University of Cincinnati

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I, John Kroner, hereby submit this original work as part of the requirements for the degree of Master of Science in Epidemiology (Environmental Health).

It is entitled:
Associated Symptoms of Chronic Migraine in Children and Adolescents

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Associated Symptoms of Chronic Migraine in Children and Adolescents

A thesis submitted to the
Graduate School
Of the University of Cincinnati
In partial fulfillment of the
Requirements of the degree of

Master of Science

In the Department of Environmental Health
of the College of Medicine
by

John Kroner

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Committee:
Susan Pinney, PhD (Chair)
MB Rao, PhD
Scott Powers, PhD
Abstract

Objective

To determine the phenotypical characteristics of migraine experienced by adolescents diagnosed with chronic migraine and to determine if behavioral treatment shown to reduce headache frequency also leads to changes in migraine characteristics.

Background

There are no evidence based interventions for children and adolescents who suffer from chronic migraine. As part of a randomized clinical trial, subjects received Cognitive Behavioral Therapy plus Amitriptyline (CBT+A) or headache education and Amitriptyline (HE+A) to determine if CBT led to improved outcomes in headache frequency and disability.

Methods

A total of 135 adolescents aged 10 to 17 diagnosed with chronic migraine (≥15 headache days/month) and a Pediatric Migraine Disability Assessment Score (PedMIDAS) greater than 20 points were assigned to the CBT group (n = 64) or the headache education group (n = 71). During the treatment phase of the trial (20 weeks) subjects kept a daily dairy that recorded headache frequency and symptoms.

Results

Subjects who received CBT+A had a greater reduction in headache frequency rate than subjects who received HE+A. There was no statistically significant difference between the groups in the proportion of associated migraine symptoms reported.

Conclusions

CBT is an effective treatment showing greater improvement in headache frequency over twenty weeks compared to HE. However, the experience of migraine (i.e., the symptoms experienced) was not different between the groups. Subjects who received CBT+A had fewer reported headaches, but when they did have a headache, there was no phenotypical difference between the treatment groups.
Acknowledgements

I’d like to thank Dr. Scott Powers for serving as my mentor for the past several years and for providing the data for this analysis, along with Dr. Pinney and Dr. Rao for serving on my thesis committee. I’d also like to thank Dr. Joe Rausch, Dan Strotman, the Powers Lab team, and the Headache Center Research team at Cincinnati Children’s Hospital.
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Background

Chronic Migraine (15 or more headache days per month) is a leading cause of disability in children and adolescents, affecting over one third of children who present to pediatric headache clinics\(^1\). Chronic Migraine has an estimated prevalence of 1.75% in children and adolescents\(^2\), with up to 69% of those treated in headache specialty clinics meeting the diagnostic criteria for chronic migraine\(^2,3\). Several effective prophylactic treatments have been identified, however there is still no evidence-supported gold standard treatment for chronic migraine\(^4\). Current research hopes to address this gap in knowledge, but there is a need to explore additional methods for the treatment of headache and migraine\(^5\). Cognitive Behavioral Therapy (CBT) has been shown as an effective treatment in children and adolescents with chronic pain\(^6,9\). The goal of CBT in headache treatment is to modify behavioral responses to pain and support relaxation techniques in order to reduce headache frequency and disability.

A clinical trial conducted by the research team at the Cincinnati Children’s Hospital Headache Center aimed to discover if CBT combined with Amitriptyline(CBT+A) , a standard headache medication\(^11\), leads to better outcomes in headache frequency and disability, the two most common measures of treatment effectiveness in chronic migraine\(^12\). In the study, subjects were randomly assigned to a CBT+A group or an attention control group that received headache education and Amitriptyline (HE+A). The trial, completed in 2011, showed that CBT+A was more effective when compared to headache education plus medication in reducing headache frequency and disability. During the 20-week treatment phase subjects kept daily diaries detailing their headaches. In addition to headache frequency, subjects recorded headache duration, intensity, and associated symptoms such as nausea, sensitivity to light, and
sensitivity to sound. This analysis will examine the phenotypical adolescent headache encountered in this study and determine if differences in the presence of these secondary symptoms exist between the two treatment groups over time.

Methods

Participants

A randomized Clinical Trial was conducted at the Cincinnati Children’s Hospital Headache Center between October 2006 and September 2012. Subjects were recruited from the new patient clinic. Written informed consent was obtained from the parent or legal guardian for all subjects who enrolled in the study. Informed assent was obtained for all youth aged 11 years or older. Inclusion criteria for the study included a diagnosis of chronic migraine by a board-certified headache specialist according to International Classification of Headache Disorders, 2nd Edition (ICHD-II) criteria\textsuperscript{13}, 15 or more headache days per month, aged 10-17, and a Pediatric Migraine Disability (PedMIDAS)\textsuperscript{14} score greater than 20 (indicating moderate disruption of daily activities). Exclusion criteria were medication overuse, current use of amitriptyline or other prophylactic anti-migraine medication within a period equivalent to less than 5 half-lives before study screening, other chronic pain condition such as fibromyalgia or complex regional pain syndrome II, abnormal electrocardiogram, severe orthostatic intolerance or dysregulation, documented developmental delay or impairment, severe psychiatric comorbidity, PedMIDAS greater than 140 points, pregnancy or being sexually active without use of medically accepted form of contraception, and use of disallowed medications including
opioids, antipsychotics, antimanics, barbiturates, benzodiazepines, muscle relaxants, sedatives, tramadol, or herbal products.

A total of 398 patients were approached in the Headache Center at Cincinnati Children’s Hospital. Of those approached, 197 were screened. Of those screened, 135 met all eligibility criteria and were randomized into one of the two treatment conditions. Subjects were 79% female, 89% white, with an average age of 14.4 ± 2 years. Race and ethnicity was self-reported in accordance with the categories used for reporting study findings to the National Institutes of Health. There were no group differences in baseline characteristics. During the 28 day screening period, subjects reported having an average of 21 headache days. Once randomized, the CBT+A group consisted of 64 subjects and the HE+A group consisted of 71 subjects. Group characteristics are reported in Table 1.

Study Design

The study had three specific aims: To compare the efficacy of combined behavioral and pharmacological treatment, to compare the clinical significance of the effects on headache frequency and functional disability for combined behavioral and pharmacological treatment versus pharmacological treatment and attention control, and to examine whether youth who receive combined behavioral and pharmacological treatment show sustained treatment gains at 3, 6, 9, and 12 month follow-up compared to those who receive pharmacological treatment and attention control. Both groups were prescribed Amitriptyline at a dose of 1 mg/kg, per the standard clinical practice. Eligible subjects were randomized into one of the two treatment conditions using block randomization (block sizes varied between 4 to 10). Subjects were also
stratified by age (10-13 and 14-17 years). Treatment consisted of 8 weekly 1 hour sessions followed by 2 monthly “booster” sessions, and a post-treatment assessment at 20 weeks. Subjects then entered a 12 month follow up phase with visits 3, 6, 9, and 12 months post week 20.

Face to face Cognitive Behavioral Therapy has been shown to be an effective treatment in children with chronic pain, and chronic headache in particular\textsuperscript{7-10}. This intervention was based on a coping skills protocol\textsuperscript{6} modified with a biofeedback component. The Headache Education group received generalized headache education from a trained therapist on the same schedule as the CBT group. The Headache Education group served as an attention control group, which emulates pill placebo in behavioral treatment research\textsuperscript{15-17}.

\textit{Outcome Measures}

Subjects kept a daily headache diary throughout the screening, treatment, and follow up phases of the study. The diary kept during treatment included the following: documentation of any abortive medication use, headache frequency, headache intensity as rated as average pain intensity for that day using a Visual Analog Scale (10 cm horizontal line with no numerical markings anchored with “no pain” and “worst possible pain”) and as summarized according to one of three categories: mild, moderate, or severe, headache duration (in hours and minutes), and associated symptoms for migraine: presence or absence of nausea, sensitivity to light (photophobia), and sensitivity to sound (phonophobia). The 28 day screening diary was used to determine starting headache frequency.
Statistical Analysis

During the treatment phase of the trial, 16,294 days of headache records were collected. Only the first 140 days of diaries (20 weeks of treatment) were considered for this analysis. Of those 16,294 headache records, 8,455 represented headache days. Daily headache proportion was calculated for each day of the treatment for both groups. A piecewise generalized estimation equations model was used to test for group, time, and group by time interaction effects. This analysis considered every day of screening and treatment. Headache frequency was also analyzed using the clinically meaningful outcome measure of a 50% reduction in headache frequency. The proportion of subjects who reached this threshold was calculated for each month of treatment. A chi-square test was performed to test for group differences at each month.

As associated symptoms are only present during a headache, the analysis of associated symptoms consisted of only the 8,455 headache days. Symptom presence proportions and mean duration and intensity were calculated for each day of the treatment phase. Average occurrence of associated symptoms during the treatment phase was calculated across the treatment interval. The dichotomous variables (nausea, light sensitivity, sound sensitivity) were tested for group, time, and group by time interaction effects during the treatment phase. A model was fit to determine if within subject correlation would be a factor in determining group differences. Because a correlation of approximately 0.60 was found, a generalized estimation equations approach was used. Odds ratios and proportions were calculated for these variables as well. Mixed effects models were fit to analyze longitudinal data using the mixed
procedure (SAS Institute Inc) test for group, time, and group by time interaction effects in the continuous variables (pain severity and headache duration). A predictive model was fit for each symptom.

**Results**

**Frequency**

The results of the parent trial showed a significant reduction in headache frequency from screening to follow up in both treatment groups (See Figure 1). There was also a significant difference in headache frequency between the groups, with the CBT+A group having fewer headaches than the HE+A group at post treatment. The reduction in headache frequency remained over the course of a 12 month follow up in both groups\(^\text{12}\).

This secondary analysis examined how headache frequency changed during the treatment phase, modeled over 24 weeks (28 days of screening plus 140 days of treatment). Figure 2 shows the proportion of subjects who reported a headache during the 28 day screening phase as well as each day of the treatment phase. Subjects reported headaches on 75.5\% of diaries collected during the baseline screening period (mean 21.3 ± 5.2 headaches). The CBT+A group reported headaches on 75.1\% of diary days during the screening period (mean 21.2 ± 5.1 headaches). The HE+A group reported headaches on 75.8\% of diary days during the screening period (mean 21.4 ± 5.4 headaches).

A group difference was found in headache proportion during the treatment interval (\(P = 0.01\)). The CBT+A group had a predicted initial proportion of 0.67, while the HE+A group had a predicted proportion of 0.71. These decreased to 0.23 for the CBT+A group and 0.28 for
the HE+A group by day 140. The odds of having a headache over the 140 day interval were 1.87 times higher in the HE+A group. See Figure 2.

The proportion of subjects in the CBT+A group who had a 50% reduction in headache frequency from baseline was 26.6%, 42.9%, 55.7%, 70.2%, 72.2% for months 1, 2, 3, 4, and 5, respectively. For the HE+A group, 10.1%, 20.0%, 32.8%, 47.7.1% and 44.3% saw a 50% reduction in frequency for months 1, 2, 3, 4, and 5. The differences between the groups were significant at each month (Month1: \( P < 0.03 \), Month 2: \( P < 0.01 \), Month 3: \( P = 0.02 \), Month 4: \( P = 0.02 \), Month 5: \( P < 0.01 \)). See Figure 5.

*Nausea*

Subjects reported having nausea during 26.9% of headaches. The CBT+A group reported having nausea 26.7% of headaches, and the HE+A group reported nausea for 27.0% of headaches. There was no difference between the groups (\( P = 0.56 \)), with predicted values of 0.26 for the CBT+A group and 0.23 for the HE+A group throughout the treatment phase (OR = 0.85). There was a within subject clustering correlation of 0.59. See Figure 4.

*Sensitivity to Light*

Subjects reported light sensitivity during 61.9% of headaches. The CBT+A group reported light sensitivity for 64.1% of headaches, and the HE+A group reported light sensitivity for 60.3% of headaches. There was no difference between the groups (\( P = 0.18 \)), however there was a significant reduction in frequency over time for both groups (\( P = 0.04 \)). Subjects in the CBT+A group saw a reduction from 0.65 to 0.58 during the treatment phase, while the HE+A
group saw a reduction from 0.57 to 0.50 (OR = 0.71). There was a within subject clustering correlation of 0.57. See Figure 5.

Sensitivity to Sound

Subjects reported sound sensitivity during 51.2% of headaches. The CBT+A group reported sound sensitivity for 53.1% of headaches, and the HE+A group reported sound sensitivity for 49.9% of headaches. There was no difference between the groups ($P = 0.59$), with predicted values of 0.50 for the CBT+A group and 0.47 for the HE+A group throughout the treatment phase (OR = 0.87). There was a within subject clustering correlation of 0.61. See Figure 6.

Duration

Average headache duration was $10.42 \pm 9.61$ hours. The CBT+A group reported an average frequency of $12.07 \pm 9.80$ hours. The HE+A group reported an average frequency of $9.26 \pm 9.30$ hours. There was no difference between the groups ($P = 0.9446$). See Figure 7.

Pain Severity

Pain severity was measured during the treatment phase using a Visual Analogue Scale (VAS) that was converted to a numerical value based on how far to the right side of a horizontal line the subject indicated their pain level. The average pain level reported on the VAS scale was $5.58 \pm 2.64$ (of a possible 10). The CBT+A group reported an average pain level of $5.42 \pm 2.46$. The HA+A group reported an average pain level of $5.69 \pm 2.76$. There was no difference
between the groups ($P = 0.44$), however there was a significant reduction in pain severity over time for both groups ($P = 0.01$). See Figure 8.

Categorically, pain was reported in the CBT+A group as being mild for 32.4% of headaches, moderate for 49.5% of headaches, and severe for 18.1% of headaches. In the HE+A group, pain was reported as mild, moderate, and severe for 28.6%, 48.0%, and 23.3% of headaches, respectively. There was no difference between the groups ($P = 0.34$). See Figure 9.

Conclusions

The results of the parent trial showed that subjects in the CBT+A treatment group had fewer headaches after 20 weeks compared to those in the HA+A group. The results of this secondary analysis support these findings and describe the trajectory of improvement for both treatment groups. The results show that headache frequency started decreasing as soon as the first month of treatment. While there was a reduction in headache frequency, headache associated symptoms largely do not change. Sensitivity to light and pain severity both decreased over time, but there no group differences were found for these or any of the other associated symptoms. While the CBT+A group had fewer headaches, their headaches were phenotypically the same as the headaches of those in the HE+A group. The type of treatment does not affect the objective experience of migraine. Future research should explore if there are any differences in the subjective experience of pain in addition to the objective measures used in this and similar studies.

The mechanism by which CBT leads to an improvement in headache frequency also warrants further study. Group differences in frequency seem to separate after about two
weeks of treatment. Understanding why CBT leads to improved outcomes can lead to better treatment plans with expected milestones of improvement. The results of this analysis suggest that a pharmacological treatment is only one of multiple clinically meaningful modes of treatment. The interplay between CBT and medication not yet understood and calls for a placebo controlled trial to further elucidate the results from this analysis.
References


**Tables and Figures**

**Table 1: Baseline demographics, headache days, and migraine-related disability**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Total (N=135)</th>
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<td>N (%)</td>
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</table>

Adapted from Powers 2013.
Figure 1. Pre to Post Treatment Comparison of Headache Frequency\textsuperscript{12}
Figure 2. Headache Proportion Over Time
Figure 3. Proportion of Subjects with a 50% Reduction in Headache Frequency

Error bars indicate standard error of the mean
Figure 4. Proportion of Headaches with Nausea
Figure 5. Proportion of Headaches with Sensitivity to Light
Figure 6. Proportion of Headaches with Sensitivity to Sound
Figure 7. Mean Headache Duration
Figure 8. Mean Headache Intensity
Figure 9. Categorical Headache Pain Level