LOW-DOSE PROPOFOL FOR PEDIATRIC MIGRAINE: A PROSPECTIVE, RANDOMIZED CONTROLLED TRIAL

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Abstract—Background: Migraine headaches are a common reason for pediatric emergency department (ED) visits. Small studies suggest the potential efficacy of sub-anesthetic doses of propofol for migraine with a favorable side effect profile and potentially decreased length of stay (LOS).

Objective: The objective of this study was to compare the efficacy of low-dose propofol (LDP) to standard therapy (ST) in pediatric migraine treatment. Methods: We conducted a prospective, pragmatic randomized controlled trial from April 2014 through June 2016 in the ED at two pediatric hospitals. Patients aged 7–19 years were eligible if they were diagnosed with migraine by the emergency physician and had a presenting visual analog pain score (VAS) of 6–10. Primary outcome was the percent of pain reduction. Secondary outcomes were ED LOS, 24-h rebound headache, return visits to the ED, and adverse reactions. Results: Seventy-four patients were enrolled, but 8 were excluded, leaving 66 patients in the final analysis (36 ST, 30 LDP). Pain reduction was 59% for ST and 51% for LDP (p = 0.34) with 72.2% vs. 73.3% achieving a VAS ≤ 4 with initial therapy (p = 0.92). There was a nonsignificant trend toward shorter median LOS from drug administration to disposition favoring propofol (79 min vs. 111 min; p = 0.09). Rebound headache was significantly more common in the ST vs. LDP group (66.7% vs. 25.0%; p = 0.01). Conclusions: LDP did not achieve better pain reduction than ST, however, LDP was associated with significantly fewer rebound headaches and a nonsignificant trend toward shorter median LOS from drug administration to disposition. © 2018 Elsevier Inc. All rights reserved.

Keywords—propofol; migraine; abortive; emergency

INTRODUCTION

Migraine headaches are a common occurrence in the pediatric and adolescent population, resulting in a large number of emergency department (ED) visits each year (1,2). Several options are available for acute treatment of migraine, ranging from oral and nasal to injectable and i.v. medications (3). The most common classes of medications used for acute migraine include nonsteroidal anti-inflammatories (NSAIDs); anticholinergics, such as diphenhydramine, and various dopamine antagonists, with success rates between 50% and 70% (4–7). However, these medications are also associated with a number of potential side effects, such as drowsiness and extrapyramidal reactions, which have the potential to prolong ED length of stay (LOS) (1). In addition, when first-line agents fail, limited options for further abortive therapy exist due to insufficient evidence from small studies (3,8,9).
A few reports have noted the potential efficacy of sub-anesthetic doses of propofol, a general anesthetic, for the management of refractory headaches in adults in both inpatient and outpatient settings (10–12). Propofol has been evaluated for the treatment of acute migraine using sub-anesthetic doses that are not expected to produce sedation, respiratory depression, or hypotension associated with anesthetic doses. A recent study evaluated propofol for abortive migraine treatment in adults in the ED, with promising results (13). Based on this, experts have suggested its potential use in acute migraine treatment, but call for additional research (14,15).

Propofol has a high safety profile in the described doses, rapid onset and offset of action, and hypnotic and antiemetic effects (11). In higher doses, propofol is commonly used for pediatric procedural sedation in the ED, with an excellent record of safety, and is thus familiar to many emergency physicians and nurses and widely available in EDs (16). The rapid onset of action and short half-life may make it preferable to current therapies that result in prolonged LOS in the ED and have the potential for extrapyramidal effects.

A small control-matched case series at our center demonstrated that sub-anesthetic propofol resulted in statistically significant pain reduction compared to a standard therapy (ST) consisting of an NSAID, dopamine antagonist, and diphenhydramine (80% vs. 60%); in addition, the ED LOS was shorter for children receiving propofol than for matched cases receiving ST (122 min vs. 203 min, respectively) (17). If confirmed effective for migraine treatment, potential benefits of sub-anesthetic propofol include improved pain control, decreased ED LOS, and reduced side effects. The objective of this study was to compare sub-anesthetic propofol to ST in a pragmatic prospective randomized controlled trial (RCT) of abortive therapy for acute pediatric migraine in the ED. We hypothesized that low-dose propofol (LDP) would result in significantly better pain reduction in a shorter period of time.

PATIENTS AND METHODS

Study Design and Setting

This was a pragmatic prospective, RCT enrolling pediatric migraine patients between April 2014 and June 2016. This study was registered with ClinicalTrials.gov (NCT01604785) and was approved by the Institutional Review Boards at both hospitals. Due to national shortages of prochlorperazine during the study period, a change was implemented from the registered protocol with ClinicalTrials.gov. This study was partially funded by an American Academy of Pediatrics resident research award.

Study Setting and Population

Patients were enrolled in two tertiary care pediatric EDs in close geographical proximity in Oregon. Patients were included if they were 7–19 years of age and presented to the ED with acute migraine. The diagnosis of migraine was made by the treating physician in patients with or without a history of migraine. If a patient was being evaluated for a headache, was believed to have a primary headache disorder most consistent with a migraine subtype, and the treating provider was aiming to treat a migraine headache, they were eligible. To be eligible, patients had to have a visual analog pain score (VAS) ≥6 out of 10 at enrollment. Patients were excluded if they had a known allergy to any study medication, signs of a secondary headache, acute head injury or major surgery within the last 7 days, intracranial shunt, history of tumor or malignancy, chronic lung disease, congenital or acquired heart disease with poor cardiac function or single ventricle, or known renal failure.

Protocol

Patient opaque folders were pre-randomized and evenly split between the two hospitals by the principal investigator before the study start date. They were then utilized sequentially with each enrollment after eligible patient consent without the provider having the ability to change group assignment. Patients who met the inclusion criteria and consented to the study, including patient assent, were randomized 1:1 to one of two groups: ST or LDP. Patients in both groups received 20 mL/kg (maximum 1 L) of normal saline over 30 min before other study drugs. The ST arm consisted of ketorolac (0.5 mg/kg, maximum of 30 mg i.v.), diphenhydramine (1 mg/kg, maximum 50 mg i.v.), and metoclopramide (0.1 mg/kg, maximum 10 mg i.v.). Metoclopramide was used due to a national shortage of prochlorperazine. Five patients received prochlorperazine (0.1 mg/kg, maximum 10 mg) before the shortage. After normal saline, patients in the LDP group received individual boluses of 0.25 mg/kg (maximum 30 mg) propofol i.v., every 5 min until resolution of their pain (VAS ≤4) to a maximum five doses. At both hospitals, propofol is considered a deep sedative regardless of dose, thus deep sedation monitoring policies were followed for all patients in the propofol arm: all patients had continuous cardiorespiratory and pulse oximetry monitoring and blood pressure checked every 5 min with a nurse continuously at the bedside. It was recommended that patients failing the initial arm cross over to receive the other treatment arm, but the choice of rescue therapy was ultimately left to the discretion of the treating physician.

In addition to the treatment protocol, patients in both groups were asked to self-report their pain using a VAS.
0–10 rating scale. Pain scores were obtained every 5 min in the LDP arm to direct further treatment. If the pain score remained > 4 after five boluses, they were deemed a treatment failure. In the ST arm, patients were asked every 15 min for a pain score, but if they were sleeping or drowsy they were not awakened to provide a score. After 1 h, or when the patient woke up if still sleeping at 1 h, pain was assessed and a VAS > 4 out of 10 at 1 h after ST was deemed a treatment failure. All patients were contacted by telephone at 18–24 h after discharge and asked if they had returned to a medical facility for further treatment of headache, as well as their current rating of headache pain on a 0–10 scale. Though patients were not blinded to the study medication, they were not overtly told what they were receiving. Due to the differences in administration, the only true blinding would have been to create a sham procedure where patients got an infusion of medications (ST) as well as intermittent boluses (LDP) and only one being real medication based on treatment arm. Due to the constraints of the ED and staffing, this was not possible. Providers were not blinded due to the obvious differences in medication administration.

**Measurements or Key Outcome Measures**

The primary outcome was pain reduction after initial treatment. Secondary outcomes included two measures of LOS: ED LOS defined as arrival in the ED to discharge from the ED; and treatment LOS defined as time from first study medication to discharge from the ED; ED return visits; rebound headache at 24-h follow-up; and adverse reactions, including extrapyramidal reactions, or significant changes to vital signs, including hypotension or hypoxia/respiratory depression. Rebound headache was defined as VAS pain score higher at 24-h follow-up than at ED discharge. Based on the differences seen in pain reduction in our pilot retrospective data, we calculated a sample size of 37 patients in each group to detect a 20% difference in pain reduction with a power of 80%, and an \( \alpha \) of 0.05, based on a two-sample \( t \)-test using the Satterthwaite method to allow unequal variances.

**Data Analysis**

Descriptive statistics of patient characteristics were calculated overall and within each treatment group. Characteristics with a standardized difference of > 20% between the two treatment groups were examined for confounding and cofounders were planned to be included in the final analysis. Given no confounding was revealed, to determine if there was a difference between the ST and propofol groups, two-sample \( t \)-tests were used for normally distributed continuous data (e.g., percent change in pain), and Wilcoxon two-sample tests were used for right-skewed continuous data (e.g., LOS). For categorical outcomes, \( \chi^2 \) tests were performed, except in the case of sparse data, in which Fisher’s exact tests were used (e.g., return to ED).

Patients admitted on their index visit were excluded from analyses of return visit and rebound headache, and analysis of rebound headache was limited to patients

**Figure 1. Enrollment flow diagram.**

646 patients assessed for eligibility
*hospital B not included

609 Excluded
593 Not meeting inclusion
14 Patient refusals
2 Provider refusals

74 randomized

37 standard therapy

36 visits included in analysis
1 patient excluded due to repeat visit

37 low dose propfol

30 visits included in analysis
5 patients excluded due to repeat visit
**1 patients had more than 2 visits**
that experienced treatment success to avoid confounding with rescue medications for those that failed the allocated treatment. For the LDP group, we calculated descriptive statistics for the number of propofol boluses received by success (VAS after first arm ≤4) or failure. All analyses were performed using SAS, version 9.4 (Cary, NC).

**RESULTS**

*Characteristics of Study Subjects*

Between the two study sites, the research infrastructure at hospital A allowed us to monitor the number of screened patients relative to those enrolled, while hospital B enrolled patients prospectively at provider discretion, precluding the ability to track the number of screened patients at this site. Patients at both sites underwent the same procedures and follow-up. Figure 1 depicts the enrollment for hospital A; hospital B data are not available and therefore not presented. There were 74 total patients enrolled in the study, however, 6 had more than one study visit: 5 patients had two visits each, and 1 patient had four visits. For these 6 patients, only the first study visit was included in the final analyses.

Table 1 shows patient demographic characteristics in both study arms. Two patient characteristics were imbalanced between the treatment groups: personal history of migraine and use of daily prophylaxis for migraine, however, there was no association between either of these characteristics and the primary outcome. Therefore, we did not control for any patient characteristics in the final analysis, and all final analyses were bivariate comparisons of each outcome by treatment group.

*Pain Reduction/Rebound Headache*

There was no statistically significant difference in either percent pain reduction between the ST and LDP groups (59% vs. 51%, respectively; \( p = 0.34 \)) (Figure 2) or absolute pain reduction (4.83 vs. 4.03; \( p = 0.24 \)). A similar proportion of patients in each group achieved a VAS ≤4 with initial treatment (72.2% ST vs. 73.3% LDP; \( p = 0.92 \)). Twenty patients received rescue medication after their assigned treatment protocol: 8 patients in the ST arm and 11 patients in the LDP arm. For LDP patients with treatment success, the mean number of propofol boluses was 3.3 (standard deviation [SD] 1.3) and the median was 4 (range 1–5). Significantly more patients in the ST group experienced a rebound headache compared to patients who received LDP (66.7% vs. 25.0%; \( p = 0.01 \)).

*Adverse Effects*

Three patients in the ST arm experienced extrapyramidal symptoms (8.3%). One patient in the LDP arm (3.3%) experienced transient oxygen desaturation to 89% that self-resolved without the need for intervention.

*Length of Stay/Return Visits*

There was no difference in either measure of LOS between groups, though there was a trend (\( p < 0.10 \)) toward decreased treatment LOS in the LDP group. The median LOS from the administration of medication to discharge or admission was 111 min for ST and 79 min for LDP (\( p = 0.09 \)). Median total LOS was 219 min for the ST and 229.5 min for LDP (\( p = 0.97 \)). There was no difference in return to the ED within 24 h (ST 6.5% vs. LDP 3.7%). A total of 5 patients (3 in the ST group and 2 in the LDP group) were admitted to the hospital for refractory headache and excluded from the follow-up calls.

**DISCUSSION**

In this pragmatic prospective RCT of abortive therapy of pediatric migraine in the ED, LDP was not significantly better than ST for either mean reduction in headache pain (51% vs. 59%) or the proportion of patients...
achieving a VAS pain score \( \leq 4 \) (73.3% vs. 72.2%) after treatment. However, the rate of rebound headaches was significantly lower in the LDP arm compared to ST. The number of adverse events was low in both treatment groups. Finally, we identified a trend toward decreased LOS from medication administration to disposition in the LDP arm, but no overall significant difference between groups in total ED LOS. Based on these results, larger studies are required to confirm noninferiority of LDP to current ST.

Patients in the ST group were significantly more likely to have a rebound headache compared to LDP patients (66.7% vs. 25.0%; \( p = 0.01 \)). This may support the theory that propofol has a more direct effect on the hypothesized pathophysiologic mechanism of migraine compared to ST. While the exact mechanism of action of propofol in this setting remains unclear, studies demonstrate that propofol has effects on glial cell potassium levels, interacts with \( \gamma \)-aminobutyric acid receptors, and has an effect on cortical spreading depression, which is a leading theory in the progression of acute migraine headache (18–20).

One potential benefit of propofol is that it has a rapid onset of action and short half-life. This has the potential to lead to more rapid pain reduction and less post-treatment drowsiness. Our earlier case study found a large difference in LOS with LDP, allowing patients to be discharged more than an 1 h earlier (17). In the current study, the LDP group experienced a 30-min shorter LOS after receiving study medication than ST. Though not statistically significant, we believe this is clinically significant. Interestingly, the overall total LOS was similar between groups. We believe this is a result of the experimental study design and the fact that both institutions require deep sedation protocols for all patients in the LDP treatment arm. This requires a nurse throughout the duration of treatment, which might have delayed initiation of study medication. The requirement to use deep sedation protocols with propofol is its primary limitation. Though reasonable in the current climate given limited data on safety, this may change as additional literature supports the safety of LDP.

**Limitations**

This study had several limitations. First, due to limitations in research infrastructure at site B, we were unable to track screened patients at that site, however, both pediatric EDs are tertiary children’s hospitals near one another and the populations of screened patients are likely similar. It is likely that a smaller proportion of

![Figure 2. Pain reduction.](image-url)
eligible patients were enrolled at site B, as enrollment was performed on a voluntary basis by the treating physician. Second, in this pragmatic trial, we did not utilize strict international headache criteria for the diagnosis of migraine, but included patients diagnosed by the ED provider with migraine, with exclusion criteria aimed to eliminate secondary causes of headache. While this pragmatic approach reflects real-world clinical practice, it may have led to inclusion of non-migraine primary headaches and potential underestimation of the efficacy of both LDP and ST, which are believed to be migraine-specific. Third, in keeping with this pragmatic approach, our study design took into account the different mechanisms of action of drugs, and pain scores were assessed at different frequencies in each arm, as propofol has a much faster onset than ST, and sequential boluses of LDP are administered every 5 min based on reported pain. While we did not discuss with patients what they were receiving, based on the administration differences in treatment arms, a patient may have discovered their treatment and, therefore, impacted their response to treatment. Fourth, there were a small number of patients with multiple visits who were enrolled. To decrease this bias, we only included their initial index visit. This is in an attempt to decrease the bias of patients knowing the treatment therapies and affecting results. Unfortunately, while we enrolled the planned number of patients in our power analysis, we did not have 74 visits to analyze so the study was slightly underpowered. Lastly, there is no accepted dose of LDP for migraine treatment. Therefore, a dose was selected based on retrospective data and aiming to not stack doses, resulting in sedation (17).

CONCLUSIONS

In this study, LDP was not significantly better than ST for pain reduction in pediatric migraine, but did result in fewer rebound headaches at 24 h and showed a trend toward shorter median LOS from drug administration to disposition. Larger studies are needed to confirm the non-inferiority of LDP to ST, to determine the safety of LDP, and to determine optimal dosing and necessary levels of monitoring at these doses.

REFERENCES

ARTICLE SUMMARY

1. Why is this topic important?
   Pediatric acute migraine is a relatively common presentation to the emergency department. Abortive treatment options are limited and result in approximately 10% admission rates.

2. What does this study attempt to show?
   This is a randomized controlled trial of low-dose propofol compared to standard treatment. Significant clinical outcomes include percent pain reduction, rebound headache, and length of stay in the emergency department.

3. What are the key findings?
   Low-dose propofol resulted in a shorter length of stay after medication administration and decreased rebound headache at 24 h, but was not statistically significantly better at pain reduction.

4. How is patient care impacted?
   Low-dose propofol may serve as a reasonable alternative for patients being treated in the emergency department for migraine headaches.