals.

6.3 Participants:

Participants in this study will include patients between 18 and 60 years of age who have been diagnosed with a concussion. Participants will be randomized into one of two groups:

1. Treatment: participants in this group will receive a SPG block using an aqueous 1% lidocaine solution.
2. Control: participants in this group will receive an identical a placebo SPG block using a normal saline solution.

6.4 Inclusion criteria:

Participants will be eligible for this study if they are between the ages of 18 and 60 years of age, have been diagnosed with a concussion by a specialist trained in the care of concussion based on clinical history and physical examination findings consistent with most recent consensus guidelines,[1] are

greater than 14 days from the date of their injury, and are experiencing ≥4 occurrences of headache per week lasting at least 1 hour per occurrence, each with a headache severity score ≥2 out of 6.

6.5 Exclusion criteria:

Patients will be excluded if they have an allergy to local anesthetic of the amide type (e.g. lidocaine), frequent epistaxis (i.e. more than one nose bleed per month), bleeding disorders, are pregnant, are at increased risk for methemoglobinemia (including patients with glucose-6-phosphate dehydrogenase deficiency, congenital or idiopathic methemoglobinemia, cardiac or pulmonary compromise, and concurrent exposure to oxidizing agents or their metabolites and drugs associated with methemoglobinemia), have history of any of the following: nasal or facial fracture, nasal septal defect, any other craniofacial abnormality, hepatic disease, Adam-Stokes syndrome, Wolff-Parkinson-White syndrome, or severe degrees of sinoatrial, atrioventricular, or intraventricular heart block, or if they begin a different headache treatment at the time of study enrollment.

6.6 Recruitment:

Patients between the ages of 18 and 60 years of age with post-traumatic headaches due to concussion will be recruited from concussion clinics at the University of Michigan. Patients will be identified by providers at their clinics if they are eligible for the study, and they will be recruited by an approved study team member.

6.7 Informed Consent:

Eligible patients will be consented in person, over the telephone, or over a video visit after a discussion that includes the risks, benefits, and alternatives to participating in the study. An informed consent document that is approved by the IRB will be used to document consent. The informed consent process will be completed by a trained, approved member of the study team at the clinic visit at which the patient is identified for participation in the study. Patients will be provided a paper copy of the signed informed consent document.

6.8 SPG Block Procedure

Participants will lay supine on an examination table with their chin elevated. Each nares will be visually inspected. A SphenoCath device attached to a 5mL syringe will be coated with a lubricating gel. The SphenoCath catheter tip will be inserted 3-4cm into the left nares, guided above the middle turbinate, and 2.5mL of solution will be deposited. Participants in the treatment arm will receive a 1% lidocaine solution. Participants in the control arm will receive a saline solution. The same process will be repeated in the right nares. The participant will then remain in the same supine position for five minutes before sitting up. Participants will be asked to refrain from using any new as-needed headache treatments for the one week following the procedure.

6.9 Outcome measures

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-Primary outcome data points:
1. Headache severity scores: the patient will be asked to use an online survey to report their average daily headache severity score every 24 hours, starting one week prior to the SPG block procedure, until one week following the procedure. They will be asked to rate their headache on a scale of 0 to 6, with 0 corresponding to "absent" and 6 corresponding to "severe." Additionally, at the SPG block research visit, the patient will be asked to report a headache severity score immediately before the procedure, 15 minutes after the procedure, and two hours after the procedure.

-Secondary outcome data points:
1. Patient Global Impression of Change (PGIC): a rating scale of global improvement with treatment on which participants use a seven-point scale ("1" = very much improved, "4" = no change, "7" very much worse). Using the online survey, participants will rate their change at two hours and 24 hours following the SPG block procedure.

2. Headache frequency/duration: at baseline prior to the procedure, using the aforementioned online survey, the patient will be asked to report the number of headache episodes and hours with headache every 24 hours over the one week prior to the SPG block. Every 24 hours after the SPG, for up to one week after the procedure, as part of the online survey the patient will be asked to record the number of headache episodes and hours with headache in identical fashion.

3. As-needed headache treatment usage: at baseline prior to the procedure, using the aforementioned online survey, the patient will be asked to report the number of uses of as-needed headache medications used every 24 hours in the one week prior to the SPG block. Every 24 hours after the SPG, for up to one week after the procedure, as part of the online survey the patient will be asked to record the number of uses of as-needed headache medications.

-Exploratory outcome data points:
1. Sport Concussion Assessment Tool Version 5 (SCAT5) symptom scores: A symptom checklist survey from the SCAT5 will be given to the patient at baseline at the beginning of the study and every 24 hours during the study period, until one week following the SPG block procedure. From this checklist, the patient will be asked to rate all 22 symptoms on the checklist as 0 (absent) to 6 (severe).

2. Heart rates: immediately prior to the procedure, and 15 minutes following the procedure, the patients' heart rates will be recorded in identical fashion using a Polar (Bethpage, NY) chest-worn heart rate monitor. Heart rate and R-R interval will be recorded at rest in the supine position. R-R interval will be recorded for five minutes. Root mean square of successive differences (RMSSD) will be calculated from the R-R interval to measure heart rate variability using Kubios HRV (Kuopio, Finland). Following this, heart rate will be checked immediately upon standing and after standing for two minutes.

6.10 Schedule of Visits and Testing Requirements:

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Potential participants who are eligible for the study will be identified from a concussion clinic at the University of Michigan and will complete the informed consent process. After enrolling in the study, they will be linked to a daily online survey which will ask them to record daily symptom severity scores using the Sport Concussion Assessment Tool version 5 (SCAT5) symptom checklist, rating symptoms (including headache) on a scale of 0 to 6, with 0 corresponding to "absent" and 6 corresponding to "severe." They will also be asked to record the number of headache episodes, the number of hours with headache, and the number of doses of as-needed headache medication usage every 24 hours for the one week prior to the research visit.

Participants will take part in one in-person research visit, during which the SPG block procedure will be performed. At the beginning of the visit, participant demographic information and baseline characteristics will be recorded, including age, sex, height, weight, date of concussion, history of baseline migraine, depression, anxiety, or ADHD, and history of previous concussions. The participant also will complete the 22-item SCAT5 symptom checklist, as before. Participants will then be fitted with a chest-worn Polar heart rate monitor, which will record resting heart rate and R-R interval while in the supine position. Heart rate will then be recorded immediately after standing, and after standing for two minutes. Next, the SPG block procedure will be performed, as described below. 15 minutes after the procedure, heart rate and R-R interval will be recorded in identical fashion to the pre-procedure recordings. Finally, the participant will again complete the SCAT5 symptom checklist.

Following the research visit, they will record SCAT5 symptom scores, headache episodes, headache hours, and as-needed headache medication usage every 24 hours for the one week following the research visit, identical to the pre-procedure recordings. Additionally, they will complete the SCAT5 symptom checklist and rate their status on the PGIC scale at two hours post-SPG on the day of the research visit. Their direct participation in this study will conclude after the one week post-SPG block survey data is recorded.

The following detail summarizes the time points and components of data collection during the research study.

	SCAT5	oHR	HRV	HA episodes	HA hours	# PRN doses	PGIC	AEs
Every 24 hours, before the SPG block	x			x	x	x		x
SPG visit (pre-procedure)	x	x	x					x

SPG visit (15 min post-procedure)	x	x	x					x
2h post-procedure	x						x	x
24h post-procedure	x			x	x	x	x	x
Every 24 hours, before the SPG block	x			x	x	x		x

-SCAT5: Sport Concussion Assessment Tool version 5, 22-item symptom checklist, including headache; each symptom rated between 0 and 6.
-oHR: Orthostatic heart rates (HR); HR measured while laying supine at rest, immediately after standing, and after standing for two minutes.
-HRV: R-R interval measured while laying supine at rest
-HA episodes: The number of discrete headache episodes of any duration that occurred during the 24 hour period.
-HA hours: The number of cumulative hours with headache during the 24 hour period.
-# PRN doses: The number of doses of as-needed headache treatments (e.g. acetaminophen, ibuprofen) used during a 24 hour period.
-PGIC: Patient Global Impression of Change, 7-item rating scale ("1" = very much improved, "7" = very much worse)
-AEs: Adverse events

6.11 Early Withdrawal/Premature Discontinuation of Subjects:
A participant may voluntarily withdraw from this study at any time, and participants also can be withdrawn from the study at the investigator's discretion. If a participant is withdrawn from the study, their collected data up to the time in which their participation in the study ends will remain included in the study data and will be used for analysis.

6.12 Handling of Lost-to-Follow-Up Subjects:
If a participant does not complete any part of the pre- and post-procedure survey data, the study coordinator will make efforts to contact the participant to complete the missing data. Any correspondence with participants will be documented and maintained as part of the participant's study file.

6.13 Sample size and power calculation:

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Sample size calculations were based on previous studies on the use of SPG blocks in acute migraine headache[11] and chronic migraine,[5] in addition to considering the expected recruitment potential from the clinic in the one year study grant period. A sample size of 24 participants (12 per group) was calculated to achieve 80% power with an alpha cutoff 0.05.

6.14 Randomization

To achieve two groups with equal numbers balanced by treatment type (i.e. SPG block with lidocaine vs placebo with saline), a block randomization method will be utilized. To maintain blinding, the study coordinator will prepare SPG block materials based on the randomization scheme in advance of the participant study visit.

7. Adverse Events

Adverse events (Aes) will be queried as part of the daily online survey every 24 hours. Participants also will be encouraged to contact the study team with any concerns for AEs. All AEs, regardless of severity will be recorded and followed by the principal investigator.

7.1 Anticipated Clinical Signs and Symptoms:

It is anticipated that during the SPG block procedure, participants may experience brief discomfort when the catheter tip is inserted into the nares. The participant may experience a brief, unpleasant taste sensation from the inserted liquid (either lidocaine or saline solutions). In the case of the lidocaine treatment, participants may experience transient numbness of the nasopharyngeal mucosa. These anticipated signs and symptoms will not be considered AEs and are not expected to lead to any Aes.

7.2 Severity of Adverse Events:

All AEs will be assessed for their severity and will adhere to the UM IRBMED's standard AE adjudication table. AE severity will be classified as follows:

> -Minor: An AE of either no consequence requiring no therapy, or of no consequence requiring only nominal therapy (e.g. overnight hospital admission for observation).
> -Major: An AE requiring therapy and a non-complicated hospital stay (<48 hours); requiring major therapy or prolonged hospitalization (>48 hours); causing permanent adverse sequelae; causing death.

7.3 Reporting Adverse Events:

If an AE event occurs, it will be documented by a trained member of the study team. The study PI will determine AE severity and relatedness to study. Any AEs related to the study will be reported according to the UM IRBMED's standard AE/ORIO reporting timetable.

8. Statistical Design

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For the primary outcome, an analysis of covariance (ANCOVA) model will be used to determine treatment effect. The post-treatment headache severity score will be the dependent variable, and the pre-treatment headache severity score and treatment type (lidocaine or placebo) will be independent variables in the model. An ANCOVA model will be used to evaluate for treatment effect in post- vs pre-treatment mean headache severity scores in the 48 hours following the SPG block compared to the 48 hours before the SPG block.

Similar ANCOVA models also will be used to evaluate for between-group treatment effect for the following secondary and exploratory outcomes:
-mean number of days with headache in the one week post-SPG block compared to one week pre-SPG block.
-mean number of headache occurrences within both 48 hours pre- and post-SPG block and one week pre- and post-SPG block
-mean number of headache hours per day within both 48 hours pre- and post-SPG block and one week pre- and post-SPG block
-mean number of as-needed headache treatment uses per day within both 48 hours pre- and post-SPG block and one week pre- and post-SPG block
-mean symptom severity scores in all 22 symptoms on the SCAT5 symptom checklist in both the 48 hours and one week pre-SPG block compared to 48 hours and one week post-SPG block
-mean orthostatic heart rate on standing, and mean orthostatic heart rate change from supine to standing, post-SPG block compared to pre-SPG block
-root mean square of successive differences (RMSSD) post-SPG block compared to pre-SPG block

For the following secondary outcomes, a mixed design analysis of variance (ANOVA) will be used, with a within-subjects factor of time (e.g. pre- vs post-SPG block) and a between-subjects factor of treatment (SPG block with lidocaine vs SPG block with saline):
-mean headache severity score within 15 minutes, 2 hours, 24 hours, and one week post-SPG block compared to immediately prior to procedure, 24 hours, and one week pre-SPG block.
-values on the PGIC rating scale at 2 hours and 24 hours post-procedure in those who received an SPG block with lidocaine compared to a placebo SPG block

For post-hoc analyses, an independent samples t-test (for normal distributions) or Wilcoxon rank-sum test (for non-normal distributions) will be used to compare mean differences, and chi-square tests (for normal distributions) or McNemar's tests (for non-normal distributions) will be used to compare proportional differences.

Participant characteristics will be reported by treatment group, and these will be evaluated for any differences between groups in any characteristic variables, including age, sex, baseline history of migraine, baseline history of depression or anxiety, baseline history of ADHD, previous history of concussions, and referral for cervical and/or vestibular physical therapy. If any differences in these

characteristics exist between-groups, they will be adjusted for in the analysis as independent variables in the ANCOVA model.

To control for multiple comparisons, a false discovery rate (FDR) will be used. In the event of missing data due to participant withdrawal from study or failure to complete all online survey data, we will use multiple imputation to estimate the missing values. All statistical analyses will be performed using SPSS (IBM, Armonk, NY).

9. Risks/Benefits

9.1 Risks:

Risks related to the procedure are expected to be mild and temporary and include:

-No improvement or worsening of headache
-Allergic reaction to the medication
-Tearing of the eye
-Nose discomfort
-Nose bleeding
-Damage to surrounding structures, including the nasal passage
-Mouth or throat numbness
-Coughing
-Nausea
-Vomiting
-Dizziness
-Light-headedness
-Fainting

9.2 Methods to Minimize Risks:

Prior to enrollment in the study, participants will be screened for any known conditions which would increase the risk of the SPG block procedure that may make reasonably safe participation in the study not possible. If any such conditions exist, participants will be excluded from the study (see section 6.5 for exclusion criteria).

All participants will be monitored for an additional ten minutes after completion of the SPG block. Although no adverse events related to heart rate are expected from the procedure, as part of the study protocol, the participants will have their heart rates rechecked following the 15 minute monitoring period after the procedure. Additionally, blood pressure, respiratory rate, and oxygen saturation will be checked before completion of the study visit. In the event of a life-threatening emergency, resuscitative equipment, oxygen, and other resuscitative drugs will be available for immediate use.

Participants in the study will be identified by a numbered study ID code that is distinct from any identifiable information (e.g. date of birth). All study data that is analyzed for publication in the future will be de-identified. A code sheet linking study ID to identifiable information will be maintained as a separate secure electronic file.

9.3 Benefits:

The potential benefits of the SPG block performed as part of this study may include a reduction in the severity, frequency, and/or duration of post-traumatic headache as well as other symptoms caused by the concussion. The procedure may lead to improved recovery from concussion. The findings from this study will contribute to the scientific understanding of treatments for post-traumatic headache and concussion that may lead to improvements in the treatment of these conditions in the future. It also is possible that there is no clinical benefit from participation in this study.

9.4 Alternative Treatment:

If a patient declines to participate in the study or withdraws from the study before completion of the SPG block, they will still receive the standard medical care as directed by the concussion clinic, which may include forms of treatment including medications, physical therapy, and exercise.

10. Study Documentation

10.1 Electronic Data Capture:

REDCap (Research Electronic Data Capture) will be used for study data collection and data management. REDCap is a HIPAA-compliant database and allows for development of online surveys which study participants will directly enter outcome data, as previously described. The participant's study identification number will be included in the REDCap database, but no other identifiable information (such as date of birth) will be included. Access to REDCap requires a unique username and password. Only approved study team members will have access to the database, and access will be limited for each user to only that which is necessary for the study team member to perform their study duties.

10.2 Record Storage and Retention:

Subject identification numbers and group assignments will be stored for a minimum of two years following the completion of the study. Each study participant will have a study file maintained which includes the study identification number, records of study data, informed consent, any adverse event documentation, and documentation of any correspondence with the participant. Paper records will be stored in a locked cabinet in a locked office room. The study investigator will have access to the keys to this cabinet and office. Other study data will only be collected and maintained electronically on REDCap. Any study data that is published, such as in a professional journal or scientific meeting, will only include de-identified data.

10.3 Data and Safety Monitoring Plan:

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Subject safety: The PI will be present during all research visits to assure that all appropriate procedures are followed. If an adverse event occurs during the study, the PI will immediately record and report the event to the UM IRB-MED in accordance with the institutional policies and procedures. The study group also will review adverse events on a regular basis to determine if any alterations to the study protocol are needed.

Data integrity: The PI or another member of the study group will review all data collection forms, and the data will be electronically audited on a monthly basis to ensure that the study's inclusion and exclusion criteria are being met, there are no missing data elements, and that data entry is performed accurately. We will immediately address any data integrity issues and report these to the UM IRB-MED in accordance in the institutional policies and procedures.

Subject privacy: The PI will be responsible for obtaining informed consent from the subjects. On a monthly basis, the PI or another member of the study group will review all study documents to ensure that the consent process has been completed in a private setting. Any subject privacy breaches will immediately be addressed and reported to the UM IRB-MED in accordance with the institutional policies and procedures.

Data confidentiality: Each subject will be assigned a unique study ID, which will be used to identify them on data collection forms and in the electronic study database. On a monthly basis, the PI or another member of the study group will review all paper and electronic data files to ensure that the participants' names are not directly associated with their data. All study paperwork will be stored in a locked University office, and all electronic study records will be maintained on a password-protected REDCap database.

Study documentation and coordination: All members of the study group will participate in a quarterly debriefing session to review that all study procedures are being followed, and to clarify the roles and expectations of each member of the study group.

Data safety monitor: If requested by the IRB, a safety monitor will be chosen and will review study records to ensure compliance with the study protocol, relevant regulations, and IRB requirements. If requested by the IRB, a formal data safety monitoring board also will be convened to oversee all aspects of the research study.

10.4 Ethical Conduct of the Study:

The investigator will ensure that the study will conform with the Federal Regulations for Protection of Human Research Subjects.

10.5 Institutional Review Board:

The University of Michigan IRB (UM IRBMED) will serve as the IRB for this study and will approve all protocols and documents related to the study before participant recruitment and enrollment begins.

10.6 Protocol Deviations:

If any deviations from the approved study protocol occur by the investigator or other members of the study team, they will be reported to the IRB by the investigator.

10.7 ClinicalTrials.gov:

This study will be registered under ClinicalTrials.gov before recruitment and enrollment of participants begins.

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11. References

1. McCrory, P., et al., *Consensus statement on concussion in sport-the 5th international conference on concussion in sport held in Berlin, October 2016.* Br J Sports Med, 2017. **51**(11): p. 838-47.
2. McCrea, M., et al., *Incidence, clinical course, and predictors of prolonged recovery time following sport-related concussion in high school and college athletes.* J Int Neuropsychol Soc, 2013. **19**(1): p. 22-33.
3. Nelson, L.D., J.K. Janecek, and M.A. McCrea, *Acute clinical recovery from sport-related concussion.* Neuropsychol Rev, 2013. **23**(4): p. 285-99.
4. Pearson, R., et al., *Survey of Child Neurologists on Management of Pediatric Post-traumatic Headache.* J Child Neurol, 2019. **34**(12): p. 739-747.
5. Cady, R.K., et al., *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. **55**(4): p. 529-42.
6. Lainez, M.J. and A.S. Marti, *Sphenopalatine ganglion stimulation in cluster headache and other types of headache.* Cephalalgia, 2016. **36**(12): p. 1149-1155.
7. Sussman, W.I., et al., *Sphenopalatine Ganglion Block for Management of Refractory Chronic Posttraumatic Headaches After a Sport-Related Concussion.* Clin J Sport Med, 2017. **27**(2): p. e6-e8.
8. Robbins, M.S., et al., *The Sphenopalatine Ganglion: Anatomy, Pathophysiology, and Therapeutic Targeting in Headache.* Headache, 2016. **56**(2): p. 240-58.
9. Obah, C. and P.G. Fine, *Intranasal sphenopalatine ganglion block: minimally invasive pharmacotherapy for refractory facial and headache pain.* J Pain Palliat Care Pharmacother, 2006. **20**(3): p. 57-9.
10. Purkayastha, S., M. Stokes, and K.R. Bell, *Autonomic nervous system dysfunction in mild traumatic brain injury: a review of related pathophysiology and symptoms.* Brain Inj, 2019. **33**(9): p. 1129-1136.
11. Binfalah, M., et al., *Sphenopalatine Ganglion Block for the Treatment of Acute Migraine Headache.* Pain Res Treat, 2018. **2018**: p. 2516953.