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Safety of perioperative ketorolac administration in pediatric appendectomy

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ABSTRACT

Background: Recent studies in adults undergoing gastrointestinal surgeries show an increased rate of complications with the use of ketorolac. This calls into question the safety of ketorolac in certain procedures. We sought to evaluate the impact of perioperative ketorolac administration on outcomes in pediatric appendectomy.

Methods: The Pediatric Health Information System database was queried for patients aged 5-17 y with a primary diagnosis of appendicitis and a primary procedure of appendectomy during the period 2010-2014. Patients with procedures suggesting incidental appendectomy, those records with data quality issues, deaths, and extracorporeal membrane oxygenation were excluded. Variables recorded included age, sex, race, ethnicity, discharge year, complex chronic conditions, geographic region, intensive care unit admission, mechanical ventilation, and whether appendicitis was coded as complicated. The exposure variable was ketorolac administration on the day of or day after operation. The primary outcomes of interest were any surgical complications during the initial encounter, postoperative length of stay (LOS), total cost for the initial visit, any readmission to ambulatory, observation, or inpatient status within 30 d, and readmission with a diagnosis of peritoneal abscess or other postoperative infection or with transabdominal drainage performed.

Results: A total of 78,926 patients were included in the analysis cohort. Mean age was 11.4 y (standard deviation 3.3 y), the majority were males (61%), White (70%), and non-Hispanic (65%). Few had a complex chronic condition (3%) or required mechanical ventilation (2%) or an intensive care unit admission (1%). Patients with complicated appendicitis comprised 28% of the cohort. Most (73%) received ketorolac on postoperative day 0-1; those with complicated appendicitis were more likely to receive ketorolac. In all, 2.6% of the cohort had a surgical complication during the index visit, 4.3% were readmitted within 30 d, and 2% had a postoperative infection or transabdominal drainage (1% in the uncomplicated group and 5% in the complicated group). Median postoperative LOS was 1 d and mean cost was \$9811 ± \$9509. On bivariate analysis, ketorolac administration was associated with a decrease in same-visit surgical complications ($P = 0.004$) and cost (\$459 decrease, $P < 0.001$) but was not associated with readmission, postoperative LOS, or postoperative infection. On

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multivariate analysis, ketorolac administration was associated with a significant decrease in any complication (adjusted odds ratio 0.89, 95% confidence interval 0.80-0.99) and cost (analysis of variance $P < 0.001$) but was not associated with readmission, postoperative LOS, or postoperative infection.

Conclusions: Based on a large, contemporary data set from children's hospitals, ketorolac administration in the immediate postoperative period after appendectomy for appendicitis is common and was not associated with an increase in postoperative LOS, postoperative infection, or any-cause 30-d readmission. Ketorolac was, however, independently associated with a lower overall rate of postoperative complications and cost in this population.

Introduction

Acute appendicitis is the most common gastrointestinal surgical urgency in the pediatric population.[1] Several recent publications have supported same day discharge as safe and appropriate after laparoscopic appendectomy for uncomplicated appendicitis.[2,3] One of the barriers to same day discharge is postoperative pain control.[3,4] With increasing scrutiny of the use of narcotic pain control, there is a greater need for alternatives.[5] Ketorolac is a well-known nonsteroidal anti-inflammatory drug and has been FDA approved for the management of acute pain since 1989.[6] The bleeding risks of ketorolac and NSAIDS have been well studied.[7-9] Ketorolac has been theorized to impair wound healing and scar tissue formation through its anti-inflammatory mechanisms, which has been demonstrated in several animal studies.[10,11] In addition, a recent study in adults undergoing gastrointestinal surgeries by M. Kotagal *et al.* showed an increased rate of complications ranging from increased emergency department visits, increased readmission, and increased risk of reintervention, calling into question the safety of ketorolac in certain procedures.[12]

We aimed to reproduce these findings among pediatric patients undergoing appendectomy. We hypothesized that ketorolac would be an independent predictor of increased complications such as abscess formation, readmission, and reoperation.

Methods

We conducted a retrospective cohort study of Pediatric Health Information System (PHIS) database, a comparative pediatric database administered by the Children's Hospital Association (Overland Park, KS) that collects clinical and resource utilization data in inpatient, ambulatory, and emergency department settings at over 45 US children's hospitals. We included encounters for subjects aged 5-17 y who were discharged between 2010 and 2014 with a primary diagnosis of appendicitis (International Classification of Diseases, Ninth Revision [ICD-9] codes 540, 540.0, 540.1, 540.9) who had an appendectomy coded (ICD-9 procedure codes 47.0, 47.01, 47.09). We excluded incidental appendectomy (47.11 and 47.19) as well as deaths, extracorporeal membrane oxygenation (ECMO), and records with data quality issue because of hospital day and operative day being mismatched and therefore creating inaccurate perioperative timeline for ketorolac exposure. Deaths and ECMO were excluded to minimize confounding factors in the clinical decision to prescribe ketorolac. We assumed that both these outcomes were because of severity of disease and comorbidities rather than ketorolac administration. Variables recorded included age, sex, race, ethnicity, discharge year, complex chronic conditions (CCC), geographic region, intensive care unit (ICU) admission, mechanical ventilation, and whether appendicitis was coded as complicated. The primary predictor was ketorolac administration on postoperative day 0 or day 1.

The primary outcome of interest was readmission with postoperative infection within 30 d. Secondary outcomes were surgical complications during the initial encounter, postoperative length of stay (LOS), total cost for the initial visit, and any readmission to ambulatory, observation, or inpatient status within 30 d.

"Any surgical complication" was determined by the presence of a PHIS-generated surgical complication flag for that visit, which was triggered by the presence of one of a number of diagnosis codes chosen by PHIS. These included ICD-9 codes 99x (complications of surgical and medical care, necrotizing enterocolitis, including device, transplant, and transfusion-related complications), as well as complications specific to certain procedures, respiratory failure after trauma and surgery (518.5x), obstetric complications, and postprocedural fever (780.62). The total adjusted costs were based on the reported charges, adjusted for the Ratio of Cost to Charges submitted by each hospital on their respective Medicare cost reports, then adjusted by the Centers for Medicare and Medicaid Services wage/price index for the hospital's location (13). The postoperative infection on readmission was determined when a peritoneal abscess (ICD-9 code of 567.22), generic postoperative infection (ICD-9 diagnosis code 998.5 or 998.59), or percutaneous abdominal drainage (ICD-9 procedure code 54.91) were coded.

Descriptive statistics and bivariate comparisons used t-test, Fisher exact, and Pearson Chi-squared tests where appropriate. Multivariate analysis of binary outcomes used a binary logistic regression model and multivariate analysis of continuous outcomes used a general linear model. Statistics performed using Minitab version 17.3.1. Adjusted odds ratios (aOR) were calculated with corresponding 95% confidence intervals (CI).

Results

A total of 79,509 encounters met inclusion criteria. A total of 583 (0.7%) were excluded including 455 for incidental