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# Research Submission

## Effectiveness of Standardized Combination Therapy for Migraine Treatment in the Pediatric Emergency Department

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**Objective.—To compare outcomes of pediatric migraine patients treated in an emergency department (ED) before and after implementation of a standardized combination intravenous therapy regimen aimed toward improving and standardizing abortive migraine therapy.**

**Background.—In a pediatric ED, migraines represent 8-18% of all headache visits. Despite this large number, no standard treatment for acute migraine therapy currently exists.**

**Methods.—The study utilized a retrospective chart review of patients seeking acute migraine treatment at a tertiary care, pediatric ED from August 2006 to March 2010. Inclusion criteria were pediatric migraine patients as defined by International Headache Society guidelines. The comparison population received various migraine therapies based on attending practice preference. After October 2008, patients received standardized intravenous combination therapy involving a normal saline fluid bolus, ketorolac, prochlorperazine, and diphenhydramine. Occasionally, metoclopramide was substituted during prochlorperazine shortages. Reduction in headache pain score was the primary outcome. Secondary outcome measures included length of ED stay, hospital admission rate, and ED readmission rate within 48 hours.**

**Results.—The study yielded 87 patients who received standardized combination therapy and 165 comparison patients. No significant difference in patient characteristics existed when evaluating patient demographics, outpatient medication use, and initial headache pain score. When compared with the non-standardized therapy population, the combination therapy patients revealed significant reductions in pain score (decrease of 5.3 vs 6.9, difference –1.6, 95% confidence interval –2.2 to –0.8, $P < .001$), length of ED stay (5.3 vs 4.4 hours, difference 0.9, 95% confidence interval 0.2-1.6, $P = .008$), and hospital admission rate (32% vs 3%, $P < .001$) without changes in ED return rate (7% vs 2%, $P = .148$).**

**Conclusion.—Standardized combination therapy is effective for acute pediatric migraine therapy in the ED by significantly reducing headache pain scores, length of ED stay, and hospital admission rates.**

**Key words:—migraine, child, treatment**

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## BACKGROUND

Migraines comprise the most common acute and recurrent headache syndromes in children and adolescents with a prevalence rate estimated at 8%.[1] Although migraines occur at all ages, around half of cases begin before the age of 20 and often lead to a high morbidity rate at an early age. Children with migraines have a high risk of severe disability including depression and an overall decrease in quality of life.[2-4]

A significant number of children present to the emergency department (ED) with their first migraine or with a severe migraine intractable to outpatient therapy.[5] In a pediatric ED, migraines represent 8-18% of all headache visits.[6,7] The pediatric presentation of

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migraines varies widely at different ages with an unclear polygenetic and multifactorial pathophysiology that confounds treatment decisions.[8] Despite the large number of migraine cases in the pediatric ED, no standard treatment for acute migraine therapy currently exists. This is further complicated by a lack of research on pediatric migraines with many current migraine therapies extrapolated from adult studies.[9] Current abortive treatments for pediatric migraines include: intravenous (IV) hydration, non-steroidal anti-inflammatory drugs, acetaminophen, combination analgesics, opioids, benzodiazepines, barbiturates, dopamine antagonist anti-emetics, ergotamines, triptans, anticonvulsants, valproic acid and derivatives, antipsychotics, magnesium sulfate, immunosuppressants, and tricyclic antidepressants.[2,3,5,10-14]

The American Academy of Neurology in 2004 also recognized the scarcity of research on the treatment of primary headache disorders in children and adolescents.[15] Few articles comment on pediatric acute migraine treatment efficacy in the ED, except for studies examining prochlorperazine and ketorolac use.[16-18] Only a limited number of studies explore standardized therapy use for acute migraine therapy in the ED. One study documents a practice variation in migraine treatment among ED providers after treatment protocol implementation.[19] Other research reveals no significant difference in ED length of stay when comparing ED migraine visits both before and after establishment of a treatment protocol.[20] No study to date demonstrates effective use of a standardized migraine treatment regimen in the pediatric ED.

## OBJECTIVES

To compare outcomes of pediatric migraine patients treated in an ED before and after implementation of a standardized combination IV therapy regimen aimed toward improving and standardizing abortive migraine therapy. Reduction in headache pain score was the primary outcome measure with a goal of complete pain elimination.

## METHODS

The study utilized a retrospective chart review of patients seeking acute migraine treatment at an urban, academic, tertiary care, pediatric ED from August 2006 to March 2010. Approval of the study protocol was obtained from the institutional review board prior to initiation of the study. Chart abstractors then reviewed medical records of all pediatric ED visits with a headache diagnosis during the study period.

A search for headache International Classification of Diseases, Ninth Revision codes revealed a group of patients who presented to the pediatric ED for headache treatment over the study period. These patient charts were subsequently reviewed using a standardized data collection form. The audit followed suggested guidelines for chart review in emergency medicine research.[21] Data abstractors included a senior pediatric resident, a recent medical school graduate, and a board certified pediatric emergency medicine faculty member. Initially, several charts were jointly reviewed by the primary investigator and each abstractor to ensure an understanding of the data collection form. Subsequent charts were then evaluated by one abstractor, and a total of 10% of the charts were randomly re-reviewed by the emergency medicine faculty member as a quality assurance measure. Abstractors were not blinded to the study goals.

Study participants had inclusion criteria applied to identify patients presenting to the pediatric ED with a primary migraine headache. Inclusion criteria for the study included proper headache classification as a migraine according to International Headache Society (IHS) guidelines and proper documentation of study outcome measures.[22] Primary outcome measure of acute migraine therapy was a reduction in headache pain score. Secondary outcome measures included length of ED stay, hospital admission rate, and ED readmission rate within 48 hours after discharge suggesting headache treatment failure.

Patients were classified according to ED treatment methods. In the comparison population, patients did not utilize a specific migraine treatment plan and received various single or combination medication therapies based on attending practice preference. The assortment of treatments included: normal saline IV fluids, acetaminophen, ibuprofen, ketorolac, prochlorperazine, metoclopramide, magnesium

sulfate, divalproex sodium, dihydroergotamine, and narcotics.

Beginning in October 2008, pediatric patients presenting to the ED with a migraine headache received an IV combination therapy regimen developed by the ED and neurology department based on recommendations by Kabbouche et al in hopes of standardizing abortive migraine treatment to improve acute migraine management while enhancing ED efficiency and ultimately decreasing migraine-associated morbidities.[16,23-31] The standardized IV combination therapy involved a normal saline bolus (20 cc/kg, maximum dose 1 L), ketorolac (0.5 mg/kg, maximum dose 30 mg), and prochlorperazine (0.15 mg/kg, maximum dose 10 mg), with diphenhydramine (1 mg/kg, maximum dose 50 mg) to help reduce prochlorperazine side effects. Occasionally, IV metoclopramide (0.1 mg/kg, maximum dose 10 mg) was substituted in the protocol during shortages of prochlorperazine. The protocol was administered as follows: ketorolac was given IV over 1-2 minutes, followed by the IV diphenhydramine over 10 minutes, and then the prochlorperazine or metoclopramide over 10-15 minutes IV. The saline bolus was given over 1 hour throughout the medication infusions. Patients were evaluated 30-60 minutes after combination therapy completion. Those with resolution of headache symptoms were discharged home, and patients with a continued headache were admitted for inpatient therapy.

Headache severity for all patients was measured at the beginning and completion of therapy using a numeric-based pain scale of 0-10, with a goal of pain reduction to 0. Older children verbalized pain severity according to the pain scale, and younger children utilized a visual analog scale known as the Wong–Baker FACES scale to describe headache intensity. This scale was administered by the bedside nurses using the following statement, "See this line of faces. They show children who have different amounts of pain. At this end the child has no pain and at this end the child has the most pain you can imagine (they would point to each end while describing). You point to the face that shows how much pain you are having right now." This was standard pain assessment both pre- and post-guideline implementation.

After data collection by chart abstractors, the primary investigator and biostatistician analyzed results using the SPSS statistical analysis software (SPSS Inc, Chicago, IL, USA) to describe patient characteristics and investigate significant differences in outcome measures between the combination therapy and comparison patient populations. Patient characteristics of age and initial headache pain score along with outcome variables of reduction in headache pain score and length of ED stay were compared using independent *t*-tests with Levene's test for equality of variances. Additional patient characteristics of gender, ethnicity, and use of outpatient migraine therapy prior to ED presentation as well as outcome variables of hospital admission rate and ED return rate for headache treatment after discharge were analyzed using cross-tabulation with Pearson's chi-square or Fisher's exact test, when appropriate.

## RESULTS

Four hundred eighty-eight pediatric patients presented to the pediatric ED with a headache diagnosis code from August 2006 to March 2010 (Fig. 1). Of these patients, 338 had a primary diagnosis of headache and then had IHS migraine classification guidelines applied to create a population of 280 migraine patients. Incomplete or missing outcome variable documentation reduced the control population from 190 to 165 patients and decreased the protocol popu-

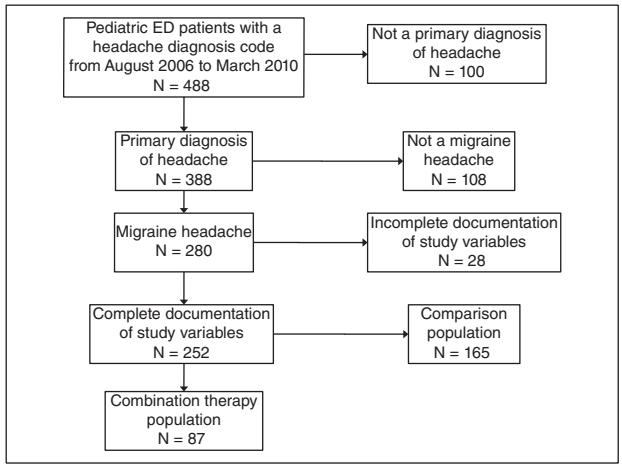


**Fig 1.—Study enrollment distribution. ED = emergency department.**

**Table 1.—Patient Demographics**

| Patient Characteristics | Control Mean ± SD (n = 165) | Protocol Mean ± SD (n = 87) | Difference in Means | 95% Confidence Interval for the Difference in Means | *P* Value |
|---|---|---|---|---|---|
| Age (years) | 13.0 ± 2.8 | 13.3 ± 2.8 | –0.3 | –1.0 to 0.4 | .381 |
| Gender | | | | | |
| Male | 38% | 34% | — | — | .681 |
| Female | 62% | 66% | — | — | |
| Ethnicity | | | | | |
| Caucasian | 64% | 55% | — | — | .181 |
| Hispanic | 32% | 40% | — | — | |
| African American | 2% | 5% | — | — | |
| Other | 2% | 0% | — | — | |
| Use of headache medication prior to ED presentation | 78% | 85% | — | — | .185 |
| Initial headache pain score (0-10) | 7.7 ± 1.9 | 7.5 ± 2.2 | 0.2 | –0.3 to 0.7 | .469 |

ED = emergency department; SD = standard deviation.

lation from 90 to 87 patients. Despite a reduction in study participants after application of inclusion criteria, a post-hoc power of 97% was found for the standardized combination therapy population.

No significant difference in various patient characteristics (age, ethnicity, gender, and use of pain medications prior to ED presentation) existed between the 2 patient populations (Table 1). The initial pain scores were 7.7 ± 1.9 and 7.5 ± 2.2 for the control group and protocol group, respectively. Data analysis revealed significant reductions in headache pain scores, with the control groups pain decreasing by 5.3 and the protocol group by 6.9 ($P < .001$). The length of ED stay was 5.3 hours in the control group and 4.4 hours in the protocol group ($P = .008$), and hospital admission rate for the control group was 32% vs 3% in the protocol group ($P < .001$). There was no significant difference in return rate to the ED for rebound headaches within 48 hours of initial treatment, with 7% returning in the control group and 2% in the protocol group ($P = .148$) (Table 2, Fig. 2).

Both patient populations had similar rates of analgesic medication use prior to ED arrival. The effect of outpatient medication on ED treatment course was not analyzed because exact medication dosing was not reliably recorded in all patient records. Prior medication use could have resulted in improved pain scores after ED admission. Data on side effects were unfortunately not recorded in the study.

Sixteen patients in each study population received ondansetron in addition to analgesic medications.

**Table 2.—Outcome Measures**

| Patient outcomes | Control Mean ± SD (n = 165) | Protocol Mean ± SD (n = 87) | Difference in Means | 95% Confidence Interval for the Difference in Means | *P* Value |
|---|---|---|---|---|---|
| Reduction in pain score | 5.3 ± 3.1 | 6.9 ± 2.5 | –1.6 | –2.3 to –0.8 | <.001 |
| Hospital admission rate | 32% (n = 52) | 3% (n = 3) | — | — | <.001 |
| Length of stay in ED (hours) | 5.3 ± 3.4 | 4.4 ± 2.0 | 0.9 | 0.2 to 1.6 | .008 |
| Return to ED for migraine treatment within 48 hours | 7% (n = 12) | 2% (n = 2) | — | — | .148 |

ED = emergency department; SD = standard deviation.

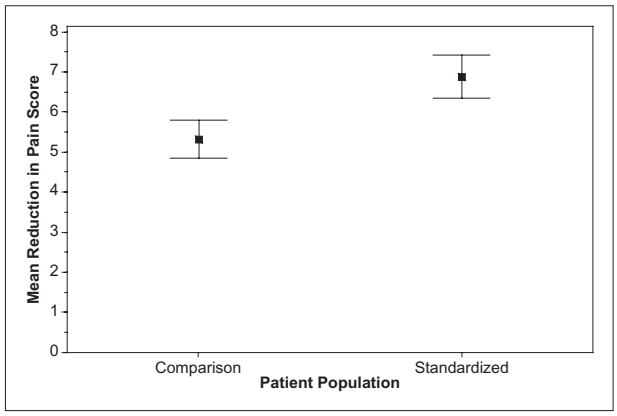


**Fig 2.—Interval plot of mean reduction in pain score. Mean reduction represented as the plotted point with extension to the 95% confidence interval for the mean.**

Because ondansetron was administered as an antiemetic in both patient populations and not used for analgesic properties, these patients were included in the study.

Patient charts were reviewed from only one pediatric hospital. When reviewing repeat ED visits for headache treatment within 48 hours, the possibility of patients seeking treatment at an alternate hospital should be considered.

## DISCUSSION

In 2008, Bailey and McManus performed a systematic review of treatment of children with migraine in the ED. They reviewed the Cochrane database of systematic reviews, database of abstracts of reviews of effects, Cochrane controlled trials register, MedLine, and EMBASE, and searched for randomized, controlled trials that evaluated migraine treatment practices for children. Of the 14 trials included in the review, only one was performed in an ED and noted that prochlorperazine was more effective than ketorolac in relieving headache pain after 1 hour.[5] This highlights the lack of evidence addressing the question of ED treatment of children with migraines. However, we have shown that implementation of a standardized approach in children with migraines can have significant reductions in pain scores, length of ED visits, and hospital admission rates.

Brousseau et al performed the only ED-based prospective, randomized, double-blind clinical trial to date assessing migraine therapy in children aged 5-18 years. Study participants were randomized to receive IV ketorolac or IV prochlorperazine with successful treatment defined as a 50% or greater reduction in the 9 Faces Pain Scale score at 60 minutes. Sixty-two children were enrolled; 55.2% of those who received ketorolac and 84.8% of those who received prochlorperazine were successfully treated (95% confidence interval 8-52%). The study concluded that IV prochlorperazine was superior to IV ketorolac in the acute treatment of migraine headaches in children.[16] While this was a well-conducted study, the goal of migraine management is complete resolution of headache pain, and the study aimed for a 50% reduction in pain score. Additionally, the study evaluated single medication ED pediatric migraine therapy, but no studies have addressed effectiveness of polypharmacy ED migraine treatment in children whom our study examines.

Studies by Trottier et al evaluated changes in migraine treatment practices over a 10-year period in a pediatric ED after the implementation of a treatment protocol. The study employed a comparative retrospective chart review of children diagnosed with a migraine in an ED during 2 study periods from 1996-1997 to 2006-2007. A protocol suggesting a specific ED management approach was implemented in 1999. The primary outcome was a description of migraine medications used in the ED that was found to be different when comparing the 2 study periods.[19] Trottier et al concluded that there was a variation in the treatment of migraines after the implementation of a treatment protocol but never assessed the patient outcomes. Our study is the only large series examining the efficacy of a standardized combination therapy regimen and showed improved patient outcomes after standardized therapy implementation.

Because this study was retrospective, other time-dependent changes could account for some of the differences in outcome: (1) ED length of stay could have been affected by crowding; however, our annual volumes have steadily risen every year without a change in staffing pattern during the study period making this unlikely. (2) Hospitalization rates may be affected by changes in institutional culture or educa-

tion, and dissemination of guidelines for admission. However, prior to institution of these guidelines, the end point for ED treatment was not often a pain score of 0. This would make it more likely that children pre-guideline implementation would have been sent home sooner than was the case after guideline implementation. (3) The samples are not random and the institution of the protocol may have improved outcome assessment, and it may be that care was changed in other ways (eg, nursing attention). We also could not determine how many children presented with a first-time migraine episode vs having an established diagnosis and whether this could have had an effect on the response to treatment.

A paucity of evidence on acute migraine treatment in the pediatric ED currently exists, and no prior research study has illustrated the utility of a standardized migraine treatment regimen in the pediatric ED. This retrospective study reveals how use of a standardized ED headache treatment regimen significantly decreases headache pain scores, ED length of stay, and hospital admission rates. No significant differences were found when evaluating the patient characteristics of the comparison and standardized combination therapy populations. By successfully treating acute migraine attacks, it appears that standardized ED treatment regimens can change acute migraine outcomes and help decrease migraine morbidities. In conclusion, this retrospective study suggests that use of a standardized IV combination treatment regimen is effective for acute pediatric migraine therapy in the ED by reducing headache pain scores, length of ED stay, and hospital admission rates, and supports further clinical trials in this area.

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