Perioperative Single Dose Ketorolac to Prevent Postoperative Pain: A Meta-Analysis of Randomized Trials

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BACKGROUND: Preventive analgesia using non-opioid analgesic strategies is recognized as a pathway to improve postoperative pain control while minimizing opioid-related side effects. Ketorolac is a nonsteroidal antiinflammatory drug frequently used to treat postoperative pain. However, the optimal dose and route of administration for systemic single dose ketorolac to prevent postoperative pain is not well defined. We performed a quantitative systematic review to evaluate the efficacy of a single dose of perioperative ketorolac on postoperative analgesia.

METHODS: We followed the PRISMA statement guidelines. A wide search was performed to identify randomized controlled trials that evaluated the effects of a single dose of systemic ketorolac on postoperative pain and opioid consumption. Meta-analysis was performed using a random-effects model. Effects of ketorolac dose were evaluated by pooling studies into 30- and 60-mg dosage groups. Asymmetry of funnel plots was examined using Egger regression. The presence of heterogeneity was assessed by subgroup analysis according to the route of systemic administration (IV versus IM) and the time of drug administration (preincision versus postincision).

RESULTS: Thirteen randomized clinical trials with 782 subjects were included. The weighted mean difference (95% confidence interval [CI]) of combined effects showed a difference for ketorolac over placebo for early pain at rest of −0.64 (−1.11 to −0.18) but not at late pain at rest, −0.29 (−0.88 to 0.29) summary point (0−10 scale). Opioid consumption was decreased by the 60-mg dose, with a mean (95% CI) IV morphine equivalent consumption of −1.64 mg (−2.90 to −0.37 mg). The opioid-sparing effects of ketorolac compared with placebo were greater when the drug was administered IM compared with when the drug was administered IV, with a mean difference (95% CI) IV morphine equivalent consumption of −2.13 mg (−4.1 to −0.21 mg). Postoperative nausea and vomiting were reduced by the 60-mg dose, with an odds ratio (95% CI) of 0.49 (0.29–0.81).

CONCLUSIONS: Single dose systemic ketorolac is an effective adjunct in multimodal regimens to reduce postoperative pain. Improved postoperative analgesia achieved with ketorolac was also accompanied by a reduction in postoperative nausea and vomiting. The 60-mg dose offers significant benefits but there is a lack of current evidence that the 30-mg dose offers significant benefits on postoperative pain outcomes. (Anesth Analg 2011;X:::)

Postoperative pain is the most common undesirable outcome for patients who undergo surgical procedures. Besides causing patients to suffer, postoperative pain can delay recovery and prolong hospital stay. Evidence suggests that postoperative pain is not optimally managed in the United States and Europe. Opioid-sparing techniques using different analgesic mechanisms of action is recognized as an important component strategy for postoperative pain management.

Ketorolac is an injectable nonsteroidal antiinflammatory drug with analgesic properties. Smith et al. evaluated the efficacy of a single dose of ketorolac given postoperatively for the treatment of moderate to severe postoperative pain in a quantitative review and their results demonstrated a beneficial effect. The majority of studies involved in the analysis performed by Smith et al. examined the oral formulation of ketorolac and only 1 study examined a systemic dose higher than 30 mg. In addition, none of the studies examined the IV administration of ketorolac. The review was also inconclusive on the efficacy of ketorolac to reduce opioid-related side effects such as nausea and vomiting. The systematic review performed by Smith et al. evaluated the effect of ketorolac after the establishment of moderate postoperative pain but anesthesia providers frequently administer single dose systemic ketorolac before the end of surgical procedures in an attempt to reduce postoperative pain; the efficacy of ketorolac as well as the dose dependency effects in that circumstance have not been established.

The objective of this quantitative systematic review is to assess the efficacy and dose dependency effects of single dose perioperative ketorolac on postsurgical pain outcomes. We also examined the efficacy of a single dose of systemic ketorolac in reducing postoperative nausea and vomiting.

METHODS

This systematic review was performed according to the guidelines established by the PRISMA statement.
Ketorolac Postoperative Pain

Systematic Search
Published reports of randomized trials testing the effects of ketorolac on surgical postoperative pain were searched using the National Library of Medicine’s PubMed database, the Cochrane database of systematic reviews, Embase, and Google Scholar inclusive to March 1, 2011. The initial search was performed using the free-text and MeSH terms “ketorolac” or “toradol.” The “and” function was used to combine the initial search with the terms postoperative or preoperative. No language restriction was used. The search was limited to randomized controlled clinical trials in subjects older than 18 years of age. An attempt to identify additional studies not retrieved by the primary search was made by reviewing the reference lists from identified studies. No search was performed for unpublished studies. This initial search yielded 431 studies.

Inclusion and Exclusion Criteria
We included only randomized clinical trials of a single perioperative (preoperative or intraoperative) systemic ketorolac with an inactive (placebo or “no treatment”) control group. Included studies had to report at least pain scores or opioid consumption on postoperative pain outcomes. Excluded were trials reporting analgesia after nonsurgical or dental pain. Trials evaluating >1 dose of perioperative ketorolac were also excluded to maximize clinical homogeneity. Studies containing a concurrent use of a different analgesic regimen were excluded if a direct comparison of ketorolac and placebo could not be established. No minimum sample size was required for inclusion in the meta-analysis.

Selection of Included Studies
The study’s inclusion and exclusion criteria were determined before the systematic search. Two authors (GSD and DA) independently evaluated the abstract and results of the 431 articles obtained by the initial search. Articles that were clearly not relevant based on our inclusion and exclusion criteria were excluded at this phase. Disagreements on inclusion of the articles were resolved by discussion among the evaluators. If an agreement could not be reached, the dispute was resolved with the help of a third investigator (HTB).

Validity Scoring
Two authors (GSD and DA) independently read the included reports and assessed their methodological validity using a modified Jadad 5-point quality scale. The scale evaluates the study for the following: randomization, double-blind evaluation, concealment of study group to evaluator, valid randomization method, and completeness of follow-up. Discrepancies in rating of the trials were resolved by discussion among the evaluators. If an agreement could not be reached, the dispute was resolved with the help of a third investigator (HTB). Because we only included randomized trials, the minimum score of an included trial was 1 and the maximum 5. Trials were not excluded or weighted in the analysis based on score assessment.

Data Extraction
Two authors (GDO and DA) independently evaluated the full manuscripts of included trials and performed data extraction using a data collection form specifically developed for this systematic review. Data extracted from trials included ketorolac dose, time of administration, sample size, follow-up period, type of surgery, pain outcomes, time to hospital discharge, and reported side effects. Visual analog scale or numeric rating scales were converted to a 0 to 10 Numeric Rating Scale. Postoperative opioid consumption was converted to equivalent dose of IV morphine. Data were initially extracted from tables. For data not available in tables, attempts to contact authors were made; if the authors did not respond or did not have current contact information, the data were extracted from available figures. Dichotomous data on the presence or absence of adverse effects were collected and converted to incidence whereas continuous data were recorded using mean and standard deviation. Data presented only as median and range were converted to means and standard deviation using previously described methodology. If required, the standard deviation for pain scores was estimated using the most extreme values.

Definition of Relevant Outcome Data
Our primary outcomes were early (0–4 hours) acute postoperative pain scores at rest and at movement; late (24 hours) acute postoperative pain scores at rest and at movement; and cumulative opioid consumption (IV morphine equivalents) in the postoperative period.

Our secondary outcomes were incidence and severity of chronic pain, time to hospital discharge (minutes), and adverse events including postoperative nausea and vomiting, pruritus, postoperative bleeding, gastrointestinal symptoms, and renal failure.

Meta-Analyses
The weighted mean differences with 95% confidence interval (CI) were determined and reported for continuous data. For dichotomous data (adverse effects), the Peto odds ratio (to account for the potential of 0 counts in the cells for low-frequency outcomes) and 95% CI are reported. A significant effect compared with placebo required that the 95% CI for continuous data did not include 0 and for dichotomous data, the CI did not include 1. Because of the different surgical procedures, we used a random-effects model in an attempt to generalize our findings to studies not included in our meta-analysis. Publication bias was evaluated by examining for asymmetric funnel plots using the Egger regression test. A 1-sided P < 0.05 was considered as an indication of an asymmetric funnel plot. A file drawer analysis described by Rosenthal was planned to be performed in the case of an asymmetric funnel plot.

Heterogeneity of the included studies was considered to be present if the I² statistic was >30%. Further analysis was planned a priori to explore relevant heterogeneity. Subgroup analysis was performed to investigate the effect of time of ketorolac administration (preincision versus postincision) and route of administration (IV versus IM) on pain outcomes. A Q statistic was used to compare the effects between subgroups. The proportion of the total variance
explained by the covariates ($R^2$) was calculated by dividing random-effects pooled estimates of variance ($\hat{\tau}^2$) within studies by total variance (total $\tau^2$). The value obtained was then subtracted from 1. When values were outside the range of 0% to 100%, they were set to the closest value (0% or 100%).

Subgroup comparisons on the effect of the different routes of drug administration (IM versus IV) on postoperative opioid consumption and pain scores were made using the Z test. Analysis was performed using Comprehensive Meta-Analysis software version 2 (Biostat, Englewood, NJ).

**RESULTS**

Of the 413 initially evaluated studies, 23 trials met the inclusion criteria and 10 trials were subsequently excluded (Fig. 1). In 5 studies, patients received multiple doses of ketorolac,13–17 1 study evaluated a continuous infusion,18 2 studies evaluated ketorolac as a postoperative medication,19,20 and 2 studies did not report on the outcomes defined by our inclusion criteria or the authors did not provide enough information to analyze the data.21,22 We analyzed 13 trials with data on 782 patients. Doses ranged from 30 to 60 mg of systemic ketorolac. We did not retrieve any unpublished data. Characteristics of included studies and data extraction methods for each study are listed in Table 1. The reports were published between 1994 and 2010.23–35 The median number of patients receiving ketorolac was 30 and the median modified Jadad scale score was 4. The trials tested a single dose of ketorolac given perioperatively in a large variety of surgical procedures. Four studies examined the 30-mg dose25,26,30,35 and 9 studies examined the 60-mg dose.23,24,27–29,31–34 All 13 studies reported on opioid consumption and/or pain scores. Only 1 study reported on pain scores at movement.31

### Early (0–4 Hours) Pain at Rest

The overall effect of ketorolac on early pain at rest compared with placebo-favored ketorolac with a weighted mean difference (95% CI) of $−0.64 (−1.11$ to $−0.17$) (summary point on a 0 to 10 scale) (Fig. 2). The funnel plot did not demonstrate significant asymmetry ($P = 0.23$) (Fig. 3).

The aggregate effect of the 3 trials evaluating 30 mg ketorolac on early pain at rest25,30,35 demonstrated a wide CI relative to a clinically significant difference on the effect of 30 mg ketorolac compared with placebo (Fig. 2).

Eight studies examined the effect of 60 mg ketorolac compared with placebo on early pain at rest23,27–29,31–34 Three studies provided data for 2 comparisons and both were included in the analysis.27,29,31 The combined effect of the 8 studies examining 60 mg ketorolac on early pain suggests a decrease in early pain: $−2.09 (−3.24, −0.95$) (summary point on a 0 to 10 scale). The analysis showed high heterogeneity ($I^2 = 93\%$). A subgroup analysis examining the route of administration demonstrated a bigger effect when 60 mg ketorolac was administered IM, $−2.81 (−3.11, −2.51$) compared with 60 mg ketorolac administered IV, $−1.23 (−1.76, −0.70$ ($P < 0.0001$) (summary point on a 0 to 10 scale). Heterogeneity was decreased by the IV administration ($I^2 = 55$). Fourteen percent of the total variance was explained by the route of drug administration. Heterogeneity could not be explained by time of drug administration (preincision versus postincision).

### Early (0–4 Hours) Pain at Movement

No studies examined the effect of 30 mg ketorolac on early pain at movement. Only 1 study examined the effect of 60 mg ketorolac on early pain at movement.31 It examined the effects of 60 mg ketorolac IV administered pre- and post-surgical incision compared with placebo. Early pain at movement was reduced by pre- and postincision 60 mg ketorolac, $−3.00 (−4.38, −1.61$) and $−1.90 (−3.28, −0.51$) (summary point on a 0 to 10 scale), respectively.

### Late (24 Hours) Pain at Rest

The overall effect of ketorolac on late pain at rest compared with placebo showed a wide CI relative to a clinically significant difference (Fig. 4). The funnel plot did not demonstrate asymmetry ($P = 0.21$) (Fig. 5).

Two studies examined the effects of 30 mg ketorolac on late pain at rest25,35 suggesting no statistically significant effect with a mean difference (95% CI) of $−0.11 (−0.71, 0.56$) (summary point on a 0 to 10 scale). Four studies examined the effect of 60 mg ketorolac on late pain at rest.23,29,31,33 Two studies29,31 provided data for 2 comparisons and both were included in the analysis. No statistically significant effect of the 60-mg dose on late pain at rest compared with placebo was observed (Fig. 4).
Late Pain (24 Hours) at Movement

No studies examining the effect of 30 mg ketorolac reported on late pain at movement. Only 1 study evaluating 60 mg ketorolac reported on late pain at movement.31 The study examined the effects of 60 mg ketorolac IV administered pre- and postsurgical incision compared with placebo. Late pain at movement was not reduced by pre- and postincision 60 mg ketorolac (Table 2).

Postoperative Opioid Consumption

We compared the overall effect of ketorolac on postoperative opioid consumption with placebo-favored ketorolac with a mean difference (95% CI) of −1.73 (−2.82 to −0.59) (summary point on milligrams of IV morphine equivalents) (Fig. 6). The funnel plot did not demonstrate asymmetry indicating that there was not substantial publication bias ($p = 0.21$) (Fig. 7).

Three studies examined the effect of 30 mg ketorolac on postoperative opioid consumption compared with saline.26,30,35 One study provided data for 2 comparisons and both were included in the analysis.26 The aggregate effect of 30 mg ketorolac on postoperative opioid consumption compared with placebo demonstrated a wide CI relative to a clinically significant difference (Fig. 6). The analysis was limited by some heterogeneity ($I^2 = 37$). All the studies examined IM ketorolac. One hundred percent of the total variance was explained by the time of drug administration (preincision versus postincision). The removal of the only comparison that examined the postincision administration of ketorolac substantially reduced the heterogeneity between the remaining comparisons studies ($I^2 = 0$).

Eight studies evaluated the effect of 60 mg ketorolac on postoperative opioid consumption demonstrating an

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**Table 1. Summary of Studies Included in Analysis**

<table>
<thead>
<tr>
<th>Authors and year of publication</th>
<th>Procedures</th>
<th>No. treatment/control</th>
<th>Treatment</th>
<th>Type of anesthesia</th>
<th>Postoperative analgesia</th>
<th>Modified Jadad score (1–5)$^7$</th>
<th>Method of data extraction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alexander et al.,23 2002</td>
<td>Total hip and knee arthroplasty</td>
<td>31/32</td>
<td>Ketorolac 60 mg IV preincision</td>
<td>Thiopental/isoflurane/nitrous oxide</td>
<td>Morphine sulfate PCA</td>
<td>5</td>
<td>Table/figure</td>
</tr>
<tr>
<td>Mack et al.,24 2001</td>
<td>Lumbar discectomy</td>
<td>10/10</td>
<td>Ketorolac 30 mg IV postincision</td>
<td>Fentanyl/propofol/isoflurane/nitrous oxide</td>
<td>Morphine sulfate PCA</td>
<td>3</td>
<td>Table/text</td>
</tr>
<tr>
<td>Tarkkanen and Saarnivaara,25 1999</td>
<td>Tonsillectomy</td>
<td>20/20</td>
<td>Ketorolac 30 mg IV preincision</td>
<td>Alfentanil/propofol/sevoflurane/nitrous oxide</td>
<td>Oxycodeone 0.05 mg/kg IV</td>
<td>4</td>
<td>Table/figure</td>
</tr>
<tr>
<td>Gabot et al.,26 1997</td>
<td>Abdominal hysterectomy</td>
<td>65/36</td>
<td>Ketorolac 30 mg IV pre and postincision</td>
<td>Propofol/nitrous oxide/isoflurane</td>
<td>Morphine sulfate PCA</td>
<td>4</td>
<td>Table/text</td>
</tr>
<tr>
<td>Green et al.,27 1996</td>
<td>Gynecologic laparoscopy</td>
<td>63/63</td>
<td>Ketorolac 60 mg IV preincision</td>
<td>Propofol/nitrous oxide</td>
<td>Fentanyl 25–50 μg pm</td>
<td>4</td>
<td>Table/text</td>
</tr>
<tr>
<td>Fredman et al.,28 1996</td>
<td>Prostatectomy</td>
<td>30/30</td>
<td>Ketorolac 60 mg IM postincision</td>
<td>Fentanyl/thiopental/isoflurane/nitrous oxide</td>
<td>Morphine sulfate PCA</td>
<td>4</td>
<td>Table/text</td>
</tr>
<tr>
<td>Lane et al.,29 1996</td>
<td>Laparoscopic cholecystectomy</td>
<td>51/23</td>
<td>Ketorolac 60 mg IV preincision</td>
<td>Fentanyl/isoflurane</td>
<td>Meperidine 0.25 mg/kg IV q 10 min pm</td>
<td>3</td>
<td>Figure/text</td>
</tr>
<tr>
<td>Murrell et al.,30 1996</td>
<td>Gynecologic laparoscopy</td>
<td>51/49</td>
<td>Ketorolac 30 mg IM preincision</td>
<td>Fentanyl/propofol/isoflurane/nitrous oxide</td>
<td>Fentanyl 10 μg q 5 min of paracetamol 500 mg/codeine 8 mg</td>
<td>3</td>
<td>Table/text</td>
</tr>
<tr>
<td>Fletcher et al.,31 1995</td>
<td>Total hip replacement</td>
<td>40/20</td>
<td>Ketorolac 60 mg IV preincision</td>
<td>Fentanyl/thiopental/nitrous oxide/isoflurane</td>
<td>Morphine sulfate PCA</td>
<td>4</td>
<td>Table/figure</td>
</tr>
<tr>
<td>Fredman et al.,32 1995</td>
<td>Laparoscopic cholecystectomy</td>
<td>19/19</td>
<td>Ketorolac 60 mg IM postincision</td>
<td>Fentanyl/thiopental/nitrous oxide/isoflurane</td>
<td>Morphine sulfate PCA</td>
<td>4</td>
<td>Figures/text</td>
</tr>
<tr>
<td>Higgins et al.,33 1994</td>
<td>Laparoscopic gynecologic</td>
<td>15/15</td>
<td>Ketorolac 60 mg IV preincision</td>
<td>Fentanyl/thiopental/nitrous oxide/isoflurane</td>
<td>Morphine 3 mg IV pm</td>
<td>4</td>
<td>Table/figure</td>
</tr>
<tr>
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<td>Orthopedics or lower abdominal surgery</td>
<td>15/15</td>
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<td>Anesthetic regimen not standardized</td>
<td>Morphine sulfate pm</td>
<td>3</td>
<td>Table/text</td>
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<td>Shapiro and Duffy,25 1994</td>
<td>Laparoscopic gynecologic</td>
<td>20/20</td>
<td>Ketorolac 30 mg IM preincision</td>
<td>Fentanyl/propofol/isoflurane/nitrous oxide</td>
<td>Fentanyl, morphine, or meperidine</td>
<td>3</td>
<td>Table/text</td>
</tr>
</tbody>
</table>

PCA = patient-controlled analgesia; pm = as needed; q = every.

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*Note: The image contains a table with data on studies included in the analysis, with columns for authors, procedures, number of treatment/control, treatment, type of anesthesia, postoperative analgesia, modified Jadad score, and method of data extraction. The table compares the effects of ketorolac 30 mg and 60 mg on postoperative pain at movement.*
opioid-sparing effect of \( \frac{1.64}{1.1002} \) (\( 2.90, 0.37 \)) (summary point on milligrams of IV morphine equivalents) compared with placebo.\(^{23,24,27,28,31–34}\) Two studies provided data for 2 comparisons and both were included in the analysis. The analysis was limited by heterogeneity (\( I^2 = 71 \)). Heterogeneity was high when the medication was given IM (\( I^2 = 86 \)) and low when the medication was given IV (\( I^2 = 0 \)). A subgroup analysis was performed to evaluate the effect of route of administration of the drug (IM or IV) on opioid sparing. Four studies examined the 60-mg ketorolac dose given IM \(^{24,28,32,34}\) and 4 studies examined the effects of the 60-mg dose given IV.\(^{23,27,31,33}\) Among the studies evaluating IV administration, 2 provided 2 comparisons and both were included in the analysis.\(^{27,31}\) Ketorolac administered IM had greater opioid-sparing effects than ketorolac administered IV with a mean difference (95% CI) of \(-2.13 \text{ mg} \) (\(-4.10 \text{ to } -0.21 \text{ mg} \)) (summary point on milligrams of IV morphine equivalents) (\( P = 0.03 \)).

### Chronic Pain (≥3 Months)

None of the included studies reported on chronic pain.

### Time to Hospital Discharge

Two studies examined the effect of systemic ketorolac on time to hospital discharge.\(^{27,33}\) One study provided data for 2 comparisons and both were included in the analysis.\(^{27}\) The combined effects resulted in a wide CI relative to a clinically significant difference in the reduction in time to hospital discharge of systemic ketorolac compared with placebo (Table 2).

### Postoperative Nausea and Vomiting

Eight studies examined the effect of ketorolac on postoperative nausea and vomiting.\(^{23–25,27,28,31,33,35}\) Two studies provided 2 comparisons and both were included in the analysis.\(^{27,31}\) The overall effect of ketorolac in reducing postoperative nausea and vomiting, odds ratio (95% CI), was 0.57 (0.36–0.88) (Fig. 8). Number needed to treat was 12.5 patients. There was no evidence of an asymmetric funnel plot (\( P = 0.29 \)).

Three studies examined the effect of 30 mg ketorolac on postoperative nausea and vomiting.\(^{24,25,35}\) The aggregate effect did not demonstrate a statistically significant benefit of 30 mg ketorolac compared with placebo (Fig. 8). Five studies evaluated the effect of 60 mg ketorolac on postoperative nausea and vomiting.\(^{25,27,28,31,33}\) Two studies provided 2 comparisons and both were included in the final analysis.\(^{27,31}\) The combined effect suggested a reduction in postoperative nausea and vomiting with 60 mg ketorolac compared with placebo with an odds ratio (95% CI) of 0.50 (0.29–0.85).
Pruritus
Two studies examined the effect of ketorolac on postoperative pruritus.\textsuperscript{23,25} The aggregate studies did not suggest a reduction in postoperative pruritus of ketorolac compared with placebo (Table 2). The analysis was limited by high heterogeneity ($I^2 = 90$) that could not be explained by the route of systemic administration, because both studies evaluated IV administration of the drug.

Safety Analysis
Nine studies did not report on adverse side effects related to ketorolac.\textsuperscript{23,24,27–30,32,34,35} Two studies reported on abnormal bleeding.\textsuperscript{25,31} One study provided 2 comparisons and both were included in the analysis.\textsuperscript{31} The combined effect did show a statistically significant increase in abnormal bleeding with ketorolac compared with placebo (Table 2). One study reported an increase in postoperative bleeding but no changes in the number of blood transfusions or a need for surgical reintervention.\textsuperscript{26} Two studies reported on postoperative gastritis symptoms.\textsuperscript{25,33} The aggregate effect did not suggest an increase in postoperative gastritis symptoms with ketorolac compared with placebo (Table 2).

**DISCUSSION**
Several important findings have emerged from this quantitative systematic review. Although a single dose of systemic ketorolac can be effective to prevent postoperative pain, the effect may be dependent on the dose and route of administration. The 60-mg dose decreased early postoperative pain and had opioid-sparing effects but there was a lack of evidence for a statistically significant effect for the 30-mg dose. Our analysis also suggests a greater analgesic effect of IM administration compared with IV administration but the analysis was limited by a low number of patients in the subgroups. These findings may have important clinical implications because anesthesia providers frequently administer IV 30-mg dose of ketorolac.\textsuperscript{36}

Previous investigators have demonstrated a beneficial effect of the 30-mg dose of ketorolac for the treatment of postoperative pain.\textsuperscript{5} The question examined by those investigators was different than the one examined in the current analysis. They evaluated the effect of ketorolac to treat moderate to severe pain after surgery, whereas in the current study, we examined the preventive effect of a single dose of perioperative ketorolac on postoperative pain. Our subgroup analysis examining dose efficacy was limited by the small size of the available studies. Nonetheless, because anesthesia providers frequently use 30 mg ketorolac preoperatively to prevent postoperative pain, it is important to state that evidence corroborating this practice is still needed.

Another important finding that has emerged from this study is the beneficial effect of ketorolac in reducing postoperative nausea and vomiting. These findings are significant because there are not enough data showing the
beneficial role of opioid-sparing strategies in improving patients’ recovery. The effects of ketorolac in reducing postoperative nausea and vomiting were present for the 60-mg dose but our analysis failed to detect an effect for the 30-mg dose group. This finding is parallel to the opioid-sparing effects of the different dose groups suggesting a possible association between postoperative opioid reduction and a decrease in postoperative nausea and vomiting. The lack of effect of a single dose of ketorolac on late pain is expected because of the relatively short half-life of the drug (5 hours). The lack of strong antiinflammatory properties can also be a possible explanation for the absence of longer duration effects. The longer time to peak concentration of the 60-mg IM injection (30–50 minutes) compared with the 30-mg IV dose (3–5 minutes) of ketorolac with a similar peak concentration is a possible reason for the higher analgesic effect during the postoperative course when the medication is given in the intraoperative period. The analgesic effect of ketorolac is based on the racemic concentration of S and R enantiomers but this fact was not considered in early pharmacokinetic studies of the drug. The IM administration of drug may have a slower clearance of the active (S) enantiomer form than the IV administration, which can result in better analgesic effects as we observed in clinical studies.

### Table 2. Aggregate Results of Single Dose Perioperative Ketorolac Compared with Saline

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Intervention</th>
<th>Summary point</th>
<th>95% confidence interval</th>
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</thead>
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<tr>
<td>Late pain at movement</td>
<td>Ketorolac 60 mg preincision</td>
<td>−0.1 (0–10 scale)</td>
<td>−1.34 to 1.14</td>
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<td>Late pain at movement</td>
<td>Ketorolac 60 mg postincision</td>
<td>−0.2 (0–10 scale)</td>
<td>−1.86 to 1.46</td>
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<tr>
<td>Time to hospital discharge</td>
<td>Ketorolac 60 mg</td>
<td>−1.7 min</td>
<td>−64 to 28.7</td>
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<td>Pruritus</td>
<td>Ketorolac 30 and 60 mg</td>
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<td>0.18–1.19</td>
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<td>Abnormal bleeding</td>
<td>Ketorolac 30 and 60 mg</td>
<td>2.43</td>
<td>0.5–11</td>
</tr>
<tr>
<td>Postoperative gastritis</td>
<td>Ketorolac 30 and 60 mg</td>
<td>1.0</td>
<td>0.26–3.78</td>
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</table>

<table>
<thead>
<tr>
<th>Group by Comparison</th>
<th>Study name</th>
<th>Comparison</th>
<th>Outcome</th>
<th>Difference in means</th>
<th>Standard error</th>
<th>Variance</th>
<th>Lower limit</th>
<th>Upper limit</th>
<th>Z-Value</th>
<th>P-Value</th>
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<tr>
<td>30mg</td>
<td>Gabbot 1</td>
<td>30mg</td>
<td>opioid</td>
<td>−8.300</td>
<td>4.694</td>
<td>16.789</td>
<td>−16.294</td>
<td>−0.296</td>
<td>−2.032</td>
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<td>30mg</td>
<td>Gabbot 3</td>
<td>30mg</td>
<td>opioid</td>
<td>−5.609</td>
<td>3.893</td>
<td>15.152</td>
<td>−11.029</td>
<td>2.229</td>
<td>1.387</td>
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<td>30mg</td>
<td>Murrey</td>
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<td>opioid</td>
<td>−6.808</td>
<td>4.402</td>
<td>16.215</td>
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a Weighted mean difference.
b Odds ratio.

### Meta Analysis

**Figure 6.** Pooled data evaluating the effect of ketorolac dose on opioid consumption (IV morphine equivalents) compared with placebo. Data evaluated using a random-effects model. Weighted mean difference for individual study represented by square on Forest plot with 95% confidence interval of the difference shown as solid line. Larger sized square and thicker 95% confidence interval line denote larger sample size. The diamond represents the pooled estimate and uncertainty for the effects of the 30- and 60-mg doses of ketorolac, respectively.

**Figure 7.** Opioid-sparing effect of ketorolac funnel plot assessing publication bias. Plotted is the standard error (SE) versus weighted mean difference (effects). Vertical line is the combined effect for early pain with diagonal lines representing the expected 95% confidence interval from the combined effect. Studies outside the funnel indicate heterogeneity. Egger regression suggests absence of asymmetry (P = 0.23, 1-sided).
It is conceivable that by promoting greater patient comfort in the immediate postoperative period, the administration of a single dose of systemic ketorolac would result in faster hospital discharge. We were unable to demonstrate that effect in our analysis. The studies involved in our analysis did not measure time to meet hospital discharge criteria but did measure the actual hospital discharge time. Not using validated discharge criteria has been considered a major reason for the inability to demonstrate an effect of better postoperative pain control in reducing hospital discharge time. The use of actual hospital discharge time was probably responsible for the high heterogeneity observed in our analysis.

Our analysis demonstrated a wide CI relative to a clinically significant difference of a single dose of ketorolac 30 mg to prevent postoperative pain; the studies included in the analysis did not involve the use of other non-opioid analgesic strategies and only examined the effect of a single dose of ketorolac administration. It is possible that 30 mg ketorolac, when used as part of a multimodal therapy in conjunction with other analgesics such as acetaminophen or when given as multiple doses, may reduce postoperative pain; however, further studies are necessary to confirm this assumption.

Our systematic review was not able to detect an increase in complications, including postoperative bleeding and gastrointestinal symptoms, caused by the use of ketorolac. Because only few studies reported on the incidence of these side effects, the analysis was limited by a low number of subjects per group. Cases of renal failure were also not reported by any of the studies. Despite the fact that 2 studies reported on abnormal bleeding effects of ketorolac, those reports were not based on objective laboratory information and they did not result in more meaningful outcomes such as the need for allogenic blood transfusion or surgical reoperation. Clinical investigations designed to examine the effect of single dose systemic ketorolac in increasing postoperative bleeding failed to detect a harmful effect. It is important to note the potential for increased side effects when higher doses of perioperative ketorolac (60 mg) are followed by other nonsteroidal antiinflammatory drugs during the postoperative period.

The findings of this systematic review are only valid when interpreted in light of its limitations. We included a diversity of surgical procedures, types of rescue analgesics, and described outcomes. Ideally, a meta-analysis would only include homogeneous studies with a similar group of patients. Different surgical procedures were used to optimize the number of subjects and to generalize our findings to different surgical settings. We attempted to minimize heterogeneity by only including trials using a single dose of systemic ketorolac and rejecting the ones using the drug in the postoperative period. Another potential limitation is that most trials had a small sample size and most were performed before the year 2000; since then, significant changes have occurred in the perioperative management of patients. The quality of included studies is an important factor to achieve reliable results in meta-analysis of small trials.47 The median Jadad score for the studies included in our systematic review was 4, indicating an overall good quality of the included studies.

Some areas for future research on the effect of a single dose of ketorolac as part of a multimodal strategy to prevent postoperative pain were identified by this systematic review. Large randomized trials, adequately powered to examine dose-response effects, are clearly needed. Studies examining the analgesic effects of both IV and IM 30-mg dose are also necessary. Further direct comparisons of the IM administration versus the IV administration are also warranted to confirm our findings. Because the effect of ketorolac seems to be more pronounced in the earlier postoperative period, studies examining ambulatory patients should include time to discharge using validated criteria such as the Post-Anesthetic Discharge Scoring System (PADSS) as one of the evaluated outcomes.48

In conclusion, systemic single dose ketorolac is an effective multimodal strategy to reduce postoperative pain. Benefits on postoperative analgesia and postoperative nausea and vomiting outcomes can be achieved by using a
DISCLOSURES

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Contribution: Conduct of the study, manuscript preparation.

Name: Honorio T. Benzon, MD.
Contribution: Conduct of the study, data analysis, manuscript preparation.

This manuscript was handled by: Spencer S. Liu, MD.

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