Pediatric Surgery International (2018) 34:769–774
https://doi.org/10.1007/s00383-018-4274-9

ORIGINAL ARTICLE

Effectiveness of gabapentin as a postoperative analgesic in children undergoing appendectomy

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Accepted: 30 April 2018 / Published online: 4 May 2018

Abstract

Purpose Though gabapentin is increasingly used as a perioperative analgesic, data regarding effectiveness in children are limited. The purpose of this study was to evaluate gabapentin as a postoperative analgesic in children undergoing appendectomy.

Methods A 12-month retrospective review of children undergoing appendectomy was performed at a two-hospital children's institution. Patients receiving gabapentin (GP) were matched (1:2) with patients who did not receive gabapentin (NG) based on age, sex and appendicitis severity. Outcome measures included postoperative opioid use, pain scores, and revisits/readmissions.

Results We matched 29 (33.3%) GP patients with 58 (66.6%) NG patients ($n=87$). The GP group required significantly less postoperative opioids than the NG group (0.034 mg morphine equivalents/kg (ME/kg) vs. 0.106 ME/kg, $p<0.01$). Groups had similar lengths of time from operation to pain scores ≤ 3 (GP 12.21 vs. NG 17.01 h, $p=0.23$). GP and NG had similar rates of revisit to the emergency department (13.8 vs. 10.3%, $p=0.73$), readmission (6.9 vs. 1.7%, $p=0.26$), and revisits secondary to surgical pain (3.4 vs. 3.4%, $p=1.00$).

Conclusion In this single-center, retrospective cohort study, gabapentin is associated with a reduction in total postoperative opioid use in children with appendicitis. While promising, further prospective validation of clinical effectiveness is needed.

Keywords Gabapentin · Appendectomy · Abdominal surgery · Opioid epidemic · Analgesic

Abbreviations

ERP	Enhanced recovery protocol
VAS	Visual analog scale
LOS	Length of stay
ME	Morphine equivalents in mg

Introduction

Opioid medication overdose, diversion and abuse is a major dilemma currently in the forefront of U.S. healthcare [1]. Although primarily affecting adults, opioid abuse is also a problem among adolescents, with approximately 8% of individuals age 12–17 years reporting nonmedical use of prescription opioids [3]. Addiction and abuse of opioids is less common in children, but physical dependence can develop in as little as 5–7 days [4]. In addition, adverse effects of opioid drugs are significant, including respiratory depression and delayed return of bowel function. There is a wide variation in surgeon prescribing patterns for postoperative pain, and the quantity of opioid medication prescribed is often excessive when compared to actual patient needs [5]. There is a growing need to find effective non-opioid alternatives to treat postoperative pain.

Gabapentin, a drug originally developed as an anti-epileptic, is now increasingly used as a perioperative analgesic in adults across a wide range of surgical subspecialties [6]. The drug is part of many surgical enhanced recovery protocols (ERPs) as an opioid-sparing analgesic [7, 8]. In practice, the current applications of gabapentin as an analgesic are broad and highly variable, with some using a single preoperative dose and others following a prolonged postoperative course. The available literature examining the effectiveness of gabapentin is limited, especially in children. The drug has

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been most studied in the setting of spinal surgery [9, 10]. Although results have been mixed, a recent meta-analysis in adult spinal surgery showed that gabapentin was effective for decreasing pain scores, decreasing opioid use, and demonstrated a favorable adverse-effect profile [11].

The use of gabapentin as an analgesic in abdominal surgery is more nascent. A limited number of studies have examined the effects of gabapentin for elective abdominal procedures with mixed but promising results [12–14]. Given success in adult patients, perioperative gabapentin has been adapted to pediatric surgery. At our own institution, gabapentin is used both as a formal part of the colorectal ERP [8], as well as a non-protocolized opioid-sparing analgesic adjunct after other types of abdominal surgery. However, limited data are available concerning the ideal timing and dose of the drug in children. We examined the effectiveness of gabapentin in children undergoing appendectomy using an observational study design. We hypothesized that children receiving gabapentin would have improved pain control and a lower opioid requirement postoperatively.

Methods

Patient population and matching

We reviewed all pediatric appendectomies in which gabapentin was used as an adjunct to inpatient analgesia during the year 2016 at our two-hospital healthcare system. These patients were matched to patients who did not receive gabapentin in a 1:2 fashion based on age (+/−1 year), sex, and appendicitis severity. As this was a retrospective study, the decision to use gabapentin was based solely on surgeon preference (this is currently an area of practice variation in our group). All patients in the cohort underwent laparoscopic appendectomy with both single site ($n=8$) and three-port variations included. All port sites were infiltrated with local anesthetic (0.25% bupivacaine). The amount of local anesthetic is not standardized. As part of our institutional protocol, surgeons graded appendicitis severity prospectively at the time of operation based on the degree of peritoneal contamination as follows: 1—simple appendicitis, no perforation; 2A—complicated appendicitis with gangrenous or adherent appendix; 2B—complicated appendicitis with perforation and contained abscess, 2C—complicated appendicitis with perforation and diffuse contamination. Similar appendicitis grading systems have been previously published [15]. After matching, 2A, 2B, and 2C were collapsed into a single "complicated" group for outcome analysis. Although the postoperative pain regimen was not strictly standardized, our typical order set includes acetaminophen weight-based dosing on as-needed (prn) basis as first-line pain control in addition to scheduled ketorolac in most patients except those for whom bleeding risk or renal injury is a significant concern. Opioids are ordered for breakthrough pain (typically morphine immediately postoperatively, changing to hydrocodone when patients are tolerating diet) on an as-needed basis. Hydrocodone doses administered while in the hospital were included in the total postoperative opioid dose and the conversion factor used was 3 mg oral hydrocodone to 1 mg intravenous morphine [16]. Gabapentin timing and dosage was determined by surgeon preference in this retrospective study, however it was used only postoperatively and the timing was every 8 h with variable dosing as described in our results.

Data collection and statistical analysis

Chart review was performed and baseline patient characteristics were recorded, including demographic information, total gabapentin dose, and intraoperative opioid administration. Primary outcome measures included time in hours to pain score ≤ 3 [using the 0–10 visual analog scale (VAS)] beginning at the charted operating room end time and total postoperative opioid dose (converted to morphine equivalents and standardized to patient weight). VAS pain score was documented by nurses as part of the routine vital signs measurement. Generally, this was done hourly in the PACU and then every 4 hours once on the ward. Because pain scores were not protocolized in this retrospective study, we recorded the timepoint of the second score ≤ 3. Secondary outcomes were length of stay, revisits to the emergency department and readmissions to the hospital after discharge. Outcomes were compared between gabapentin receivers and non-receivers using the independent samples Mann–Whitney U test for continuous variables and chi-square or Fisher's exact test as appropriate for categorical variables. All analyses were performed using IBM SPSS 24 (Chicago, IL). This study was approved by the Children's Healthcare of Atlanta institutional review board #IRB00077519.

Results

Cohort characteristics

A total of 29 appendectomy patients who received gabapentin were identified. These patients were matched to 58 gabapentin non-receivers (total $n=87$). The majority of patients were male (72, 82.8%) and the median age was 11 years. Complicated appendicitis was diagnosed in 45 (51.7%) patients. There was no statistical difference between groups with respect to age, sex, appendicitis severity, or race (Table 1). Children in the gabapentin group received a lower total dose of intraoperative opioids (0.142 vs. 0.246 mg/kg morphine equivalents (ME), $p<0.01$), and a higher

Table 1 Characteristics of matched gabapentin receiver and non-receiver groups in a pediatric cohort undergoing appendectomy

Variable	Gabapentin ($n=29$)	No gabapentin ($n=58$)	P value
Age (mean years)[†]	10.34 (SD ± 3.66)	10.29 (SD ± 3.56)	0.950
Sex (male)[†]	24 (82.8)	48 (82.8)	1.000
Appendicitis severity[†§]			
1	14 (48.3)	28 (48.3)	1.000
2A	6 (20.7)	12 (20.7)	
2B	5 (17.2)	10 (17.2)	
2C	8 (13.8)	4 (13.8)	
Race			
Caucasian	14 (48.3)	36 (62.1)	0.525
African American	10 (34.5)	11 (19.0)	
Other	5 (17.2)	11 (19.0)	
Intraoperative opioid dose (ME/kg)	0.142 (SD ± 0.059)	0.216 (SD ± 0.109)	0.001*
Intraoperative ketorolac[a] *n* (%)	21 (72.4)	40 (69.0)	0.740
Postoperative ketorolac[a] *n* (%)	25 (86.2)	38 (65.5)	0.042*

[a]Number and percentage of patients who received any ketorolac. Dosing was 0.5 mg/kg or 30 mg maximum (scheduled every 6 h postoperatively)

[†]Denotes variables on which patient matching was based, * $p<0.05$

[§]Severity scoring system: 1 = simple acute appendicitis, 2A = gangrenous or adherent appendix, 2B = perforation with contained abscess, 2C = perforation with diffuse contamination

percentage of children in the gabapentin group received postoperative ketorolac (86.2 vs. 65.5%, $p<0.001$). No patients received gabapentin pre-operatively. For those receiving postoperative gabapentin, the median dose was 10.1 mg/kg/day (oral, divided every 8 h), with a range of 4.4–30.4 mg/kg/day.

Outcome comparison

Gabapentin receivers and non-receivers had similar mean lengths of time from operation to pain scores ≤ 3 (12.21 vs. 17.01 h, $p=0.20$), and this held true when stratified by appendicitis severity (Fig. 1). The gabapentin group received significantly less postoperative opioids (0.034 mg/kg ME vs. 0.106 mg/kg ME, $p<0.01$). When stratified by appendicitis severity, gabapentin receivers required less postoperative opioids in both simple (0.010 vs. 0.055 mg/kg ME, $p=0.01$) and complicated (0.057 vs. 0.153 mg/kg ME, $p=0.03$) appendicitis groups (Fig. 2). When stratified by ketorolac, those who received ketorolac plus gabapentin had lower opioid requirements than those who received ketorolac only (0.016 vs. 0.036 mg/kg ME, $p=0.002$). Length of stay was similar between the gabapentin and no gabapentin groups (2.24 vs. 2.86 days, $p=0.16$). Overall rates of revisit to the emergency department did not differ between gabapentin receivers and non-receivers (13.8 vs. 10.3%, $p=0.73$), including revisits secondary to surgical pain (3.4 vs. 3.4%, $p=1.00$). Readmission rate within 30 days was also similar between the groups (6.9 vs. 1.7%, $p=0.26$). No adverse events related to gabapentin were reported with the exception of two cases of emesis shortly after administration which may not have been drug related.

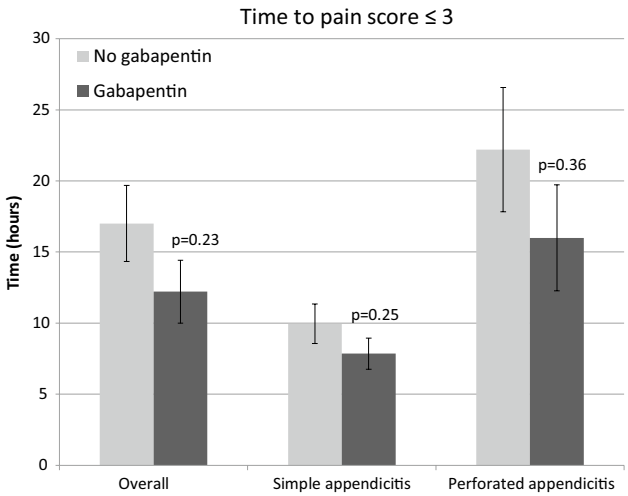

Fig. 1 Hours from operation completion to pain score less than or equal to 3 for gabapentin vs. no gabapentin groups in children status post-appendectomy

Discussion

In light of the current opioid epidemic in the US, there is a keen focus on identifying non-opioid alternatives for analgesia. Although drugs such as gabapentin are being widely used for postoperative pain in many institutions, there is a

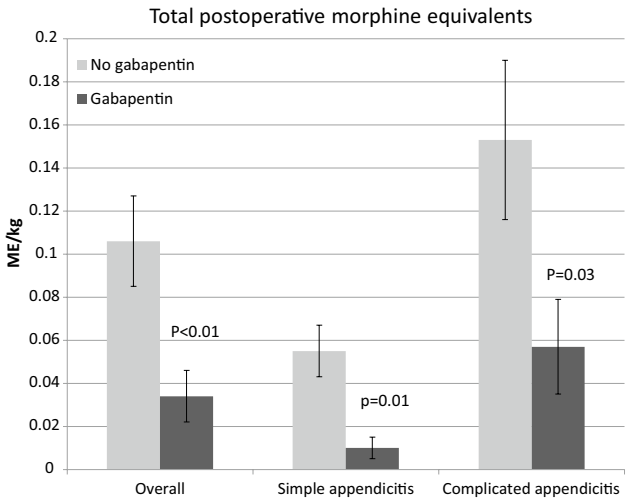

Fig. 2 Total postoperative opioid dose in morphine equivalents per kg body weight in children status post-appendectomy

paucity of literature examining their clinical effectiveness in children. In addition, much of the adult literature on the subject comes from elective colorectal surgery, while few studies have investigated gabapentin in the acute care surgery setting [7, 14, 17, 18]. In this retrospective study, we demonstrate that postoperative gabapentin is an effective analgesic adjunct in children undergoing appendectomy. Although pain scores were not significantly improved in the gabapentin group, the trend was toward shorter time periods from operation to controlled pain in that group. The use of postoperative gabapentin significantly decreased opioid use and did not result in additional returns to the system for pain or other reasons. This study is pragmatic in nature with limited control of other pain medications, but provides the first evidence that gabapentin may be useful in the treatment of postoperative pain for pediatric appendicitis.

Gabapentin has been studied as a perioperative analgesic in adults for many years, with special interest in orthopedic procedures such as hip and knee arthroplasty, and spinal procedures. The results of individual studies have been mixed, with negative studies often having limited sample sizes [19, 20]. However, a recent systematic review and meta-analysis by Doleman et al. compiled the results of 133 trials of perioperative gabapentin and demonstrated consistent reduction of opioid consumption and pain scores in the first 24 h [21]. These associations were demonstrated across a wide range of surgical specialties including orthopedic, neurosurgical, gynecologic and general abdominal procedures.

In children, there are few studies of perioperative gabapentin utilization and most are limited to spinal procedures. Mayell et al. randomized 35 children undergoing scoliosis surgery to gabapentin or placebo as a single preoperative dose and found no difference in postoperative opioid consumption [9]. Rusy et al. studied 59 children undergoing spinal fusion, randomized them to pre- and postoperative gabapentin vs. placebo, and found significant reduction in opioid consumption and postoperative pain scores in the gabapentin group [10]. Zhu et al. reviewed these two papers as part of a systematic review of nonopioid analgesics in children. They concluded that there was not enough evidence to either support or discourage the use of perioperative gabapentin in children, but that evidence does support the efficacy of other nonopioid classes such as acetaminophen and NSAIDS, among others. An early discharge protocol using a gabapentin load pre-operatively and post-operatively at 5 mg/kg/dose TID was used as part of a "fast track" protocol for pediatric spinal fusion patients with adolescent idiopathic scoliosis. This resulted in decreased LOS of $>40\%$ for the protocolized patients compared to historical controls [22]. A non-randomized study of pediatric spinal fusion patients using historical controls found that gabapentin alone, as well as gabapentin plus clonidine was effective in reducing opioid use, improving pain scores and was associated with earlier ambulation [23].

In pediatric general surgery, a non-randomized study of children undergoing surgery for inflammatory bowel disease was managed with an ERP using a loading dose of gabapentin at 15 mg/kg, and then 10 mg/kg/dose every 8 h for post-operative pain control. This strategy dropped the post-operative narcotic usage dramatically with early discharge from the hospital, compared with a historical control group managed with traditional narcotics for pain [24]. The study presented here is the first to our knowledge to evaluate gabapentin in the setting of pediatric appendectomy. Although we did not find a statistically significant reduction in pain scores, this may represent a type II error as a result of small sample size. Additionally, no preoperative gabapentin was given in our study which may have led to reduced effectiveness, in addition to inconsistent gabapentin dosing. The appropriate timing and dose of gabapentin for perioperative pain relief in children remains unclear, although according to the current small body of literature, analgesic and opioid-sparing effects appear to be most marked in patients receiving both pre- and postoperative gabapentin. The safe dosing range of gabapentin is quite wide (5–50 mg/kg/day) with much of this information being taken from the epilepsy literature. Notably, younger children (<5 years) appear to have increased clearance and may require higher doses [25]. Adverse events are few and primarily involve vomiting and drowsiness.

Limitations of this study include a non-randomized retrospective design. Although patients were not randomized, they were matched to non-receivers using several factors, the most important of which was graded appendicitis severity. Despite this, unmeasured bias may be present in the selection of patients to receive gabapentin, as well as in

post-operative management including length of stay. Also due to the retrospective study design, the overall pain control regimen was not standardized, and we found that a larger proportion of patients in the gabapentin group also received ketorolac postoperatively. This limits the comparability of our groups and suggests that the opioid-sparing observed in this group could be related to ketorolac instead. However, based on our stratified analysis, the addition of gabapentin remained associated with a significant decrease in total opioid use. The number of patients in this cohort is relatively small, owing to the fact that gabapentin analgesia for postoperative appendectomy patients remains nascent and is not yet widespread at our institution. Additionally, due to our study design, no placebo control was used. Therefore, opioid sparing associated with gabapentin may be related to placebo effect, although the body of previous literature suggests that gabapentin has superior performance to placebo in other trials [14, 21, 26]. Lastly, gabapentin dosing was not standardized and did vary substantially across study subjects in this cohort. Our results and others suggest that a postoperative dose of 10–15 mg/kg/day divided every 8 h is effective, but also that higher doses up to 30 mg/kg/day can be used with minimal adverse effects [24].

In conclusion, reducing narcotic use while compassionately treating post-surgical pain is a challenge. Non-opioid analgesics such as gabapentin may be used in combination with other analgesics to offer improved pain relief without the risks of dependence, respiratory depression and decreased gut motility. Although perioperative gabapentin has been studied extensively in adults, there is a dearth of research in pediatric patients. These results suggest that a postoperative regimen including gabapentin along with standard acetaminophen and ketorolac is effective in reducing opioid needs in pediatric appendectomy patients. Prospective, placebo-controlled trials are needed to further define the role of gabapentin in pediatric abdominal surgery.

Funding This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Compliance with ethical standards

Conflict of interest The authors have no conflicts of interest to declare. Institutional Review Board approval was obtained prior to chart review and all protected health information was kept strictly confidential. Informed consent was waived given the retrospective nature of the study.

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