Ketorolac: Its Role as Part of a Multimodal Analgesic Regimen

Paul F. White, PhD, MD, FANZCA,*† Johan Raeder, MD, PhD,†§ and Henrik Kehlet, MD, PhD‖

It is well known that effective perioperative analgesia facilitates the rehabilitation process, improves patient satisfaction, and reduces the length of the hospital stay. Ketorolac, a highly cost-effective parenterally active nonsteroidal antiinflammatory drug (NSAID), is frequently administered during and after surgery as part of a multimodal analgesic regimen to improve pain management after both major and minor surgical procedures. The opioid-sparing effects of ketorolac can facilitate the recovery process by improving pain management and reducing opioid-related side effects (e.g., nausea, vomiting, constipation, urinary retention, cardiorespiratory depression, pruritus, and sleep disturbances).[1]

As clinicians and experienced clinical investigators in this field, we were surprised with some of the results of the meta-analysis by De Oliveira and colleagues[2] relating to the preventative use of ketorolac, described in the current issue of *Anesthesia & Analgesia*. These authors reported that there was a lack of evidence in the literature that the 30-mg dose of ketorolac offered significant benefits on clinical pain outcomes when administered for the prevention (versus treatment) of postoperative pain. This is particularly surprising because it is well established that ketorolac is effective in treating pain and most experts believe it is more difficult to treat than to prevent pain. Furthermore, these authors concluded that IM administration of ketorolac was superior to IV.

The conclusion relating to the lack of efficacy of a 30-mg dose of ketorolac for preventing pain can be questioned because some of the studies included in the meta-analysis were "underpowered" to demonstrate a difference and additionally, active comparator-controlled clinical studies were not included in their analysis. The conclusion regarding IV versus IM administration of ketorolac can be criticized because none of the cited studies directly compared these 2 routes of administration.

We are concerned that these controversial findings may discourage practitioners from using ketorolac during the perioperative period, and lead to an increase in the use of opioid analgesics for postoperative pain management.[3] It is important to point out that many well-controlled studies demonstrating the value of administering one or more doses of ketorolac during and/or after surgery in doses ranging from 10 to 60 mg as part of a multimodal analgesic regimen did not qualify for inclusion in this meta-analysis.[2] For example, a treatment study by Cepeda et al.[4] that included more than 1000 patients (350 of whom received a 30-mg dose of ketorolac) was excluded from this analysis. The latter investigators reported that adding ketorolac, 30 mg IV, to an analgesic regimen for treating postoperative pain reduced morphine "rescue" dose requirements and opioid-related side effects in the early postoperative period. Whereas a single dose of ketorolac may be effective for preventing pain after minor (ambulatory type) surgery, optimal use of ketorolac for pain management after major surgery typically involves the use of multiple doses of the parenteral NSAID as part of a multimodal analgesic regimen.

WHY WOULD A META-ANALYSIS INVOLVING THE USE OF KETOROLAC FOR PERIOPERATIVE PAIN MANAGEMENT PRODUCE THESE CONTROVERSIAL FINDINGS?

The purpose of a meta-analysis is to shed light on evidence that may not be apparent by pooling data from many studies into one large mega study with greater statistical power to detect significant differences. The idea is of value when there are many small studies that have been performed in a similar manner and examined the same types of clinical outcomes. In the current meta-analysis, which was restricted to the preventative use of ketorolac versus placebo,[2] only 13 studies with 782 patients met the authors' inclusion criteria, with a total of 430 patients receiving ketorolac. Of the 13 studies included in this analysis, only 5 had more than 40 patients in the ketorolac treatment group, and an even smaller number of studies could be used for each of the specific clinical outcomes that were examined. For example, movement-related pain was not examined in any of the studies, bleeding and discharge time were addressed in only 2 studies, and time to discharge (home) readiness was not reported in any of the cited studies. Of

From the *Department of Anesthesia, Cedars-Sinai Medical Center in Los Angeles, Los Angeles, California; †Research Unit of Anesthesia and Intensive Care, Rizzoli Orthopedic Institute, University of Bologna, Bologna, Italy; ‡Department of Anesthesiology, Oslo University Hospital–Ullevaal, Oslo; §University of Oslo, Oslo, Norway; and ‖Rigshospitalet Copenhagen University Hospital, Copenhagen, Denmark.

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Address correspondence to Paul F. White, PhD, MD, FANZCA, White Mountain Institute, 144 Ashby Lane, Los Altos, CA 94022. Address e-mail to paul.white@cshs.org.

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the 3 studies[3] that included ketorolac 30 mg IV, a total of 95 patients received ketorolac in a preventative or "prophylactic" manner (compared with 66 patients who received a placebo). When analgesic drugs are given prophylactically, some patients will receive the drug even though they do not need it and therefore, much larger group sizes are typically needed to avoid a type-2 statistical error.

In this editorial, we have examined the literature regarding the efficacy of smaller doses (<30 mg) of this parenterally active NSAID, including studies that compared this dose with other analgesics administered for pain prophylaxis. Many early placebo-controlled clinical studies demonstrated that ketorolac, 60 to 90 mg IV/IM, possessed potent analgesic and opioid-sparing properties. However, concerns about potential side effects (e.g., bleeding at the wound site, renal dysfunction, and problems with bone and wound healing) led many surgeons to express concerns regarding its use during and after surgical procedures.[5] Therefore, we also examined the peer-reviewed literature related to the safety of this drug when used during the perioperative period.

IS THE ADMINISTRATION OF A SMALLER DOSE OF KETOROLAC (<60 mg) CLINICALLY EFFECTIVE IN THE PERIOPERATIVE PERIOD?

Ng et al.[6] found that ketorolac (30 mg IV) was more effective in reducing early postoperative pain than the cyclooxygenase type-2 (COX-2) inhibitor parecoxib (40 mg IV) when these 2 NSAIDs were given at induction of anesthesia in women undergoing laparoscopic sterilization. Similarly, Lenz and Raeder[7] reported that ketorolac 30 mg IV given after induction of anesthesia resulted in significantly less postoperative pain and opioid consumption during the first 4 hours after surgery compared with the long-acting COX-2 inhibitor etoricoxib 120 mg per os given immediately before surgery. In another study involving hernia repair, Thagaard et al.[8] showed the superior analgesic efficacy of ketorolac 30 mg IV compared with the glucocorticosteroids betamethasone and dexamethasone for ambulatory surgery. When the analgesic efficacy of IV ketorolac (15 or 30 mg) was compared with propacetamol (2 g) in a double-blind, placebo-controlled study involving patients undergoing total hip or knee replacement procedures,[9] both of these non-opioid analgesics were found to be superior to the placebo (saline) in treating moderate to severe pain in the postoperative period. Furthermore, Chow et al.[10] evaluated ketorolac, 15 to 30 mg IV every 6 hours, as an adjunct to opioid analgesics for perioperative pain control in patients undergoing laparoscopic urologic surgery. These investigators concluded that ketorolac improved pain control without adversely affecting surgical blood loss or renal function compared with the placebo-treated group. Similarly, DiBlasio et al.[11] compared postoperative pain control with ketorolac and opioids with opioids alone in patients undergoing partial nephrectomy and found that patients receiving parenteral ketorolac demonstrated superior postoperative recovery with an earlier return to solid diet and earlier discontinuation of patient-controlled analgesia.

In a randomized, double-blind, placebo-controlled study by Varrassi et al.[12] assessing the analgesic efficacy and safety of perioperative ketorolac, 30 mg for premedication followed by a continuous infusion of ketorolac, 2 mg/h, during and after upper abdominal surgical procedures, these investigators found that ketorolac improved pain scores and reduced plasma cortisol concentrations without adversely affecting operative blood loss, glucose concentration, and renal or hemostatic function. Overall, the ketorolac group had fewer adverse effects than the control group. In another study evaluating the comparative effects of ketorolac versus bupivacaine when used to supplement opioid-based epidural analgesia after thoracic surgery, Singh et al.[13] found that ketorolac (30 mg IV every 6 hours) reduced postoperative pain and the opioid analgesic requirement comparably to the local anesthetic. However, ketorolac had greater beneficial effects on pulmonary function after these thoracotomy procedures. Stahlgren et al.[14] reported that after abdominal hysterectomy or cholecystectomy procedures, the times to first bowel movement, walking without assistance, and first oral fluids were significantly shorter after IM ketorolac (30 mg followed by 10 mg every 6 hours) compared with meperidine 100 mg IM followed by acetaminophen/codeine (600 mg/60 mg per os). Furthermore, patients receiving ketorolac had lower nursing utilization scores and achieved a higher level of functioning than patients receiving opioid analgesics during the first 3 postoperative days. In addition, the times to first bowel movement, walking without assistance, and first oral fluids were significantly shorter in the ketorolac group. The administration of IV ketorolac, 30 to 60 mg followed by 15 to 30 mg every 6 hours IV, during the first 24 hours after major urologic surgery significantly enhanced postoperative pain relief and reduced the need for supplemental IV opioid analgesics without adversely affecting the incidence of side effects when compared with a placebo-treated group.[15]

Interestingly, even smaller doses of ketorolac (10–20 mg) were effective when administered as adjuvants to lidocaine for IV regional anesthesia or "Bier block" procedures. Investigators have reported that these small "preventative" doses of ketorolac improve both intra- and postoperative analgesia without increasing side effects (e.g., wound hematomas) after IV regional anesthesia.[16,17]

DOES ADJUNCTIVE USE OF KETOROLAC INCREASE POSTOPERATIVE COMPLICATIONS?

One of the major issues related to the perioperative use of ketorolac has been concern about its potential for producing gastrointestinal (GI), renal, and bleeding complications that have been associated with long-term administration of NSAIDs. Ketorolac (and other NSAIDs) has been alleged to have undesirable effects on a variety of postoperative outcomes including bleeding at both the operative site and the GI tract, interference with wound and bone healing, and renal dysfunction. What is the evidence, if any, regarding the occurrence of these side effects after a single or limited number of doses of ketorolac when administered during the perioperative period?

Interestingly, the only side effect that has been documented to occur with single-dose or short-term administration of ketorolac is increased operative-site bleeding after

surgical procedures with "raw" surface areas (e.g., tonsillectomy, adenoidectomy, total joint replacements, and major plastic surgery).[18] A prospective study by Rusy et al.[19] found that blood loss was significantly higher in tonsillectomy patients receiving ketorolac 0.9 mg/kg (blood loss of 2.67 mL/kg) compared with the acetaminophen 30 mg/kg (blood loss of 1.44 mL/kg). Hemostasis during tonsillectomy was also reportedly significantly more difficult to achieve in patients receiving ketorolac. Similar findings have been reported when ketorolac was compared with opioid analgesics.[20,21] In a retrospective chart review conducted by Gallagher et al.[22] involving patients undergoing tonsillectomy with or without adenoidectomy, the incidence of postoperative hemorrhage among patients who received ketorolac was 10.1% compared with 2.2% in those patients who received only opioid analgesics. Moreover, in a retrospective cohort study by Chin et al.[23] involving patients undergoing thyroid surgery, there was a nonsignificant increase in the incidence of hematomas in patients receiving ketorolac (2.7% vs 1.3%). Fragen et al.[24] reported a 6% greater decrease in the hematocrit on the first postoperative day after total knee arthroplasty in patients who received ketorolac 30 mg IV (compared with the placebo group); however, the difference was not clinically important with respect to the need for blood transfusion or subsequent hematocrit values measured during the postoperative period.

Of importance, studies that have reported significant increases in blood loss after administration of ketorolac have typically given the drug "preemptively" (i.e., before the surgical incision) or before achieving "primary" hemostasis during the operation. Given the fact that surgical hemostasis is dependent on platelet function for procedures involving a higher risk of operative-site bleeding, the initial dose of ketorolac should be administered near the end of surgery after the surgeon has achieved hemostasis. There are no controlled studies in the peer-reviewed literature demonstrating an increase in blood loss during or after surgery when standard doses of ketorolac were administered at the end of surgery or in the early postoperative period.

The overall associations between ketorolac use and both GI bleeding and operative-site bleeding are not very strong.[25,26] Strom et al.[25] reported that lower doses of ketorolac (<90 mg/24 hours) for fewer than 5 days had no significant bleeding side effects. Although routine use of ketorolac after cardiac surgery has been limited because of concerns of potential bleeding complications, a study by Gupta et al.[27] found that ketorolac could be successfully used to treat pain after congenital heart surgery without an increased risk of either GI or operative-site bleeding. Even a 60-mg dose of ketorolac administered during anorectal surgery procedures failed to increase blood loss, wound hematomas, or bleeding with bowel movements.[28] As expected, the bleeding risk associated with ketorolac is higher when it is administered in higher doses (>120 mg/d) to older patients (aged >75 years) for more than 5 consecutive days.[26] Although the concomitant use of anticoagulants increases the risk of surgical-site bleeding with all NSAIDs, a large randomized, comparative trial found no difference in bleeding outcomes with ketorolac, diclofenac, or ketoprofen.[29]

For many years, there has been an ongoing debate about the relative safety of NSAIDs, including ketorolac, on bone healing after spinal fusion surgery. However, a meta-analysis of the literature revealed that there was no increased risk of nonunion with NSAID exposure when only the highest-quality studies were assessed.[30] A recent literature review by Li et al.[31] revealed that short-term (<14 days) exposure to normal doses of NSAIDs (including ketorolac <120 mg/d) did not increase the risk of nonunion after spinal fusion surgery.

Although animal studies have suggested that high doses of all NSAIDs can adversely affect osteogenic activity and fracture healing, the retrospective review by Pradhan et al.[32] identified pseudarthrosis in 12 of 228 patients (5.3%) who received ketorolac after spine surgery compared with 11 of 177 patients (6.2%) who did not receive the parenteral NSAID. Busch et al.[33] investigated patients undergoing total knee arthroplasty who were randomized to receive an intraoperative periarticular injection containing a multimodal analgesic regimen with ketorolac or no periarticular injection. The patients who had received the periarticular injection of ketorolac used significantly less patient-controlled (opioid) analgesia, had higher patient satisfaction, and lower pain scores during the early postoperative period without any associated bleeding or wound-healing complications.

A literature review by Lee et al.[34] revealed that NSAIDs can produce a clinically unimportant transient reduction in renal function in the early postoperative period in patients with normal preoperative renal function. In the 14 trials specifically examining renal function, there were no reports of renal failure when ketorolac was administered for 5 days or fewer. However, when multiple doses are administered for more than 5 days, ketorolac may be associated with an increased rate of transient acute renal failure.[35] DiBlasio et al.[11] found no changes in acute renal function, blood loss, transfusion rates, or surgical complications in patients with renal cortical tumors undergoing partial nephrectomy procedures when ketorolac was administered as an adjuvant to opioid analgesics in the postoperative period.

Of note, there is a single case series reported in which the authors suggested that the postoperative use of oral diclofenac (or a COX-2 inhibitor) was associated with an increased risk of anastomotic leakage after colorectal surgery.[36] However, these findings have not been duplicated, and there are no data to support this complication in studies involving the use of ketorolac or any other nonselective NSAID.

Finally, regarding common side effects such as postoperative nausea and vomiting,[37,38] constipation/ileus,[39] and cardiorespiratory depression,[40] ketorolac offers significant advantages over the parenteral opioid analgesics. For example, compared with the potent, short-acting opioid analgesics, ketorolac administered intraoperatively exerted no adverse effects on cardiorespiratory functions (i.e., no changes in heart rate, arterial Pco_2, or mean arterial blood pressure, and no associated apnea) while providing for

superior postoperative analgesia.[40] In a recent study involving cardiac surgery patients undergoing revascularization procedures,[41] use of ketorolac was associated with a lower rate of angiographically proven graft closure and suggests a possible explanation for the previously reported survival benefit in patients receiving ketorolac after coronary artery bypass graft surgery.[42] Another unexpected benefit of the perioperative use of ketorolac was reported in patients with breast cancer; a recent retrospective analysis by Forget et al.[43] suggested that intraoperative administration of ketorolac can decrease the risk of breast cancer relapse compared with using opioid alone during surgery.

In summary, ketorolac clearly remains a valuable adjuvant as part of a multimodal analgesic regimen for the management of pain in the perioperative period.[44] Both IV and IM doses of ketorolac are safe and effective in the vast majority of elective surgical patients when administered as an analgesic adjuvant during the perioperative period. The potential benefits of using ketorolac clearly "outweigh" any potential disadvantages in most surgical patients. The short-term use of recommended doses of ketorolac does not increase postoperative complications except for the increased risk of operative-site bleeding in high-risk operations (e.g., tonsillectomy). It is important to remember the old adage that the "lack of evidence of effect" is not the same as "evidence of lack of effect."

DISCLOSURES

Name: Paul F. White, PhD, MD, FANZCA.
Contribution: This author helped write the manuscript.
Name: Johan Raeder, MD, PhD.
Contribution: This author helped write the manuscript.
Name: Henrik Kehlet, MD, PhD.
Contribution: This author helped write the manuscript.
This manuscript was handled by: Spencer S. Liu, MD.

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