**STUDY INFORMATION**

Title: Does Triptan Therapy Improve Outcomes for Pediatric Post-Traumatic Headache (PTH)?

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

Population: Patients between ages 8-17 seen in CHOP Neurology clinic (including general and headache sub-specialty clinics) within 1 year of concussion who filled out the headache intake questionnaire and meet criteria for ICHD-3 PTH diagnosis

Intervention: Triptan therapy tried within 1 year of concussion

Comparison: NSAID therapy tried within 1 year of concussion

Primary Outcome: Effectiveness of NSAID only vs. triptan only vs. triptan + NSAID acute treatment of headache exacerbations

Secondary outcomes:

1. Determine if triptans were more effective at resolving headache exacerbations with migraine-like features
2. Determine if the efficacy of triptan therapy varied by time that has passed since the injury
3. How often were side effects of triptans and NSAIDs reported, and did they limit their use?

Background:

Headache is the most common symptom after concussion, with more than 80% of children and adolescents reporting post-traumatic headache (PTH), which may continue beyond one month in 25% of children and beyond three months in 8% of children.1,2 Observed in up to 46.5% of cases, migraine is the most common phenotype of pediatric PTH.2,3 Children with migraine-like PTH may benefit from directed therapy, as expert opinion supports treating PTH based on headache phenotype.4,5,6,7 The current American Academy of Neurology (AAN) guidelines for acute treatment of migraine recommend ibuprofen and triptan therapy to relieve pain in adolescents.8 In the setting of pediatric PTH, several review articles have recommended the use of triptans as an acute pharmacological agent, particularly for migraine-like PTH and in patients unable to relieve headaches with ibuprofen and acetaminophen.9,10,11 Despite these recommendations, a survey of 95 child neurologists demonstrated that less than 50% prescribe triptans for acute treatment of PTH, compared to more than 90% for NSAIDs.12 Furthermore, a similar survey of 137 pediatric ED physicians indicated a strong preference for IV treatments and NSAIDs, with less than 10% endorsing the use of triptans.13 This low usage of triptans may reflect the fact that limited high quality evidence supports their efficacy in acute treatment of pediatric PTH.

The primary literature evidence for the use of triptans in PTH is a retrospective cohort study in a military population, which found that 70% of PTH subjects who used a triptan experienced reliable headache relief within 2 hours, compared to 42% of subjects using other headache acute medications.14 For pediatric PTH, the best evidence of triptan efficacy comes from older case reports. In 1993, Gawel and colleagues presented a case series of seven patients with PTH who were treated with subcutaneous sumatriptan.15 For all seven patients, the throbbing temporal component of the headache was relieved within 20 minutes, but the occipital pain was unaffected. In 2008, Abend and colleagues described an adolescent with migrainous PTH who did not respond to other medications but experienced rapid improvement with subcutaneous sumatriptan.16

In the past 10 years, several abstracts have discussed the efficacy of triptans in pediatric PTH. A small retrospective cohort study noted that triptans provided the most rapid relief for PTH, though specific data were not reported.17 In contrast, a retrospective cohort study found that subjects who used triptans reported greater headache severity than those who used NSAIDs.18,19 However, this finding may be confounded by differences in headache severity at baseline, which were not reported.

There is a need for additional, higher quality research into the use of triptans as an acute therapy for PTH in the pediatric population. This retrospective study will investigate 1) treatment responses to triptans; and 2) whether migraine-like PTH phenotypes predict treatment response**.**

Hypothesis: Intervention with acute triptan therapy will be more effective than NSAIDs alone at treating post-traumatic headache exacerbations in youth, particularly for those with migraine-like features.

**DESIGN PLAN**

Study type: Single center retrospective observational cohort study

Timepoints:

First time point: First neurology visit where an acute medication was recommended (visit must be within 1 year of concussion). If it is the first visit, this could include a continuation of acute therapy.

Second time point: First visit or communication that indicated the effectiveness of acute therapy (must be within 6 months of the initial visit).

Comparator Groups:

NSAID only group – only used an NSAID for acute headache exacerbations

Triptan only group – only used a triptan for acute headache exacerbations

Triptans + NSAIDs – used combination treatment for acute headaches

Inclusion criteria:

* Age: 8-17 at time of first visit
* Meet ICHD-3 classification for post-traumatic headache (PTH) determined by participant questionnaire and confirmed by chart review.
* First neurology clinic visit with filled out headache questionnaire was collected within 1 year of concussion
* First clinic visit must be between February 2017 to January 2023

Exclusion criteria:

* Concussion between first visit and follow up visit
* Did not try the prescribed triptan and/or NSAID at least once
* Did not have follow-up information within 6 months of the prescribing visit

The following additional factors will be considered in data analysis:

* Family history of migraine
* History of migraine, or prior headaches, and their frequency if noted (sub-analysis)
* Headache is continuous or intermittent, headache frequency, and severity
* Number of acute medications tried before first visit
* Number of preventive medications tried before first visit
* Days post-injury – as measured from the days post-injury the triptan and/or NSAID was used (if known), or if not known, the days post-injury the triptan and/or NSAID was prescribed (if first used at separate time points, take the median of the two dates)
* Severity of head trauma (minor head injury, concussion, moderate traumatic brain injury, severe traumatic brain injury)
* When the medication was taken (at the beginning of the headache exacerbation or when the pain was bad)
* Sex assigned at birth
* Age
* The presence or absence of migraine-like headache, defined based on ICHD-3 criteria C – D adjusted for the pediatric population) as follows:
  + At least 2/4 characteristics – (1) focal location, (2) pulsating quality, (3) moderate-severe pain intensity, (4) aggravated/causing avoidance of physical activity
  + At least one of the following: (1) nausea and/or vomiting, (2) photophobia and phonophobia

Outcomes:

Primary outcomes:

1. Effectiveness of NSAIDs, triptans, and NSAIDs + triptans

Definition:

* Effective – aborts the headache exacerbation (to baseline for continuous headache, to no pain for intermittent headache) >50% of the time
* Partially effective – some benefit documented, but does not meet criteria for effective
* No response – lack of response documented
* Worsened response – no response, and worsened headache indicated as a side effect

Secondary outcomes:

1. Determine if triptans were more effective at resolving headache exacerbations with migraine-like features
2. Determine if the efficacy of triptan therapy varied by time that has passed since the injury
3. How often were side effects of triptans reported, and did they limit the use of triptans?

Data Dictionary – in RedCap

**ANALYSIS PLAN**

Statistical comparison:

The primary outcome will be determined by Kruskal-Wallis to compare the 4 ranked effectiveness outcomes across the NSAID only, triptan only, and NSAID + triptan treatment groups. Relevant factors (identified above) will be compared across the three groups: continuous variables (mean and standard deviation for normal distribution, median and interquartile range for non-normal distribution), and categorical variables will be reported as proportions of participants. To determine if there are factors that correlate with response to NSAIDs, triptans, or NSAIDs + triptans, we will compare across multiple potentially relevant and confounding factors. Univariate analyses will be used to compare multiple factors (outlined above) based on response to triptan using Chi squared analysis (categorical variables) or ANOVA (continuous variables with normal distribution), or Kruskal-Wallis test (continuous variables, non-normal distribution). Ordinal logistic regression will be pursued, which will include variables that were statistically significant in univariate analysis. Depending on the differences between the three treatment groups, and the percentage of missing data, marginal structural modeling may be employed if it is needed.

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