Clinical Science

Use of ketorolac is associated with decreased pneumonia following rib fractures

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Abstract

BACKGROUND: The effectiveness of the nonsteroidal anti-inflammatory drug ketorolac in reducing pulmonary morbidity after rib fractures remains largely unknown.

METHODS: A retrospective cohort study was conducted spanning January 2003 to June 2011 assessing pneumonia within 30 days and potential adverse effects of ketorolac among all patients with rib fractures who received ketorolac <4 days after injury compared with a random sample of those who did not.

RESULTS: Among 202 patients who received ketorolac and 417 who did not, ketorolac use was associated with decreased pneumonia (odds ratio, .14; 95% confidence interval, .04 to .46) and increased ventilator-free days (difference, 1.8 days; 95% confidence interval, 1.1 to 2.5) and intensive care unit–free days (difference, 2.1 days; 95% confidence interval, 1.3 to 3.0) within 30 days. The rates of acute kidney injury, gastrointestinal hemorrhage, and fracture nonunion were not different.

CONCLUSIONS: Early administration of ketorolac to patients with rib fractures is associated with a decreased likelihood of pneumonia, without apparent risks.

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Rib fractures are a common manifestation of blunt thoracic injury, with approximately 10% of hospitalized trauma patients sustaining radiographically apparent fractures. The mortality of such patients ranges from 3% to 13%, attributable both to associated injuries and pulmonary complications. The elderly are particularly susceptible to these complications, with about 13% to 30% developing pneumonia. Despite their prevalence, there have been few rigorous evaluations of the treatment of rib fractures. Typical measures include breathing exercises and other maneuvers to improve pulmonary hygiene and pain control using opiates and epidural analgesia. Local and regional rib blocks, transcutaneous electrical nerve stimulation, and the slow infusion of local analgesics from a subcutaneous pump have been reported but are used less commonly. Opioids cause drowsiness and decreased respiratory effort that can promote atelectasis. Epidural infusions appear to
decrease ventilator days and pneumonia rates. However, in practice, epidural catheters frequently cannot be used: >70% of patients with ≥3 rib fractures who were screened for participation in a randomized trial evaluating epidural analgesia either had contraindications to or refused epidural placement. Moreover, epidural catheter placement and maintenance are resource intensive and can cause rare but serious complications such as epidural hematomas and meningitis.

Nonsteroidal anti-inflammatory drugs are often used as an adjunct to other analgesics. They are inexpensive and usually well tolerated. Their mechanism of action involves inhibition of cyclooxygenase, thus decreasing prostaglandin synthesis and limiting activation of pain receptors at the site of injury. Ketorolac is a potent member of this class that reduces postoperative pain. Numerous studies have demonstrated decreases in opiate requirements when nonsteroidal anti-inflammatory drugs are added to post-thoracotomy analgesic regimens. Such patients also report better pain control and increased respiratory function with nonsteroidal anti-inflammatory drugs. However, injured patients may be at increased risk for known adverse effects of these medications, including hemorrhage (gastrointestinal or otherwise) and acute kidney injury, as well as hypothesized risks, such as fracture nonunion and impaired soft tissue healing. Although physicians often prescribe nonsteroidal anti-inflammatory drugs to patients with rib fractures, their effectiveness and safety have not been well studied for this particular indication.

In this study, we set out to determine whether ketorolac, when used as an adjunct for pain control in patients with rib fractures, is associated with decreased likelihood of pneumonia.

Methods

Study design

We conducted a single-center retrospective cohort study. We hypothesized that the administration of ketorolac early after injury would decrease the likelihood of developing pneumonia during the first 30 days of hospitalization. The University of California, Davis, institutional review board approved of our planned study before we commenced.

Study setting and population

We identified hospitalized trauma patients using our center’s trauma registry. We included patients hospitalized from January 1, 2003, to June 30, 2011, who had International Classification of Diseases, 9th Edition, Clinical Modification discharge diagnoses of rib fractures (807.0x, 807.1x, and 807.2 to 807.4). (Because discharge diagnoses are coded primarily on the basis of physician documentation, these diagnoses do not necessarily require radiographic confirmation.) We excluded patients <18 years of age and those who died <48 hours after arrival. We electronically linked the trauma registry records to inpatient pharmacy records to determine which patients received ketorolac. On an a priori basis, we defined ketorolac exposure as requiring both (1) the administration of the first dose of ketorolac <96 hours after presentation and (2) continuation of ketorolac for ≥24 hours. We defined control status by the same criteria as ketorolac exposure (adults with diagnoses of rib fractures who survived ≥48 hours), except that they did not receive any ketorolac during their hospitalization. (Thus, implicitly, we excluded from the analysis patients who otherwise met control criteria but first received ketorolac ≥96 hours after presentation or received ketorolac for <24 hours.) We identified 202 ketorolac-exposed patients, and we planned to compare them with a random sample of control patients in an approximately 2:1 control/ketorolac ratio.

Data collection

Two abstractors (Y.Y., J.B.Y.) (who were not blinded to the study hypothesis) recorded additional data from electronic and paper medical records using a pretested electronic abstraction instrument through Research Electronic Data Capture software. We verified information from the trauma registry (demographic data, mechanism of injury, Injury Severity Score, and Abbreviated Injury Scale scores) and recorded admission creatinine, comorbidities (congestive heart failure, chronic obstructive pulmonary disease, and chronic kidney disease), history of smoking, presence of pleuritic chest pain, number of radiographically apparent rib fractures, use of epidural analgesia, and administration of any nonsteroidal anti-inflammatory drugs other than ketorolac. For patients in the ketorolac group, we recorded the time of initial dose, duration of continuous use, starting dose, total cumulative dose, and route of administration.

Outcomes

We defined the primary outcome as an attending physician’s diagnosis of pneumonia on or after hospital day 2 (to restrict cases to hospital-acquired pneumonia) but <30 days after presentation. For each case of pneumonia, we recorded the presence of a focal infiltrate on chest radiography, fever (≥38.5 °C) or hypothermia (<35 °C), leukocytosis (>10,000 white blood cells/mm³) or leukopenia (<3,000 cells/mm³), purulent sputum, cultures of a pathologic organism, and duration of antibiotics.

To conduct a sensitivity analysis, we also assessed 3 alternative definitions of pneumonia: (1) attending physician’s diagnosis on or after hospital day 4 (rather than 2) but <30 days after presentation (to ensure that the cases were hospital acquired); (2) attending physician’s diagnosis that also met American Thoracic Society criteria for pneumonia (to minimize subjectivity in the diagnosis): focal infiltrate on chest radiography plus 2 of 3 clinical features (fever >38 °C,
leukocytosis or leukopenia, and purulent secretions; and (3) diagnosis as determined by our hospital’s quality improvement committee. The latter assessment, though based in part on physician diagnoses, was completely independent of this study and blinded from the primary outcome as determined by our study team.

We assessed use of epidural analgesia and nonsteroidal anti-inflammatory drugs besides ketorolac as possible cointerventions. We determined 30-day ventilator-free days, 30-day intensive care unit–free days, and 90-day mortality as secondary outcomes.

We recorded the occurrence of acute kidney injury (as defined by the Acute Kidney Injury Network: an absolute increase in serum creatinine of $\geq 0.3 \text{mg/dL} \ (\geq 26.4 \mu \text{mol/L}$) or an increase in serum creatinine $\geq 50\%$ from baseline), gastrointestinal bleeding, myocardial infarction, and stroke <30 days after presentation as potential complications. We also assessed whether nonunion of a long bone fracture occurred within 180 days of presentation.

Analysis

Assuming that the risk for pneumonia without ketorolac was 10%, we determined that we would be able to detect a reduction in the absolute risk for pneumonia with ketorolac to $\leq 3.8\%$ with 80% power at the .05 $\alpha$ level if we evaluated the 202 ketorolac subjects in a 2:1 control/ketorolac ratio.

We compared baseline characteristics between the groups using $t$ and chi-square tests. We evaluated the primary outcome using multivariable logistic regression, adjusting for covariates we selected on an a priori basis: the number of rib fractures, Abbreviated Injury Scale chest and extremity scores, and presence of chronic obstructive pulmonary disease. We included both the number of rib fractures and Abbreviated Injury Scale chest score because each characterizes different aspects of chest injuries, chronic obstructive pulmonary disease as an important predictor of pneumonia risk, and Abbreviated Injury Scale extremity score because the orthopedic surgeons at our center tend to discourage the use of nonsteroidal anti-inflammatory drugs in patients with long bone fractures, which may contribute to pneumonia risk as a result of immobility.

We conducted a sensitivity analysis of the primary outcome by examining the association of ketorolac administration with the 3 aforementioned alternative definitions of pneumonia. We characterized the interrater reliability of our assessment of the primary outcome with the quality improvement committee’s assessment using the $\kappa$ statistic.

We used multivariable Poisson regression (and linear regression, for greater interpretability) to determine the association of ketorolac with 30-day ventilator-free days and 30-day intensive care unit–free days, adjusting for the same covariates as the model involving the primary outcome. We compared complications between the 2 groups (acute kidney injury, myocardial infarction, stroke, gastrointestinal hemorrhage, fracture nonunion, and death) using logistic regression. We inferred the absence of complications if the last follow-up time was subsequent to the time frame of interest and there was no mention of a complication in the medical record; if follow-up ceased before the time frame closed, we assumed that no additional outcomes occurred.

We conducted all analyses using Stata version 10.1 (StataCorp LP, College Station, TX). We used 2-tailed tests with an $\alpha$ level of .05.

Results

We abstracted records for 417 control hospitalizations, which we compared with the 202 constituting the ketorolac group. All patients had either radiographic evidence of rib fractures or pleuritic pain on physical exam. The average age of the combined cohort was 48 ± 18 years, and the average Injury Severity Score was 12 ± 9 (Table 1). Motor vehicle collisions accounted for >50% of the hospitalizations in both groups. Abbreviated Injury Scale head and abdominal scores were greater in the control group. Abbreviated Injury Scale chest scores, presence of radiographic rib fractures, total number of ribs fractured, comorbid chronic obstructive pulmonary disease, and current smoking all were significantly greater in the ketorolac group. The control group included more patients with chronic kidney disease and had a slightly higher initial creatinine level.

In the ketorolac group, the mean time to the first dose of ketorolac was 1.6 ± 0.9 days, with an average continuous duration of 2.2 ± 1.7 days. The mean cumulative dose was 132 ± 70 mg, all administered via the intravenous route. Eighty-one percent of patients received an initial dose of 15 mg, with the remainder receiving 30 mg. Clinicians administered other nonsteroidal anti-inflammatory drugs to 23 patients (11%) in the ketorolac group and 11 (3%) in the control group ($P < .001$). Twelve patients in the control group and 3 in the ketorolac group had epidural catheters placed for analgesia.

We identified 24 patients with pneumonia documented by attending physicians during hospital days 2 to 30, including 19 in the control group and 5 in the ketorolac group. Most cases involved a radiographic infiltrate (79%), leukocytosis (92%), and purulent sputum (79%). There were no significant differences in the proportions of patients with pneumonia in the control and ketorolac groups that had a chest x-ray infiltrate (74% vs 100%, respectively), fever or hypothermia (58% vs 40%), leukocytosis or leukopenia (89% vs 100%), purulent sputum (74% vs 100%), a positive culture (58% vs 40%), or ventilator-associated pneumonia (79% vs 40%). The time from injury to pneumonia diagnosis was 6 ± 4 days among control subjects and 8 ± 2 days among ketorolac subjects ($P = .33$). Antibiotics were administered in all cases, with mean durations of 8 ± 4 days in the control group and 6 ± 1 days in the ketorolac group ($P = .15$).

The unadjusted odds ratio of pneumonia with ketorolac was .54 (95% confidence interval, 0.20 to 1.46). After adjustment for the number of rib fractures, Abbreviated Injury Scale chest and extremity scores, and comorbid
chronic obstructive pulmonary disease, the odds ratio decreased to .14 (95% confidence interval, .04 to .46) (Fig. 1).

Six cases of pneumonia in the control group (and none in the ketorolac group) occurred on hospital day 2 or 3, and 6 cases in the control group (and none in the ketorolac group) failed to meet American Thoracic Society criteria. Our hospital’s quality improvement committee classified 3 cases in the control group (and again none in the ketorolac group) as pneumonitis rather than pneumonia. Nonetheless, these alternative definitions of pneumonia did not substantially change the magnitude of the association of ketorolac with pneumonia (Fig. 1). Additional adjustment for age and sex had no effect on the observed association for any of the definitions of pneumonia. Interrater agreement between our study team’s and the quality improvement committee’s ascertainment of pneumonia was excellent (κ = .93).

With and without adjustment for confounding factors, both Poisson and linear regression modeling suggested that ketorolac was associated with a 6% (95% confidence interval, 2% to 9%) increase in time alive and off the ventilator and a 7% (95% confidence interval, 4% to 11%) increase in time alive and not in the intensive care unit. In the adjusted Poisson regression model, ketorolac was associated with 1.8 more days (95% confidence interval, 1.1 to 2.5 days) alive and off the ventilator and 2.1 more days (95% confidence interval, 1.3 to 3.0 days) alive and not in the intensive care unit (Fig. 2).

Important adverse events potentially related to ketorolac use appeared to be rare, with no obvious differences between the groups in the occurrence of acute kidney injury, myocardial infarction, stroke, gastrointestinal hemorrhage, and fracture nonunion (Table 2). Seven deaths occurred in the control group and none in the ketorolac group (P = .06, Fisher’s exact test).

**Comments**

Our study suggests that the administration of ketorolac early after injury significantly decreases the risk for

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Control (n = 417)</th>
<th>Ketorolac (n = 202)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (y)</td>
<td>48 ± 19</td>
<td>48 ± 16</td>
<td>.89</td>
</tr>
<tr>
<td>Men</td>
<td>258 (62%)</td>
<td>118 (58%)</td>
<td>.47</td>
</tr>
<tr>
<td>Mechanism</td>
<td></td>
<td></td>
<td>.66</td>
</tr>
<tr>
<td>Blunt</td>
<td>402 (96%)</td>
<td>195 (96%)</td>
<td></td>
</tr>
<tr>
<td>Motor vehicle</td>
<td>237 (56%)</td>
<td>104 (51%)</td>
<td></td>
</tr>
<tr>
<td>Motorcycle</td>
<td>28 (7%)</td>
<td>21 (10%)</td>
<td></td>
</tr>
<tr>
<td>Auto</td>
<td>36 (9%)</td>
<td>15 (7%)</td>
<td></td>
</tr>
<tr>
<td>Fall</td>
<td>72 (17%)</td>
<td>40 (20%)</td>
<td></td>
</tr>
<tr>
<td>Assault</td>
<td>29 (7%)</td>
<td>15 (7%)</td>
<td></td>
</tr>
<tr>
<td>Penetrating</td>
<td>11 (3%)</td>
<td>3 (1%)</td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td>7 (2%)</td>
<td>4 (2%)</td>
<td></td>
</tr>
<tr>
<td>Abbreviated Injury Scale scores</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Head</td>
<td>2 (0–2)</td>
<td>1 (0–2)</td>
<td>.01</td>
</tr>
<tr>
<td>Face</td>
<td>0 (0–0)</td>
<td>0 (0–0)</td>
<td>.53</td>
</tr>
<tr>
<td>Chest</td>
<td>2.1 ± 1.0</td>
<td>2.6 ± 1.1</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Abdomen</td>
<td>0 (0–0)</td>
<td>0 (0–0)</td>
<td>.04</td>
</tr>
<tr>
<td>Extremity</td>
<td>0 (0–2)</td>
<td>0 (0–2)</td>
<td>.41</td>
</tr>
<tr>
<td>External</td>
<td>0 (0–1)</td>
<td>0 (0–1)</td>
<td>.16</td>
</tr>
<tr>
<td>Injury Severity Score</td>
<td>12 ± 10</td>
<td>12 ± 7</td>
<td>.99</td>
</tr>
<tr>
<td>Radiographic rib fracture</td>
<td>200 (48%)</td>
<td>139 (69%)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Number of radiographic rib fractures, subjects* with ≥1 such fracture†</td>
<td>3.1 ± 2.3</td>
<td>3.7 ± 2.6</td>
<td>.02</td>
</tr>
<tr>
<td>Congestive heart failure</td>
<td>7 (2%)</td>
<td>5 (2%)</td>
<td>.50</td>
</tr>
<tr>
<td>Chronic obstructive pulmonary disease</td>
<td>7 (2%)</td>
<td>9 (4%)</td>
<td>.04</td>
</tr>
<tr>
<td>Chronic kidney disease</td>
<td>12 (3%)</td>
<td>0 (0%)</td>
<td>.02</td>
</tr>
<tr>
<td>Smokers</td>
<td>60 (14%)</td>
<td>69 (34%)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Initial creatinine (mg/dL)</td>
<td>1.1 ± 0.6</td>
<td>0.9 ± 0.2</td>
<td>.01</td>
</tr>
</tbody>
</table>

*Data are expressed as mean ± SD, number (percentage), or median (interquartile range).
†Includes subjects who did not have any radiographic rib fractures (ie, the patient experienced pleuritic pain but did not have any apparent fractures on chest x-ray or, if available, computed tomographic scan).
‡Includes only the 200 control and 139 ketorolac subjects who had radiographic rib fractures.
pneumonia among patients with rib fractures. It also appeared to reduce time on the ventilator and in the intensive care unit without any prominent increase in such known or hypothesized risks of nonsteroidal anti-inflammatory drugs as acute kidney injury, myocardial infarction, stroke, gastrointestinal hemorrhage, or fracture nonunion. Because pneumonia was a relatively rare outcome, the odds ratio approximates the relative risk, suggesting possibly a 7-fold reduction in the risk for pneumonia with ketorolac use. This degree of risk reduction—and the lack of an increase in adverse effects, including fracture nonunion, in this and other analyses—suggests that efforts to control pain with ketorolac should prevail over concerns about its orthopedic effects in injured patients.

Although nonsteroidal anti-inflammatory drugs have been studied extensively in other settings, relatively few studies have examined their effectiveness in controlling pain or reducing pulmonary morbidity after rib fractures.

Several studies have focused on regional techniques for pain control after rib fractures, but few have been methodologically rigorous enough to support broad practice changes. Bulger et al concluded from their randomized trial of patients with multiple rib fractures that epidural use decreased the risk for pneumonia and time on the ventilator, though the size of the study was modest, and the findings were significant only in an adjusted analysis. Furthermore, contraindications to epidural analgesia are frequent among injured patients, begging the question of which interventions are best when it is not an option.

Nonsteroidal anti-inflammatory drugs clearly reduce pain and opioid use after thoracic, orthopedic, and abdominal operations. Among post-thoracotomy patients, some studies have also shown better postoperative pulmonary function or improved pain control during breathing exercises with ketorolac or other nonsteroidal anti-inflammatory drugs. Although we could not characterize pain severity or pulmonary function well from review of medical records in this study, these benefits may explain why ketorolac was associated with reduced incidence of pneumonia.

We used an inclusive definition of rib fractures in which we considered pleuritic pain sufficient to make the diagnosis because ≥50% of rib fractures may be missed on plain chest x-rays. This may explain the relatively low rates of pneumonia we observed (2.5% in the ketorolac group and 4.6% in the control group), as most studies have focused on patients with radiographically apparent fractures. However, with restriction to the subpopulations evaluated in other studies, we observed a comparable incidence: among patients with ≥3 fractured ribs, approximately 8% of patients <65 years of age and 17% of those aged ≥65 years developed pneumonia.

We defined the ketorolac group on the basis of receiving the medication within the first 4 days after injury both to ensure that it was administered during a relevant time frame for prevention of pneumonia and because inflammation typically peaks within the first few days after injury. We excluded patients who received ketorolac for <24 hours on the grounds that such limited administration would be unlikely to have a significant clinical effect. The ketorolac doses we observed were much lower than the maximal safe dose of 30 mg intravenously every 6 hours for 5 days as described in the medication’s package insert. This and the fact that our study had minimal power to detect rare events may explain why we did not detect adverse effects of ketorolac.

The diagnosis of pneumonia is fraught with uncertainty. For the primary outcome, we used an attending physician’s diagnosis because it is likely the most relevant criterion standard at our center. Our trauma surgery service only infrequently obtained distal airway invasive cultures (bronchoscopic or blind technique) in either ventilated or nonventilated patients with suspected pneumonia during the study period; thus, the fact that only 54% of pneumonia cases were microbiologically confirmed is not surprising. In
the absence of microbiologic confirmation from the distal airway, we felt that attending physician judgment was the best option to minimize nonspecificity from clinical criteria and cultures of the proximal airway. In practical terms, all 24 patients diagnosed with pneumonia were treated as such. Furthermore, alternative definitions of the primary outcome—whether by restricting cases to those with an attending physician diagnosis and that met American Thoracic Society clinical criteria or as ascertained by our hospital’s quality improvement committee—confirmed our primary findings. Nonetheless, evaluation of ketorolac in a setting that uses routine invasive diagnosis of pneumonia would be worthwhile.

The ketorolac and control patients were similar in several characteristics, including age and sex, but the characteristics that differed tended, if anything, to promote pneumonia in the ketorolac group. Patients who received ketorolac had greater Abbreviated Injury Scale chest scores, a greater likelihood of radiographic rib fractures, more rib fractures, and greater prevalence of smoking and chronic obstructive pulmonary disease. Treating physicians may have used ketorolac to be more aggressive in managing the pain of these higher risk patients. Accordingly, the reduction in the risk for pneumonia associated with ketorolac only became more impressive with adjustment for these imbalances. The control group had greater Abbreviated Injury Scale head and abdominal scores as well as initial creatinine levels and prevalence of chronic kidney disease. We postulate that these differences reflect reluctance to put such patients at greater risk for potential bleeding and renal impairment from ketorolac. However, post hoc adjustment for these differences did not change the association of ketorolac with a reduced risk for pneumonia (analyses not shown).

Our study had limitations. As a nonrandomized comparison, it may have involved residual confounding from hidden differences or selection biases that we could not conceptually or measure retrospectively. Time-dependent cointerventions such as ventilator use, opioids, and other analgesic measures are particularly hard to tease apart from the effects of ketorolac. Partly because the effects of ketorolac could be partially mediated by the use or nonuse of these other interventions, we did not attempt to account for these factors in our analyses. However, even a construct of baseline opiate use (eg, during the first 24 hours) would be a problematic surrogate for the pain the patient experiences because it can be influenced by non–chest wall injuries, the mental state of the patient, and other factors that have little or no relationship to chest wall pain. Alternatively, epidural catheter and other nonsteroidal anti-inflammatory drug use both were infrequent enough that they appeared to have little influence on the risk for pneumonia in our cohort. These issues and the aforementioned challenges of using pneumonia as an outcome emphasize that our study should be considered more a source of future study hypotheses than definitive evidence. If ketorolac indeed reduces the risk for pneumonia 7-fold, even if pneumonia were an infrequent outcome, future randomized trials may be able to detect such a difference with enrollment of approximately 500 to 800 subjects.

Despite these limitations, to our knowledge, this comparison is the first to evaluate the use of nonsteroidal anti-inflammatory drugs specifically for patients with rib fractures. It suggests that the early administration of ketorolac is associated with a decreased likelihood of pneumonia, increased ventilator–free days, and increased intensive care unit–free days, all without a notable increase in adverse effects.

**Acknowledgment**

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**References**


