Black Box Warning: Is Ketorolac Safe for Use After Cardiac Surgery?

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Objective: **In 2005, after the identification of cardiovascular safety concerns with the use of nonsteroidal anti-inflammatory drugs (NSAIDs), the FDA issued a black box warning recommending against the use of NSAIDs following cardiac surgery. The goal of this study was to assess the postoperative safety of ketorolac, an intravenously administered NSAID, after cardiac surgery.**

Design: **Retrospective observational study.**

Setting: **Single center, regional hospital.**

Participants: **A total of 1,309 cardiac surgical patients (78.1% coronary bypass, 28.0% valve) treated between 2006 and 2012.**

Interventions: **A total of 488 of these patients received ketorolac for postoperative analgesia within 72 hours of surgery.**

Measurement and Main Results: **Ketorolac-treated patients were younger, had better preoperative renal function, and underwent less complex operations compared with non-ketorolac patients. Ketorolac was administered, on average, 8.7 hours after surgery (mean doses: 3.1). Postoperative outcomes for ketorolac-treated patients were similar to those expected using Society of Thoracic Surgery database risk-adjusted outcomes. In unadjusted analysis, patients who received ketorolac had similar or better postoperative outcomes compared with patients who did not receive ketorolac, including gastrointestinal bleeding (1.2% *v* 1.3%; $p = 1.0$), renal failure requiring dialysis (0.4% *v* 3.0%; $p = 0.001$), perioperative myocardial infarction (1.0% *v* 0.6%; $p = 0.51$), stroke or transient ischemic attack (1.0% *v* 1.7%; $p = 0.47$), and death (0.4% *v* 5.8%; $p < 0.0001$). With adjustment in a multivariate model, treatment with ketorolac was not a predictor for adverse outcome in this cohort (odds ratio: 0.72; $p = 0.23$).**

Conclusions: **Ketorolac appears to be well-tolerated for use when administered selectively after cardiac surgery. Although a black box warning exists, the data highlights the need for further research regarding its perioperative administration.**

KEY WORDS: ***analgesia, postoperative, cardiac surgery, safety, ketorolac, NSAIDs***

PAIN MANAGEMENT AFTER SURGERY is critical to maintaining the physical and psychological well-being of a patient. A common problem, poorly controlled pain after surgery, increases heart rate, systemic vascular resistance, and circulating catecholamines, placing patients at risk of myocardial ischemia, stroke, bleeding, and other complications.[1] Postoperative analgesia after cardiac surgery most commonly involves the use of intravenous and oral opioids. Narcotic medications provide excellent analgesia, but undesirable side effects constitute major limitations, such as respiratory depression, sedation, and nausea. To limit these adverse effects without sacrificing adequate pain management, nonsteroidal anti-inflammatory drugs (NSAIDs), such as ketorolac, increasingly are being applied in the postoperative setting.[2] Although NSAIDs have potential side effects (bleeding, gastrointestinal ulceration, and renal dysfunction), several studies have noted low complication rates associated with their short-term use after coronary artery bypass graft surgery (CABG) when administered to appropriately selected patients.[3–5]

Despite the analgesic properties and safety profile of ketorolac,[6–9] the United States Food and Drug Administration (FDA) recommended in 2005 that the labeling for ketorolac include a contraindication "for use in patients in the immediate postoperative setting after CABG surgery".[10] This FDA black box warning was issued as a result of two landmark studies that evaluated the safety of the cyclooxygenase-2 (COX-2) inhibitors parecoxib and valdecoxib after cardiac surgery. Investigators noted that the perioperative administration of these agents significantly increased the risk of adverse cardiovascular events after CABG, including myocardial infarction (MI), stroke, cardiac arrest, and pulmonary embolism.[11,12] As a consequence, valdecoxib was taken off the market, and the black box warning was issued for all NSAIDs after cardiac surgery.

In contrast to COX-2 inhibitors, ketorolac is a traditional NSAID without COX-2 selectivity (COX-1/COX-2 ratio 0.36).[13] Although ketorolac has been shown to be an effective analgesic,[6–9] to the authors' knowledge, little data are available evaluating the safety profile of ketorolac administration after cardiac surgery. In spite of the warnings regarding the theoretic risks, ketorolac has been administered selectively to cardiac surgery patients for the past 6 years at this hospital as a method of improving postoperative pain control and reducing opioid use. The aim of the current study was to review the safety of ketorolac when administered to select patients recovering from CABG and other cardiac surgery.

METHODS

The authors performed a retrospective observational study, drawing this cohort (N = 1,309) from the hospital Society of Thoracic Surgery (STS) database that includes preoperative, intraoperative, and postoperative clinical information regarding all patients who have undergone cardiac surgery procedures at Boca Raton Regional Hospital since 2006. In addition, the hospital clinical pharmacy database was used to identify all cardiac surgery patients who received ketorolac (ketorolac tromethamine, also known as Toradol, West-Ward Pharmaceuticals, Eatontown, New Jersey) in the postoperative period (n = 488). This pharmacy database is an audited and verified source for all inpatient

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medication administration and contains a record of all medications, including dosing amounts and frequencies. Additional data were collected as part of a retrospective chart review to confirm demographic and clinical information. The current study was approved by the institutional review board of the Boca Raton Regional Hospital, Boca Raton, Florida. Because of the retrospective nature of the study, the need for patient informed consent was waived by the institutional review board.

Patients who underwent cardiac surgical procedures, including on-pump or off-pump CABG, valve surgery, atrial fibrillation (Maze) procedures, and pericardial window surgery were included. Patients were included from September 2006 (program initiation date) to July 2012. Patients were categorized based on whether they did or did not receive ketorolac after surgery. Ketorolac treatment was not a randomized intervention. In general, patients were selected for ketorolac administration by the operating surgeon if they reported moderate or severe pain after surgery despite opioid analgesia, to facilitate early extubation and ambulation. Ketorolac was not administered to patients who had pain that was well-controlled with opioid medications or to those with obvious contraindications to NSAID administration (NSAID allergy, history of gastrointestinal bleeding, or renal dysfunction with creatinine >2.0 mg/dL). Patients who were expected to have longer postoperative ventilation times (eg, after complicated redo or combined operations) typically did not receive ketorolac postoperatively, because patient comfort usually could be achieved with opioid and anesthetic agents.

Patient demographic characteristics and comorbidities were determined from the hospital STS database and through retrospective chart review. The following characteristics were identified: age, gender, body mass index (BMI), preoperative diagnoses (diabetes mellitus, hypertension, hyperlipidemia, and previous MI), ejection fraction, date and type of operation, and length of hospital stay. Laboratory values also were collected preoperatively and postoperatively, including hematocrit and serum creatinine levels.

Patient exposure to ketorolac was identified from the hospital clinical pharmacy database and confirmed through chart review. Ketorolac typically was administered within 24-72 hours after cardiac surgery, and dosed at 6-hour intervals (15-30 mg per dose). Data regarding the administration of ketorolac were collected, including the timing of the first dose (relative to the arrival time in the intensive care unit after surgery), the amount of the first dose, the number of doses given after surgery, and the total amount administered in the postoperative period.

Cardiovascular safety in this study was assessed through the documentation of major adverse cardiac events, including death, stroke, or transient ischemic attack (TIA), and MI. Standard STS outcome definitions were applied. Stroke was defined as a new permanent neurologic deficit lasting more than 24 hours confirmed by computed tomography imaging, whereas TIA was defined as a new transient focal neurologic deficit with return of function within 24 hours. Myocardial infarction was defined as the appearance of a new Q wave in two or more contiguous leads and laboratory evidence of new myocardial necrosis (creatine kinase-MB fraction greater than 10 times the upper limit of normal), confirmed with either angiographic evidence of new graft or native-vessel thrombosis, or new wall-motion abnormality. Bleeding risk was evaluated by documenting gastrointestinal bleeding events and the need for chest reopening for bleeding. Gastrointestinal bleeding was defined as an upper or lower gastrointestinal bleeding event necessitating endoscopy and blood transfusion. Renal safety was determined by noting peak postoperative creatinine levels, as well as the need for dialysis for postoperative acute renal failure. Postoperative renal insufficiency was defined as an increase of serum creatinine by more than 1.0 mg/dL from baseline[4] or the need for new dialysis postoperatively. A composite outcome was developed that incorporated the adverse perioperative events of stroke, TIA, MI, postoperative renal insufficiency, gastrointestinal bleeding, or death. Risk-stratified (expected) outcomes for the patients who received ketorolac were calculated through the application of the STS database based on patient demographic and operative characteristics.

Standard descriptive statistical analyses were used. Continuous data are presented as a mean $\pm$ standard deviation, and categoric data are presented as proportions. Comparisons between patients who did ($n = 488$) or did not ($n = 821$) receive ketorolac were performed using unpaired two-sided Student's t tests or a Fisher's exact test, as appropriate. Subgroup analysis was performed focusing only on isolated primary (non-redo) CABG patients ($n = 775$) who did ($n = 328$) or did not receive ketorolac ($n = 447$), and also focusing only on male patients under the age of 70 who underwent isolated primary CABG surgery ($n = 287$) who did ($n = 167$) or did not ($n = 120$) receive ketorolac.

Multivariate logistic regression analysis was used to identify independent predictors of the composite adverse outcome. All factors that differed between the two groups (Table 1) were considered in the model. Factors tested in the model included the use of ketorolac, age, gender, BMI, diabetes, hypertension, hyperlipidemia, previous MI, ejection fraction, preoperative hematocrit, preoperative creatinine, redo surgery, off-pump surgery, cardiopulmonary bypass time, and the need for valve intervention. Stepwise forward selection and backward elimination techniques were used, with $p = 0.20$ for entry and removal criteria, except for the use of ketorolac, which was forced into the model. Odds ratios (OR) are reported with 95% confidence intervals (CI), and regression coefficients are reported $\pm$ standard error. All reported p values are two-sided. All analyses were performed using Stata/MP version 11.2 (StataCorp, College Station, TX).

In addition to the multivariate regression model, the independent effect of ketorolac on the composite outcome was examined, for confirmatory purposes, by using propensity score-based techniques. To this end, the propensity of receiving ketorolac based on patient and procedural characteristics was calculated for each patient using a logistic regression model that included patient- and surgery-related

Table 1. Patient Characteristics

Characteristic	Ketorolac n = 488	No Ketorolac n = 821	p Value
Age, years	66.7 ± 12.1	75.0 ± 9.8	<0.0001
Male gender	341 (69.9%)	567 (69.1%)	0.80
Body mass index, kg/m^2	27.7 ± 4.7	27.5 ± 4.9	0.43
Diabetes mellitus	94 (19.3%)	195 (23.8%)	0.06
Hypertension	345 (70.8%)	668 (81.4%)	<0.0001
Hyperlipidemia	356 (73.2%)	634 (77.2%)	0.11
Previous myocardial infarction	194 (39.7%)	359 (43.7%)	0.30
Ejection fraction, %	55.3 ± 11.8	53.5 ± 12.8	0.02
Preoperative hematocrit, %	38.3 ± 5.1	36.6 ± 5.6	<0.0001
Preoperative creatinine, mg/dL	1.05 ± 0.66	1.27 ± 0.71	<0.0001
Redo cardiac surgery	12 (2.5%)	55 (6.7%)	0.001
Surgery type			
CABG	386 (79.1%)	636 (77.5%)	—
Valve	82 (16.8%)	284 (34.6%)	
Other (ascending, maze, pericardial window)	90 (18.4%)	142 (17.3%)	
Use of cardiopulmonary bypass	178 (36.5%)	504 (61.4%)	<0.0001
Off-pump CABG	258 (52.9%)	282 (34.4%)	<0.0001
Cardiopulmonary bypass time, minutes	111.7 ± 42.8	140.5 ± 65.0	<0.0001
Cross-clamp time, minutes	80.1 ± 33.9	95.2 ± 45.8	0.0004
Number of distal anastomoses	3.0 ± 1.1	2.9 ± 1.1	0.38

Abbreviation: CABG, coronary artery bypass graft.

characteristics. Patients then were ranked in order of their propensity score and categorized into sextiles of patients with equivalent propensity scores. The effect of ketorolac on the composite outcome then was examined: (1) for each sextile of patients with equivalent treatment propensity scores, (2) by using the sextile of treatment propensity as an additional independent variable, and (3) by using the propensity score itself as an additional independent variable.

RESULTS

The study cohort consisted of 1,309 patients who underwent cardiac surgery between 2006 and 2012. Table 1 describes the characteristics of patients who were (n = 488) and were not (n = 821) treated with ketorolac. Compared with patients who did not receive ketorolac, those who did receive ketorolac were significantly younger, had higher baseline hematocrit levels, and had lower baseline creatinine levels before surgery ($p < 0.0001$). During surgery, ketorolac patients less commonly underwent valve surgery or redo surgery. Although most patients in the cohort underwent CABG, ketorolac patients were more often treated with off-pump CABG. These differences in baseline and operative characteristics were incorporated into the multivariate analysis for covariate adjustment.

Of the patients undergoing cardiac surgery during the time period of the study, 37.3% (488 of 1,309) received ketorolac. The use of ketorolac peaked at 47.3% in 2008. Among the 488 treated patients, ketorolac was administered on average 8.7 ± 29.3 hours after surgery. Most patients (76.4%) received ketorolac on the day of the operation. The mean initial dose of ketorolac was 27.0 ± 6.1 mg, with 80.5% of patients receiving 30 mg as their initial dose. Patients were administered a mean of 3.1 ± 1.8 doses (maximum 17) during their hospital stay. The total amount of ketorolac administered was, on average, of 81.7 ± 52.3 mg (maximum of 420 mg).

Table 2 summarizes the clinical outcomes of the patient cohort. Patients who received ketorolac had similar or better clinical outcomes compared with patients who did not receive ketorolac. No adverse outcome occurred more often among ketorolac-treated patients.

A total of 19 ketorolac patients (3.9%) required reopening in the early postoperative period for bleeding (compared to non–ketorolac patients: 5.8%; $p = 0.15$), eight of whom (1.6%) being reopened after ketorolac administration. Gastrointestinal bleeding complications developed in 1.2% of ketorolac patients, compared with 1.3% of patients who did not receive ketorolac ($p = 1.0$). Ketorolac-treated patients received significantly fewer packed red blood cell transfusions in the perioperative period ($p < 0.0001$).

For patients treated with ketorolac, the mean postoperative increase in creatinine was 0.17 mg/dL, compared with 0.37 mg/dL for patients who did not receive ketorolac ($p < 0.0001$). Six ketorolac patients (1.2%) experienced postoperative renal insufficiency (defined as an increase of serum creatinine by more than 1.0 mg/dL from baseline). Two (0.4%) ketorolac-treated patients developed acute renal failure requiring dialysis, compared with 3.0% for patients who were not treated with ketorolac ($p = 0.001$). Five ketorolac patients (1.0%) had a perioperative MI, 3 (0.6%) had a perioperative stroke, and 2 (0.4%) had a TIA, outcomes similar to patients who did not receive ketorolac (p = nonsignificant). Two ketorolac patients (0.4%) died in the perioperative period, compared with a 5.8% death rate for patients who did not receive ketorolac ($p < 0.0001$). One ketorolac patient died from multi-organ dysfunction as a complication of severe rectal bleeding and heparin-induced thrombocytopenia 29 days after surgery. The other ketorolac patient died 4 days after surgery from metabolic acidosis and multi-organ dysfunction as a result of ischemic bowel, an evolving condition that likely contributed to the patient's severe chest and abdominal pain before and after CABG surgery.

Ketorolac patient outcomes were similar to those expected applying STS database risk stratification, including reopening (2.6% *v* 1.6%, expected *v* actual), renal failure (0.8% *v* 0.4%, expected *v* actual), stroke (0.35% *v* 0.6%, expected *v* actual), and death (0.34% *v* 0.4%, expected *v* actual).

The composite outcome, incorporating stroke, TIA, MI, postoperative renal insufficiency, gastrointestinal bleeding, and death, occurred in 4.5% of ketorolac patients and 14.1% of patients who did not receive ketorolac ($p < 0.0001$). In the subgroup focusing on isolated primary CABG patients, the composite outcome occurred in 4.0% of patients who received

Table 2. Postoperative Outcomes

Outcome	Ketorolac n = 488	No Ketorolac n = 821	p Value
Reopening for bleeding (total)	19 (3.9%)	48 (5.8%)	0.15
Reopening for bleeding after ketorolac administered	8 (1.6%)	—	—
Gastrointestinal bleeding	6 (1.2%)	11 (1.3%)	1.0
Packed red blood cells transfusion, units	0.9 ± 2.0	2.5 ± 4.1	<0.0001
Peak postoperative creatinine, mg/dL	1.20 ± 0.33	1.64 ± 0.97	<0.0001
Change in postoperative creatinine, mg/dL	0.17 ± 0.26	0.37 ± 0.64	<0.0001
Renal insufficiency (increase in creatinine >1.0 mg/dL or new dialysis)	6 (1.2%)	68 (8.3%)	<0.0001
Acute renal failure requiring new dialysis	2 (0.4%)	25 (3.0%)	0.001
Perioperative myocardial infarction	5 (1.0%)	5 (0.6%)	0.51
Stroke or transient ischemic attack	5 (1.0%)	14 (1.7%)	0.47
Perioperative death	2 (0.4%)	48 (5.8%)	<0.0001
Myocardial infarction, stroke, transient ischemic attack or death	12 (2.5%)	64 (7.8%)	<0.0001
Composite outcome*	22 (4.5%)	116 (14.1%)	<0.0001
Postoperative length of hospital stay, days	6.5 ± 4.3	10.0 ± 10.2	<0.0001

*Composite outcome included the events of stroke, transient ischemic attack, myocardial infarction, postoperative renal insufficiency, gastrointestinal bleeding, and death.

ketorolac and in 10.3% of patients who did not receive ketorolac ($p = 0.001$). For young male patients who underwent isolated CABG, the composite outcome occurred in 1.8% of patients treated with ketorolac, compared with 7.5% in patients who did not receive ketorolac ($p = 0.03$).

Using multivariate logistic regression, independent predictors for the composite outcome included higher preoperative creatinine level (OR: 2.19 per each additional 1 mg/dL increase; CI: 1.65, 2.90; $p < 0.0001$), older age (OR: 1.05 per each additional year; CI: 1.02, 1.07; $p < 0.0001$), and longer duration of cardiopulmonary bypass (OR: 1.09 per each additional 10 minutes; CI: 1.06, 1.11; $p < 0.0001$). Treatment with ketorolac was not a significant factor in the multivariate model (OR: 0.72; CI: 0.42, 1.23; $p = 0.23$). Propensity-score analysis led to similar results. In a model incorporating the sextile of treatment propensity as a variable, ketorolac was associated with a significantly lower odds ratio for the composite outcome (OR: 0.58; CI: 0.35, 0.96; $p = 0.04$). In another model that included the propensity score itself, ketorolac was associated with a trend towards a lower odds ratio for the composite outcome (OR: 0.64; CI: 0.38, 1.07; $p = 0.09$).

DISCUSSION

Postoperative pain control is important to patients and clinicians alike. In addition to limiting mobility, pain that is poorly managed after surgery can lead to impairment of the cardiovascular, respiratory, and immune systems. Insufficient postoperative pain control can increase the risk of deep vein thrombosis and pneumonia and lead to harmful psychological consequences, including insomnia and demoralization.[14] Ultimately, pain that is treated inadequately can increase the cost of medical care, with longer stays in the hospital and the intensive care unit, and a greater risk of hospital readmission.[1,14] Opioids are the most commonly used medications to control postoperative pain. However, their administration is associated with troublesome effects such as respiratory depression, sedation, urinary retention, constipation, nausea and vomiting, and pruritus. Therefore, applying adjuncts to opioids, including intravenous NSAIDs, may help limit opioid-related adverse effects.

Ketorolac is effective at reducing pain, and several studies have reported its safety and efficacy in the perioperative period.[6–9] Nevertheless, the FDA issued a black box warning in 2005 recommending against the use of ketorolac in the immediate perioperative setting after CABG surgery.[10] Despite the advisory, ketorolac has been administered to select cardiac surgery patients at this hospital for the past 6 years as a method of improving postoperative pain control and limiting opioid-related side effects. Ketorolac has been preferentially prescribed to young men, because it has been the authors' experience that pain relief is most difficult to attain early after surgery in this patient population.

In the present study, the authors performed a retrospective observational study to evaluate the safety of ketorolac when administered after cardiac surgery. Of the 1,309 patients who underwent cardiac surgery at this institution between 2006 and 2012, 488 received ketorolac within 72 hours of surgery, most of whom had undergone CABG. Compared with patients who did not receive ketorolac, those who were treated with ketorolac were a select group of younger patients, with better preoperative renal function, who less commonly underwent valve or redo-surgery and more often underwent off-pump CABG. Ketorolac was administered, on average, 8.7 hours after surgery, with patients receiving a mean of 3.1 doses. The range of ketorolac doses was based on patient discomfort and surgeon discretion. Although a few patients with chronic pain disorders received numerous doses of ketorolac for several days after surgery, most patients in this study were treated with 2-4 doses during the initial 48 hours postoperatively.

Given the lower risk profile of the ketorolac patients, it was not surprising that these patients had fewer postoperative adverse outcomes compared with patients who did not receive ketorolac. Overall, patients who received ketorolac had a low risk of complications, including reopening for bleeding, MI, stroke, need for dialysis, and death. Ketorolac-treated patients had outcomes similar to those expected based on STS database risk adjustment. In the authors' experience, when administered selectively, ketorolac appears to be safe for use after cardiac surgery.

NSAIDs block the synthesis of prostaglandins through the inhibition of COX-1 and COX-2, thus lowering the production of acute inflammatory response mediators. By decreasing the inflammatory response to surgical trauma, NSAIDs reduce peripheral nociception.[15] NSAIDs also appear to have a central analgesic mechanism, possibly through the inhibition of prostaglandin synthesis within the spinal cord.[15] In general, NSAIDs have a low side-effect profile when administered for the short-term purpose of perioperative analgesia after cardiac surgery.[2] The authors previously reported the results of a randomized trial that found that oral naproxen is effective as an adjunct for the optimization of pain control and lung recovery after CABG, without increasing the risk of postoperative complications.[3] In contrast to naproxen, intravenous ketorolac can be provided earlier in the postoperative period before the resumption of oral intake. Ketorolac provides an analgesic effect similar to that of fentanyl, but with a lower incidence of postoperative nausea and somnolence, and leads to an earlier return of bowel function.[15] With these advantages over opioids, ketorolac administration ultimately may shorten hospital length of stay.[15]

The FDA black box warning recommending against the use of ketorolac after CABG came as a result of two landmark studies that noted safety concerns associated with the perioperative administration of valdecoxib and parecoxib, two COX-2 inhibitors. When administered after cardiac surgery, these agents led to an increased incidence of cerebrovascular complications, renal dysfunction, MI, and difficulty with sternal wound healing.[11,12] In a randomized study by Ott et al, investigators noted that the combination of parecoxib and valdecoxib led to a slightly greater risk of MI (1.6% *v* 0.7%, parecoxib/valdecoxib *v* placebo, $p = 0.7$) and cerebrovascular complications (2.9% *v* 0.7%, parecoxib/valdecoxib *v* placebo, $p = 0.18$) compared with patients who received placebo.[11] Thereafter, a larger randomized trial by Nussmeier et al reported similar findings, as parecoxib and valdecoxib administration caused significantly more adverse cardiovascular events (2.0% *v* 0.5%, parecoxib/

valdecoxib *v* placebo, p = 0.03).[12] Several studies have since highlighted the cardiovascular risk associated with NSAIDs in other patient populations, which is thought to be related to an imbalance between prostacyclin and thromboxane A2 production, leading to an increased risk of thrombotic events.[16]

More recent reports, however, have illustrated the absence of a uniform class effect, with varying cardiovascular risks associated with each individual NSAID.[17,18] Interestingly, these latest studies have shown that naproxen is associated with the lowest cardiovascular risk,[17,18] in accordance with this trial evaluating its use after CABG.[3] The current study further supports the view that not all NSAIDs are dangerous when administered to patients with cardiovascular disease. These data note a relatively low incidence of MI (1.0%) and cerebrovascular complications (1.0%) among cardiac surgery patients who received ketorolac—outcome rates nearly identical to those who received placebo in the parecoxib/valdecoxib trials noted above.[11,12] Similar findings also were reported by Engoren et al, who suggested that ketorolac may improve graft patency after CABG and could lead to survival benefits.[19,20]

Cyclooxygenase-1 generates prostanoids that are involved in the maintenance of the integrity of gastrointestinal mucosa and platelet aggregation.[21] Through the inhibition of prostaglandin synthesis, NSAIDs may contribute to impaired platelet aggregation and gastric mucosa ulceration, ultimately resulting in gastrointestinal bleeding.[21] In the present study, bleeding events were similar between patients who did and did not receive ketorolac. Six ketorolac-treated patients (1.2%) developed gastrointestinal bleeding, and 8 patients (1.6%) required reopening for bleeding after ketorolac administration. In the absence of a randomized trial, firm conclusions cannot be made. However, the relatively low incidence of bleeding complications found in the present study is in agreement with previous studies that have highlighted the safety of ketorolac after adult and pediatric cardiac operations.[4,19,20,22,23]

By inhibiting COX-1 and prostaglandin synthesis, ketorolac may contribute to renal insufficiency after surgery.[24] Although concerns remain, the incidence of acute renal failure after exposure to NSAIDs is very uncommon in cardiac surgery patients without underlying kidney disease.[24,25] In this study, serum creatinine levels increased, on average, by 0.17 mg/dL after ketorolac administration, and 6 ketorolac patients (1.2%) experienced renal insufficiency, defined as an increase in serum creatinine of 1 mg/dL compared with baseline. Two ketorolac-treated patients (0.4%) developed postoperative multiorgan failure and subsequently required dialysis. The data presented herein are similar to that reported in the literature, suggesting that there is a relatively low risk of renal complications after the perioperative administration of NSAIDs after cardiac and noncardiac operations.[3,24,26]

To the authors' knowledge, this is the largest study to date to evaluate the safety of ketorolac for perioperative pain control after cardiac surgery. Post hoc power calculations showed a 100% statistical power to detect a difference in the incidence of the composite outcome between the 2 groups in the study. Notwithstanding the study findings, the results must be interpreted in the context of the following limitations. The current paper is a retrospective observational study focused on the side effect profile of ketorolac. The efficacy of ketorolac for postoperative pain control was not specifically examined in this study, because this has been well-documented previously[6–9] and was not the goal of the current analysis. Because the present study was conducted at a single center, the results may not necessarily be generalizable to other patient populations with different demographic characteristics. Finally, this was not a randomized controlled trial; therefore, selection bias remains an important limitation of the study, despite the statistical adjustments applied. At this center, patients who receive ketorolac usually are selected for fast-track recovery after cardiac surgery. In contrast, patients who do not receive postoperative ketorolac tend to be older (typically developing less postoperative pain) and to have a greater burden of co-morbid disease (Table 1). These patients often have undergone longer operations (eg, combined valve and CABG, or redo surgery) with longer postoperative ventilation times. To overcome this limitation, the authors used multivariate and propensity-score analysis and compared the actual outcomes of the ketorolac patients to expected outcomes based on STS risk adjustment. Evidence of an increased risk associated with ketorolac administration was not found in this cohort, although the authors recognize that adverse effects have been reported with nonspecific NSAIDs (including ketorolac) in other settings.[18,27,28] Regardless, the authors acknowledge that these data require corroboration and hope that this analysis stimulates further interest and research in the field, ideally in the form of a randomized controlled trial.

In conclusion, ketorolac appears to be safe for use as a postoperative analgesic when administered selectively after cardiac operations. Although additional research is needed, the data call into question the need for a black box warning recommending against the use of ketorolac for all cardiac surgery patients. This patient population showed a low incidence of bleeding, cardiovascular, and renal complications associated with its postoperative administration.

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