INTRODUCTION

Headaches are common in the pediatric population, with migraine being the most common, and their prevalence increases with age (1). The American Academy of Neurology (AAN) has endorsed clinical guidelines for abortive treatment of pediatric headache and particularly migraine (2). Acute migraine headaches in pediatric patients account for nearly 100,000 emergency department (ED) visits per year in the United States, and general headaches account for almost 500,000 visits. Of the 100,000 ED visits for migraine, a large amount of variability in diagnostic work-up and treatment exists. One study using a national database found high use of narcotics with almost one-third of patients receiving these agents. Previous guidelines and reviews in the pediatric population advise against the use of narcotics for headache management in the ED (1–4). The abortive medications currently recommended have a number of potential side effects, such as drowsiness, dystonic reactions, and potential for prolonged ED length of stay (LOS). Although these medications have shown reasonable efficacy, there continue to be limitations beyond side effects. Prochlorperazine, a dopamine antagonist, has been the most studied in the pediatric migraine population, and the most effective; however, its availability has recently been limited by decreased production. A few recent studies have evaluated alternative agents for migraine,
including low-dose propofol and intravenous magnesium sulfate, with some success (5,6). These alternatives have shown reasonable efficacy, but have limitations as well. Medications with high efficacy and fewer potential side effects are desired to more effectively and efficiently treat pain, while reducing the use of narcotics in children with this chronic condition.

Intravenous sodium valproate (Depacon®) is effective for migraine headaches in adults, but has limited evidence in children and adolescents <18 years of age. This medication has been studied and used as a prophylactic medication for migraine patients with success (7,8). Literature on its efficacy as a one-time dose in abortive management in the ED setting is also promising. The pathophysiology of migraine is not completely understood. Sodium valproate (VPA) has been theorized to modulate gamma-aminobutyric acid receptors and sodium/calcium neuronal channels that inhibit the excitatory process seen in migraine headaches (9). A recent randomized trial in the adult population showed VPA to be more effective than dopamine antagonists and triptans combined in acute migraine at 2 h without any adverse effects (10). A second adult trial showed significant headache relief within 1 h of VPA infusion, and no adverse effects (9). Due to the limited literature on pediatric migraine treatments in the ED, providers are forced to apply data from adult studies to the child or adolescent in front of them. With shortcomings of current abortive treatments and national shortages, more options need to be available to emergency medicine physicians for treating headaches that have a significant impact on patient and family lives. The objective of this study was to assess the effectiveness of VPA for pediatric headache at two pediatric tertiary care pediatric EDs (PEDs) with the hypothesis that it will improve pain control for refractory headaches. To our knowledge, this is the first report of VPA use in the pediatric population for acute headache management in the PED.

METHODS

This was a retrospective case series from July 2010 to February 2014. All patients <19 years of age with a final diagnosis of migraine or headache who received parenteral VPA in the PED for symptomatic headache relief were included. Data were collected at two pediatric tertiary care centers in close geographical proximity. In both cases, data were collected from the electronic health record after searching on the diagnoses and medications ordered, as mentioned here. Data were collected by a member of the study team who was trained in data abstraction. The Institutional Review Boards at both institutions approved this study.

Data collection included basic demographics of each patient, LOS, pain reduction, need for narcotics, side effects, and final disposition. Pain scores were recorded from the standard pain assessment sheet in the medical record that rates pain from 0 to 10, with 10 being the highest level. Provider notes were reviewed for any side effects documented and vital signs throughout the visit were assessed for significant changes. Patients with missing pain scores before or after VPA administration were excluded from this study. In these centers and in each case presented here, VPA was used as a second-line agent. Therefore, LOS and pain reduction were calculated before VPA administration in the PED and after, in an attempt to isolate its effect from other medications administered. LOS and return visit within 72 h were only analyzed for patients who were discharged. Patients were excluded if full data were not available.

RESULTS

During the study period, 16 patients met inclusion criteria. Of these 16 patients, 3 were missing pain scores before VPA administration and were excluded. One additional patient was excluded because an order was placed for VPA, but the mother refused before the patient received it. The final study cohort consisted of 12 patients. A formal diagnosis of migraine was present in 67% of patients and the remaining had a final diagnosis of headache.

The mean age was 15 years and 50% were female. Seventy-five percent (9 of 12) of patients had a documented history of migraine headaches and 50% (6 of 12) had a family history of migraine headaches. All patients noted trying an abortive medication at home ranging from over-the-counter analgesics to a triptan agent. Sixty-seven percent (8 of 12) of patients were on an oral prophylactic migraine agent at home, with 5 of 12 patients taking topiramate, 2 of 12 patients taking divalproex sodium, and 1 of 12 patients taking amitriptyline. Eighty-three percent (10 of 12) of the cohort were discharged home and 2 patients were admitted to the hospital for pain control. Of the 10 patients discharged, 1 had a return visit within 72 h for headache.

Patients had a mean total LOS of 515 min (standard deviation [SD] = 309 min) (Figure 1). All patients were treated with other abortive headache medications before VPA, including nonsteroidal anti-inflammatories, dopamine antagonists, intravenous fluids, and narcotics. The mean LOS after VPA administration was 120 min (SD = 105 min). Patients admitted to the hospital were excluded from the LOS analysis, as their data were significantly affected by the ability to admit to the hospital; patient number 12 (Table 1) was admitted to PED observation without any improvement in pain before receiving VPA, which increased their LOS significantly. Mean pain reduction from time of presentation to before VPA
administration was 17% (SD = 18%). However, after VPA administration, patients experienced an additional 36% reduction (Figure 2) in pain score (SD = 34.2%). The 2 patients who were admitted had poor pain control before VPA administration and no response to VPA. When analyzing the 10 discharged patients, they had a mean additional pain reduction after VPA administration of 44% (SD = 32%) at the time of discharge. Before using VPA, 42% (5 of 12) of patients received a narcotic medication. However, only 1 patient was given a narcotic after VPA. No adverse reactions or side effects were noted with VPA administration. Pediatric neurology was consulted before VPA use in all patients in this case series.

**DISCUSSION**

Pediatric headache is a frequently encountered complaint in the PED and physicians must be comfortable with multiple treatments. Current first-line medications are in short supply or have limitations resulting in need for new agents (11). VPA has been used as a prophylactic migraine medication in the pediatric population, but until this study its utility as an abortive agent in children has been unknown. When it was used in this study, it resulted in an almost 50% reduction in pain for discharged patients which is clinically significant. Before its administration, patients had <20% reduction in pain, indicating that without VPA, patients would have required additional medications or inpatient management of pain. One interesting point is that a much larger proportion of patients received narcotics before VPA than after its administration (5 of 12 vs. 1 of 12, respectively). In this series, 67% of patients were taking prophylactic agents daily. Prophylactic medications are effective at reducing the number of migraines in some patients, however, most patients continue to require abortive medications with some frequency (1,2). Narcotics have several downsides in migraine or refractory headache patients, including the concerns for addiction and abuse, but also high rates of rebound headache (12). For this reason, avoiding narcotics in the acute phase is very important, and this has been recognized by the AAN (2). Although

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*F = female; HA = migraine headaches; M = male; Post-LOS = length of stay after administration of sodium valproate in minutes; Pre-LOS = length of stay before administration of sodium valproate in minutes; Pre-VPA = percent pain reduction before administration of sodium valproate; Post-VPA = percent pain reduction after administration of sodium valproate; VPA = sodium valproate.

*0 indicates no pain reduction.
this case series is small, we suggest considering VPA administration before narcotics for children with acute headache in the PED.

Compared to other parenteral abortive migraine therapies, VPA has a favorable side effect and safety profile. It has not been shown to cause significant drowsiness or sedation and so far has had a good safety profile. However, due to its risk for teratogenicity, all female patients should undergo a pregnancy test in the PED before receiving VPA. Using VPA for migraine may also have the benefit of lowering LOS for migraine or refractory headache patients. We found the LOS in the PED after VPA administration was one-third of the duration spent before receiving other medications. Further investigation is needed to determine the potential benefits on LOS if VPA is used first line, rather than for rescue therapy as in this case.

All patients in this case series underwent a telephone consult with pediatric neurology before receiving VPA. This, in addition to the poor pain reduction before VPA, would suggest that these patients’ headaches were refractory to standard treatment. However, after VPA, they had a relatively short LOS and clinically important pain control without significant side effects seen and a low return visit rate. We suggest that emergency physicians consider administering VPA before considering admission or further discussing with pediatric neurology if no red flags exist. The most common dose given was a single dose of either 1000 mg (9 of 12 patients) or 500 mg (3 of 12 patients); both patients admitted received 1000 mg. Further studies are needed to determine the ideal dose for acute pediatric headache, but it appears that 1000 mg was adequate in the majority of patients without side effects. However, no strict dosing regimen existed in this study and was at the recommendation of the pediatric neurologist consulted.

**Limitations**

This study has a number of limitations. The inherent restrictions of a retrospective study design are the most significant, as patients were excluded based on missing data that might not exist in a prospective data collection. In addition, there was no standard time course for collecting pain scores, and the dose of VPA used was not standardized. VPA was used in all cases after multiple other medications had failed. Pain scores were collected before and after VPA use rather than calculating the pain-reduction change from initial presentation to after its use in an attempt to isolate VPAs direct effect. However, there may be some additive effect seen with VPA and the other agents used that is unclear. The applicability of this medication to all headache patients may be limited, as this series included many children who had failed other treatments in the PED and had refractory headaches. There were 2 patients with poor pain control, but were discharged from the hospital as the parents wanted their child to go home and sleep comfortably. Of note, neither of these patients returned to the PED. Further studies will need to determine if this therapy is effective for a select subgroup of patients.

**CONCLUSIONS**

Pediatric headache is a frequently encountered problem in the PED and multiple medications need to be available for acute treatment. This case series suggests that VPA is a possible second-line agent to achieve pain reduction and avoid inpatient admission. The utility of VPA in the first-line treatment of migraine headache is unclear and further prospective studies are needed for further evaluation.

**REFERENCES**

ARTICLE SUMMARY

1. Why is this topic important?
   This topic is important as pediatric headache is a frequent complaint in the emergency department and children continue to receive non–evidence-based treatments. A significant number of children continue to receive opioids, which are advised against, and newer treatments are needed.

2. What does this study attempt to show?
   This study’s aim was to introduce a new therapeutic option for acute pediatric headache. With limited options, it is important to have new medications available.

3. What are the key findings?
   The key findings including an approximate 40% reduction in pain in a short period of time using sodium valproate in the parental form without side effects. More than 80% of the children were discharged home after receiving valproate, whereas they may have otherwise required admission for pain control after failing multiple other medications in the emergency department (mean pain reduction before valproate was <20%).

4. How is patient care impacted?
   Patient care is directly impacted, as this suggests a new medication that can be used to acutely treat headaches without significant side effects in this small series.