STUDY INFORMATION

Title: Does Early Preventative Pharmacologic or Supplement Therapy Improve Outcomes for Pediatric Post-Traumatic Headache?

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Description (PICO format – Population, intervention, comparison, outcome):

Population: patients 8-17 years of age at CHOP Neurology clinic (including general and headache sub-specialty clinics)

Intervention: Preventive pharmacologic therapy or supplement therapy started within 4 months of concussion

Comparison: patients who were started on a preventive pharmacologic therapy (Elavil, Pamelor, Topamax, etc.) vs. patients who were started on a preventive supplement (Mg, B2, CoQ10 etc.) vs. patients who were not started on a pharmacologic therapy

Primary outcomes: Degree of benefit at follow up at least 6 weeks after initiation of preventive (significant benefit, mild benefit, no change, worsening)

Secondary outcomes: N/A

Background:

Headache is the most common symptom after concussion and persists beyond one month in approximately 25% of children and beyond three months in 8% of children.1, 2 Treatment of post-traumatic headache in the pediatric population is based on expert opinion as there are no established treatments based on clinical research and no randomized control trials.3 Previous retrospective studies have looked at whether preventive medications can improve headache outcomes for patients, but these studies have been limited by small sample sizes, unclear time between treatment initiation and follow up, lack of a control population, and did not consider whether headache phenotype predicted treatment response. However, recent research suggests that a migrainous PTH phenotype is associated with a longer time to resolution and may be a target for early intervention.4 This retrospective study will investigate 1) treatment responses to commonly used pharmacologic therapies and supplements; 2) **whether migraine-like PTH phenotypes predict treatment response;** and 3) whether early intervention prior to 4 months post-injury is beneficial.

Hypotheses: Early intervention with pharmacologic therapy within 4 months of concussion will reduce post-traumatic headache severity, particularly those with migraine-like features.

DESIGN PLAN

Study type: Single center retrospective case-control study

Population: patients between ages 8-17 who were seen in CHOP Neurology clinic (including general and headache sub-specialty clinics) within 4 months of concussion

Inclusion criteria:

* Age: 8-17 at time of first visit
* Diagnosed with post-traumatic headache (PTH) based on ICHD-3 classification as determined by clinical information (patient questionnaire and provider documentation)
* First clinic visit within 4 months of concussion and a second visit and documented PCSI score within 12 months of concussion and at least 6 weeks from the first clinic visit
* First clinic visit must be between February 2017 to March 2022

Exclusion criteria:

* Concussion between first visit and follow up visit
* Documented history of chronic migraine prior to concussion
* History of chronic pain syndrome such as AMPS
* History of IBS
* History of nerve block
* Patients who are started on a preventive more than 6 weeks prior to first appointment
* History of severe neurologic disorders such as stroke, epilepsy, MS
* History of severe cardiac disease such as CHD, arrhythmias
* Non-compliance noted with preventive medication at follow up visit
* Patients started on the following medications 6 weeks to 3 months from the first neurology visit: started on a preventive pharmacologic or supplement medication

Additional information to be collected

- Comorbid anxiety and depression

- Family and personal history of migraine

- Medication overuse headache

- Concomitant concussion management including PT/CBT/vision therapy, school accommodations, and acute pharmacologic management

- History of multiple concussions

- Headache burden: continuous vs. intermittent, headache frequency, headache severity, headache-related disability (pedMIDAS where available, otherwise will defer to provider documentation)

- Presence of migraine-like features as defined by meeting criteria for migraine features based on ICHD-3 criteria C and D

- Seen in headache clinic or general neurology for headache management

Intervention:

Any preventive pharmacologic therapy as listed in RedCap form (Elavil, Pamelor, Topamax, Zonegran etc.) or any preventive supplement therapy (Mg, B2, CoQ10, fever few, fish oil) for at least 6 weeks.

Comparison: patients who did not start a preventive pharmacologic nor supplement therapy within 4 months of concussion

Outcomes:

Primary outcome: degree of benefit noted at follow up visit as defined:

Significant benefit – at least 1 month duration of a decrease of at least 30% of severity, frequency, and/or disability, or subjective report of significant benefit in provider notes.

Some benefit – benefit is noted, but does not meet criteria for significant benefit

No change – no change in headache frequency, severity, or disability

Worsening – headache frequency, severity, or disability got worse

Data dictionary – in RedCap

ANALYSIS PLAN

Statistical comparison:

Our primary outcome measure will be the degree of benefit noted at the patients’ follow-up visits (significant benefit, mild benefit, no change, worsening). As a secondary outcome measure, we will perform ordinal logistic regression analysis considering multiple covariates (as above). Covariates that are statistically significant between treatment groups or outcome will be included in the ordinal logistic regression analysis.

One of the limitations of our data set is a significant number of patients who are lost to follow up (approximately one third). We also recognize that whether a patient follows up and whether they are prescribed a medication may be non-random. For instance, those with more severe headaches, or those prescribed a prescription medication may be more likely to follow up. To account for this, we will first compare treatment groups and those lost to follow up versus those who returned for a second vision across multiple co-variates. If we find significant differences, we plan to use propensity score weighting or marginal structural modeling to model these differences. Specifically, we will first conduct univariate analyses based on **age, sex, socioeconomic status (using zipcode as a surrogate if needed), race, ethnicity, history of multiple concussions, history of migraine, family history of migraine, overall headache severity, frequency, and disability** **at initial visit** between patients who followed up and those who did not. We will conduct the same univariate analyses between patients who were prescribed a pharmacologic therapy, a supplement, or no preventive pharmacologic therapy. If there are significant differences between those who followed up and those who did not, then we will proceed with strategies to model missing data. If we find significant differences between those who followed up and those who did not and those who were prescribed something versus those who were not, then we will consider using marginal structural modeling to account for differences in treatment groups. If we find that there are no significant differences between these groups, we will use ordinal logistic regression analysis.

REFERENCES

1. Eisenberg MA, Meehan WP. Duration and course of post-concussive symptoms. Pediatrics 2014;133:999-1006.

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3. Patterson Gentile C, Shah R, Irwin SL, Greene K, Szperka CL. Acute and chronic management of posttraumatic headache in children: A systematic review. Headache 2021;61:1475-1492.

4. Kamins J, Richards R, Barney BJ et al. Evaluation of Posttraumatic Headache Phenotype and Recovery Time After Youth Concussion. JAMA Network Open 2021;4.