Low-Dose Propofol for the Abortive Treatment of Pediatric Migraine in the Emergency Department

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Objective: Limited progress has been made in the past decade for abortive treatment of migraine headache in the pediatric emergency department (PED). Propofol, a general anesthetic, has been reported to be effective in the treatment of refractory headaches in adults at subanesthetic doses but never in the pediatric population. The goal of this study was to review our institution's experience with subanesthetic doses of propofol for the abortive treatment of pediatric migraine and compare propofol with standard abortive therapy in the PED.

Methods: Retrospective review of all patients discharged from the Oregon Health and Science University PED with a diagnosis of migraine headache from January 2010 to July 2011. Patients treated with subanesthetic doses of propofol were compared with matched controls who received standard abortive migraine therapy, defined as the combined use of a nonsteroidal anti-inflammatory medication, diphenhydramine, and prochlorperazine. Outcome variables of interest included reduction of pain as measured on a self-reported visual analog scale and length of stay after administration of initial abortive medication.

Results: Patients who received subanesthetic doses of propofol achieved significantly greater reduction in pain scores (80.1% vs 61.1%; $P < 0.05$) compared with matched controls as well as shorter stay (122 minutes vs 203 minutes; $P = 0.2$) after treatment. No adverse effects (hypotension, respiratory depression, or hypoxia) were recorded in either group.

Conclusions: Propofol seems to be effective for the abortive treatment of pediatric migraine headache in the PED. Further prospective trials are warranted to either support or refute these initial findings.

Key Words: migraine, propofol, headache, abortive

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Migraine headaches are a common occurrence in the pediatric population and increase in prevalence with age.[1] The American Academy of Neurology has endorsed clinical guidelines for abortive therapy[2]; however, limited treatments are available for status migrainosis. Recommended options range from ibuprofen and acetaminophen, to the 5-Hydroxytryptamine receptor agonists (triptans)[3] for pain control in addition to antiemetics such as diphenhydramine and prochlorperazine. These abortive medications have a number of potential adverse effects such as drowsiness, dystonic reactions, and the potential for prolonged emergency department (ED) length of stay (LOS). Although these medications have shown reasonable efficacy, there have been no significant developments in abortive treatment in the recent past for children other than inpatient migraine management.[4]

Ideal treatment in the pediatric ED (PED)for acute or chronic migraine would include a regimen that is safe, is effective, and does not require a long stay. A limited number of reports in the adult population have noted the potential efficacy of propofol, a general anesthetic, for the treatment of refractory headaches (off-label use).[5–7] In these reports, propofol was administered in a subanesthetic dose that is not expected to produce the respiratory depression or hypotension that can be seen with higher doses typically used to induce general anesthesia. At subanesthetic dosing, propofol has a high safety profile as well as a rapid onset and offset of action while producing a hypnotic and antiemetic effect that makes it ideal for potential abortive treatment of headache in the ED.[7] These adult studies suggest that propofol is highly effective in reducing headache severity acutely.

Based on success in adults, members of the pediatric emergency medicine faculty at our institution have administered subanesthetic doses of propofol in the PED to treat migraine headaches in children. The goal of this study was to review the efficacy and safety of this novel therapy and compare it with standard abortive migraine treatments. To our knowledge, this is the first report of the use of propofol in children for the acute management of migraine.

METHODS

This study was approved by the institutional review board of Oregon Health and Science University (OHSU). OHSU uses an electronic medical record system (EPIC 2010) that was searched to obtain our study population. We used the following inclusion/exclusion criteria: all OHSU PED visits from January 1, 2010 (when first propofol case was identified), through July 31, 2011, by patients younger than 18 years who received propofol without diphenhydramine or prochlorperazine during their visit for the purpose of pain relief and had a final discharge diagnosis of migraine or status migrainosis were included; patients were excluded if they had a diagnosis of trauma or a history of ventriculoperitoneal shunt placement. Excluded patients were identified by discharge diagnosis of shunt malfunction, receipt of magnetic resonance image, computed tomography of the head, or ventriculoperitoneal shunt evaluation by x-ray study while in the PED. Patients who received propofol for indications other than pain relief were also excluded. During the same period, control patients were identified by searching for a discharge diagnosis of migraine; those who received standard abortive therapy with nonsteroidal anti-inflammatory drugs (NSAIDs), diphenhydramine, and prochlorperazine in our PED were included as controls. From this group, controls were matched to cases by age, sex, and use of daily migraine prophylaxis.

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Data Collection

A predetermined data collection form was used to gather information in a retrospective manner through electronic medical record. Prehospital data included personal and family history of headaches, daily prophylactic medication, and use of abortive medications within 24 hours of presentation to the PED. Data collected for the PED visit included chief complaint, duration of headache, characteristics of the pain, and associated symptoms. Data related to propofol administration included overall ED LOS, LOS after initial administration of medications, other medications administered, initial and discharge numerical pain scores documented by a physician or registered nurse using a visual analog scale, and total dose and number of boluses of propofol given. Final disposition data included whether the patient was admitted for pain control or discharged home, the final diagnosis, and whether they re-presented to the PED within 24 hours of discharge.

All patients receiving subanesthetic propofol for abortive migraine treatment were monitored according to our institutions sedation policy and guidelines. Continuous pulse oximetry and vital signs every 5 minutes after medication administration were recorded. A dedicated nurse and physician credentialed for deep sedation were present during and immediately after medication administration in the ED. Patients were asked to rate their pain using a visual analog pain scale from 0 (being no pain) to 10 (being the worst imaginable pain impairing daily activities). The staff recorded pain scores before and after propofol administration.

Outcome Measures

Variables of interest that were statistically compared included LOS in the PED and percent reduction in pain score from time of presentation to the time of discharge. An independent sample *t* test was performed on the outcome variables of interest between the 2 groups.

RESULTS

Patient Population

The strategy used to identify patients is shown in Figure 1. The clinical decision to administer propofol in individual cases was based solely on attending faculty clinical judgment without a prospective protocol, was limited to 2 providers in the PED, and was generally reserved for patients who had previously failed standard therapy.

Patient Characteristics

Characteristics of the cases and controls are presented in Table 1. There were no significant differences between cases and controls with regard to age, sex, mean duration of headache on presentation, or previous use of abortive medications. Abortive therapies used by patients in the propofol group before PED presentation included NSAIDs (100%), as well as diphenhydramine, prochlorperazine, and acetaminophen. Abortive medications tried by the control group before PED visit included an NSAID (71% of patients), triptans, opiates, diphenhydramine, prochlorperazine, and acetaminophen. Two of the propofol patients and 3 of the controls used daily prophylactic medications.

Propofol Administration

Details of the propofol-treated cases are summarized in Table 2. The dosing used was patient dependent and was approximately 0.56 mg/kg per bolus. The average total dose of propofol given in our study was 1.71 mg/kg, divided over an average of 3 boluses, with a bolus dose ranging from 10 to 50 mg. There were no adverse effects or significant sedation from propofol administration; specifically, no patient developed apnea, hypoventilation, hypoxia (defined as pulse oximetry < 92%), or hypotension.

Effectiveness

Table 1 compares the effectiveness of cases and controls. The mean total LOS from presentation to discharge was similar between cases and controls (304 minutes vs 308 minutes), although the mean LOS after medication administration was lower in the propofol group (122 minutes vs 203 minutes, $P = 0.2$). Patients receiving subanesthetic propofol for abortive migraine management had a statistically significantly greater reduction in pain score from the time of presentation to the time of discharge compared with the control group (80.1% vs 61.1%, $P = 0.02$) and twice the number of patients experiencing 100% resolution of their pain compared with control group patients. However, 2 of the 7 patients in the propofol group were admitted to the hospital, whereas none of the control patient

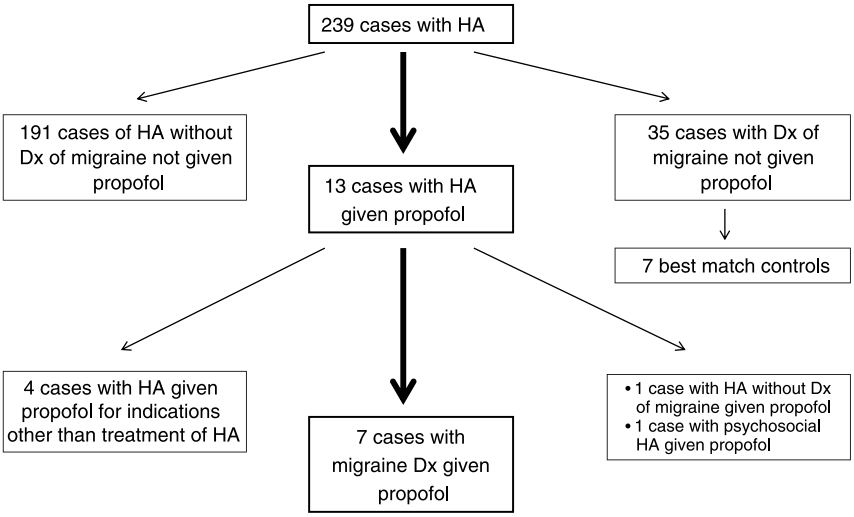

FIGURE 1. Identification of propofol cases. HA, indicates headache; Dx, diagnosis.

TABLE 1. Comparison of Propofol Cases and Controls

	Propofol	Control	*t* Test *P*
Age, mean (SD), y	12.3 (3.1)	14.7 (2.1)	Not significant
Sex	5/7 female	5/7 female	
Daily migraine prophylaxis	2/7	2/7	
Headache duration before PED, d (SD)	3.6 (2.8)	3.0 (3.1)	
Abortive medications before PED	6/7 within 24 h	7/7 within 24 h	
Mean VAS pain score on arrival	9.5 /10	7/10	
Percent reduction in pain score, mean (SD)	80.1 (27.6)	61.1 (32.0)	*$P = 0.02$
PED LOS after medication, mean (SD), min	122.0 (63.5)	202.7 (140.7)	$P = 0.2$
24-h returns	1/7	1/7	Not significant
Average propofol bolus, mg/kg	0.56	N/A	N/A

*Statistically significant.

VAS indicates visual analog scale; N/A, not applicable.

population was admitted for further management. One of these patients was admitted for a brief stay in our department's PED observation unit for further pain control. This patient had failed nonsteroidal anti-inflammatory medication and acetaminophen before her presentation to our ED; her pain on presentation was 7/10 and, after 5 doses of propofol (1.71 mg/kg total), was 4/7. She was then admitted for further pain control with ketorolac, dexamethasone, and benzodiazapenes. In addition to migraine headache, she was thought to have a significant psychosocial component to her pain and was discharged without inpatient admission. The second patient was treated for migraine headache in the ED, with a 78% reduction in his pain from time of presentation to the time of admission to the hospital but was noted to have abdominal pain with additional viral symptoms. He was subsequently admitted to the hospital for observation and serial abdominal examination. He had no complications or abdominal abnormality and was discharged with a diagnosis of migraine headache. No adverse reactions or further monitoring related to propofol was required for either patient. One patient in each groups returned to the PED within 24 hours for recurrent headache management.

DISCUSSION

Krusz et al[5] were the first to describe the incidental discovery that adults with migraine headache treated with propofol in preparation for nerve blocks experienced significant relief of their pain. Based on their initial observation in 6 patients, they recruited 77 patients with refractory migraine and treated them with subanesthetic doses of propofol. The average reduction in patient-rated visual analog pain scale was 95.4% after an average of 20 minutes; no adverse effects or outcomes were reported related to propofol administration. To date, this is the largest cohort, although additional published case reports support the use of subanesthetic doses of propofol for abortive migraine management in adults.[6,7]

This is the first study to report the use of propofol for the abortive treatment of migraine headaches in the PED. Published guidelines have supported the use of medications such as NSAIDs, diphenhydramine, and prochlorperazine for abortive treatment of pediatric migraine.[3] We chose as controls patients who received these medications and found a significant improvement in pain score reduction with subanesthetic propofol compared with standard therapy.

The pathophysiology of migraine headache is still not fully understood, and therefore, the therapeutic mechanism of propofol is also unclear. Krusz et al suggest that propofol might act through effects on calcium channels and the γ aminobutyric acid system in the central nervous system. This theory fits with the known mechanism of action of many of the standard medications used for daily migraine prophylaxis. Calcium channel antagonists such as verapamil and γ aminobutyric acid agonists such as topiramate and gabapentin are examples of such medications commonly used for migraine prophylaxis. The efficacy of propofol may provide additional insight into the underlying pathophysiology of migraine headache.

Adverse events associated with anesthetic doses of propofol include respiratory depression and hypotension, which are dose dependent.[8] The safe use of propofol by emergency physicians, however, has been documented in a number of previous studies.[9] Our series suggests that propofol has a favorable safety

TABLE 2. Propofol Group ED Clinical Course

	Triage/Discharge VAS Pain Score	Pain Reduction, %	No. Propofol Boluses	Total Dose, mg/kg	Disposition
Patient 1	8/0	100	3	0.81	Discharge
Patient 2	7/4	43	5	1.71	Admit
Patient 3	10/0	100	2	0.53	Discharge
Patient 4	9/0	100	3	0.86	Discharge
Patient 5	9/0	100	2	1.99	Discharge
Patient 6	9/2	78	3	3.72	Admit
Patient 7	10/6	40	4	2.32	Discharge

VAS pain score indicates 1 to 10 self-reported headache severity; pain reduction, percentage reduction in pain score from time of presentation to time of discharge.

profile when administered at subanesthetic doses in a monitored ED setting under the supervision of trained providers for this indication; none of the 7 cases treated with propofol experienced apnea, hypoventilation, hypoxia, or hypotension, and no additional adverse events were recorded. Krusz et al reported similar safety among 77 adult patients treated in a pain clinic with subanesthetic doses of propofol, none of whom experienced any adverse effects.[5] This is likely attributable to the fact that propofol for abortive migraine management was used in subanesthetic doses (approximately 0.5 mg/kg per bolus), whereas the dose required to achieve procedural sedation in the PED has been reported to range from 3.3 to 3.5 mg/kg.[10]

In addition to its safety and potential efficacy for the treatment of migraine headaches, the rapid metabolism of propofol makes it attractive for use in the PED for its potential to reduce patient LOS. Standard abortive medications for migraine such as diphenhydramine and prochlorperazine cause centrally mediated sedation with half-lives between 4 and 9 hours and often require a longer course of observation due to. Adult studies have shown a dramatic decrease in pain severity within 20 to 30 minutes of propofol administration. In our series, PED LOS, although not significantly different overall, trended toward decreased among the propofol group compared with controls, when considering the time from medication administration to final disposition.

This case-control series has a number of important limitations. As with all retrospective study designs, it is potentially subject to selection bias. Cases were chosen to receive propofol at the discretion of treating clinicians without prospective inclusion criteria and had typically failed previous standard therapy, which might overestimate the effect of propofol in comparison with controls who received standard therapy. In addition, cases were identified by discharge diagnosis of migraine as assigned by the treating provider, and not all patients met strict international criteria for acute migraine headache; however, controls were chosen by the same method and likely represent a similar cohort with respect to formal criteria for diagnosis of migraine. Although PED LOS was compared between cases and controls, the experimental use of propofol in the clinical setting may have led treating providers to observe patients longer after treatment than they might have if using propofol for a standard indication. This could artificially underestimate the impact of propofol on LOS. Finally, the favorable safety profile of subanesthetic dose propofol in our series, although likely dose related, may be attributed to the fact that it was administered in a highly monitored setting by PED physicians and nurses credentialed for its use in deep sedation.

This small case-control series suggests that propofol, used in subanesthetic doses, may be effective and safe as an abortive treatment for pediatric migraine headache in the ED setting. Additional research, including prospective comparisons of propofol to standard treatment regimens for pediatric migraine is warranted.

REFERENCES

1. Lewis DW. Pediatric migraine. *Pediatr Rev.* 2007;28:43–53.
2. Lewis D, Ashwal S, Hershey A, et al. Practice parameter: pharmacological treatment of migraine headache in children and adolescents: report of the American Academy of Neurology Quality Standards Subcommittee and the Practice Committee of the Child Neurology Society. *Neurology.* 2004;63:2215–2224.
3. Joseph MM, Webb K. Evidence-based assessment and treatment of acute headache in the children and adolescents in the ED. *Pediatr Emerg Med Pract*. 2005;2;1–28.
4. Kabbouche MA, Powers SW, Segers A, et al. Inpatient treatment of status migraine with dihydroergotamine in children and adolescents. *Headache*. 2009;49:106–109.
5. Krusz JC, Scott V, Belanger J. Intravenous propofol: unique effectiveness in treating intractable migraine. *Headache*. 2000;40:224–230.
6. Drummond-Lewis J, Scher C. Propofol: a new treatment strategy for refractory migraine headache. *Pain Med*. 2002;3:366–369.
7. Bloomstone JA. Propofol: a novel treatment for breaking migraine headache. *Anesthesiology.* 2007;106:405–406.
8. Shah A, Mosdossy G, McLeod S, et al. A blinded, randomized controlled trial to evaluate ketamine/propofol versus ketamine alone for procedural sedation in children. *Ann Emerg Med*. 2011;57:425–433.e2.
9. Mallory MD, Baxter AL, Yanosky DJ, et al. Emergency physician-administered propofol sedation: a report on 25,433 sedations from the pediatric sedation research consortium. *Ann Emerg Med*. 2011;57:462–468.e1.
10. Skokan EG, Pribble C, Bassett KE, et al. Use of propofol sedation in a pediatric emergency department: a prospective study. *Clin Pediatr (Phila)*. 2001;40:663–671.