The Journal of Emergency Medicine, Vol. ■, No. ■, pp. 1–7, 2018

0736-4679/$ - see front matter

https://doi.org/10.1016/j.jemermed.2018.01.003

Original Contributions

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

David C. Sheridan, MD, MCR,* Matthew L. Hansen, MD, MCR,* Amber L. Lin, MS,* Rongwei Fu, PHD,* and Garth D. Meckler, MD, MSHS†‡

*Department of Emergency Medicine, Oregon Health & Science University, Portland, Oregon, †Department of Pediatrics, Pediatric Emergency Medicine, University of British Columbia, Vancouver, British Columbia, Canada, and ‡British Columbia Children's Hospital, Vancouver, British Columbia, Canada

Reprint Address: David C. Sheridan, MD, MCR, Department of Emergency Medicine, Oregon Health & Science University, 707 SW Gaines Road, Mail Code CDRC-W; EM, Portland, OR 97239

☐ **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 final 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).

This was partially supported by an American Academy of Pediatrics resident research award.

RECEIVED: 23 October 2017; FINAL SUBMISSION RECEIVED: 3 January 2018;
ACCEPTED: 6 January 2018

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) $\geq$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 $\leq$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