Comparison of Morphine, Ketorolac, and Their Combination for Postoperative Pain

Results from a Large, Randomized, Double-blind Trial

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Background: Meta-analyses report similar numbers needed to treat for nonsteroidal antiinflammatory drugs (NSAIDs) and opioids. Differences in baseline pain intensity among the studies from which these numbers needed to treat were derived may have confounded the results. NSAIDs have an opioid-sparing effect, but the importance of this effect is unclear. Therefore, the authors sought to compare the proportions of subjects who obtain pain relief with ketorolac *versus* morphine after surgery and to determine whether the opioid-sparing effect of an NSAID reduces the magnitude of opioid side effects.

Methods: The study was a double-blind, randomized controlled trial. The authors randomly assigned 1,003 adult patients to receive 30 mg ketorolac or 0.1 mg/kg morphine intravenously. They calculated the proportion of subjects who achieved at least 50% reduction in pain intensity 30 min after analgesic administration. Further, so long as pain intensity 30 min after analgesic administration was 5 or more out of 10, patients received 2.5 mg morphine every 10 min until pain intensity was 4 or less out of 10. The authors assessed the presence of opioid-related side effects.

Results: Five hundred patients received morphine and 503 received ketorolac. Fifty percent of patients in the morphine group achieved pain relief, compared with 31% in the ketorolac group (difference, 19%; 95% confidence interval, 13–25%). The ketorolac–morphine group required less morphine (difference, 6.5 mg; 95% confidence interval, −5.8 to −7.2) and had a lower incidence of side effects (difference, 11%; 95% confidence interval, 5–16%) than the morphine group.

Conclusions: Opioids are more efficacious analgesics than NSAIDs, although historic data for these two drugs yield similar numbers needed to treat. Adding NSAIDs to the opioid treatment reduces morphine requirements and opioid-related side effects in the early postoperative period.

META-ANALYSES of randomized, double-blind, single-dose studies that evaluate opioids and nonsteroidal antiinflammatory drugs (NSAIDs) for acute postoperative pain have

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yielded overlapping numbers needed to treat (NNTs) for NSAIDs and opioids.[1–3] The NNT is a measure of the effect size of a treatment that can be used to rank treatments on the basis of effectiveness.[4] The NNTs to achieve at least 50% pain relief over 4–6 h with a single dose of the following drugs are 2.7 for 400 mg oral ibuprofen (95% confidence interval [CI], 2.5–3.0),[1] 2.6 for 30 mg intramuscular ketorolac (95% CI, 2.3–3.1),[2] and 2.9 for 10 mg intramuscular morphine (95% CI, 2.6–3.6).[3] These NNTs mean that of three patients exposed to any of these medications, one will achieve at least 50% pain relief over 4–6 h. These results contrast with clinical experience and consensus recommendations that opioids are more effective than NSAIDs for moderate-to-severe acute pain.[5,6]

The discrepancy between clinical experience and the results of meta-analyses could be due to the fact that the studies that served as a basis to estimate NNTs for opioids and NSAIDs did not directly compare agents in these two classes. Instead, in such studies, NSAIDs and opioids have been compared with placebo. The result of this indirect comparison may overestimate the efficacy of NSAIDs. The validity of the adjusted indirect comparisons depends on the internal validity and similarity of the included trials.[7] Therefore, differences in baseline pain intensity of subjects enrolled in the studies could have confounded the results because the higher the baseline pain intensity is, the greater the decrease in pain intensity must be to obtain a similar degree of pain relief.[8]

The use of both NSAIDs and opioids concurrently for the treatment of acute pain is common practice. Adding an NSAID to an opioid regimen reduces opioid requirements, which could lead to a decrease in opioid-related side effects. A key weakness of the evidence for such practical benefit, based on studies that have evaluated the opioid-sparing effect of NSAIDs, is that they were not designed to detect a difference in the incidence and severity of side effects. To detect a difference in side effects between treatment groups, in general, larger numbers of patients are needed than simply to evaluate analgesia or opioid requirements.

Therefore, we designed a large study, first to compare the analgesic efficacy of an NSAID and an opioid in a head-to-head trial by determining the proportion of subjects who obtained adequate postoperative pain relief 30 min after analgesic administration, and second to determine whether the opioid-sparing effect of NSAIDs decreases the risk of opioid side effects, by comparing opioid requirements and

side effects in patients who received ketorolac plus morphine or morphine alone.

Materials and Methods

Patients

This study was approved by the Institutional Review Board of San Ignacio Hospital (Bogota, Colombia), a tertiary care university teaching hospital. Individuals who agreed to participate provided written informed consent before surgery. We recruited patients from May 2003 until November 2003. Patients aged between 18 and 60 yr who underwent surgical procedures were potentially eligible for the study. We excluded subjects older than 60 yr because in this population, it is necessary to decrease the dose of opioids to reduce the likelihood of side effects.[9] Patients were ineligible if they were pregnant, had asthma, were allergic to NSAIDs, had a history of gastric ulcer or abnormal renal function, had received NSAIDs 6 h before surgery or during surgery, had a history of long-term opioid use, had received an opioid within 5 days before surgery, or had postoperative hemodynamic instability, *e.g.*, due to intraoperative blood loss.

We placed no restrictions on the type of anesthetic or other intraoperative medication except that the use of NSAIDs was not allowed and that fentanyl was the only opioid permitted. The intraoperative dose of fentanyl used, if any, was recorded.

Assignment

We conducted a randomized, double-blind, controlled trial. In the postanesthesia care unit, we randomly assigned patients who reported pain of at least moderate intensity to receive ketorolac or morphine. To ensure that the number of subjects with moderate to severe pain intensity was similar in each treatment arm, we performed a stratified randomization, using a computer-generated random number program.

The randomization was concealed; the operating room pharmacy was in charge of treatment assignment, preparation of the solutions, and handing the corresponding solution to the evaluator.

Intervention

When patients arrived in the postanesthesia care unit, we asked them to describe their pain as none, mild, moderate, or severe. Patients were randomized if their pain intensity was at least "moderate." The analgesic infusion of 30 mg intravenous ketorolac or 0.1 mg/kg morphine over 3–5 min then began, from the start of which we asked patients to rate their pain intensity at rest on a 0–10 numerical rating scale, where 0 represents no pain and 10 represents the worst pain imaginable, every 10 min.

If the pain intensity 30 min after initiation of the analgesic infusion was 5 or higher, patients in both groups received a bolus of 2.5 mg intravenous morphine every 10 min until their pain intensity was 4 or less. Therefore, one group received only morphine for postoperative analgesia (morphine group) and the other group received ketorolac followed by morphine (ketorolac–morphine group).

Simultaneously with the pain intensity evaluation, patients rated their pain relief using a five-point Likert scale that ranged from no relief to complete pain relief. We documented the number of rescue doses required in each group.

The dose of ketorolac is that recommended by the manufacturer,# and the dose of morphine is that commonly used for pain relief and in pharmacokinetic studies.[10-12] In addition, this morphine dose is within the dose range (6–10 mg) used in studies that evaluate the equipotency of ketorolac.[13-18]

Masking

Clinical evaluations were done by observers who were blinded to patient assignment. The evaluators received the solutions from the pharmacy personnel in 100-ml normal saline bags that were identical in appearance. Each solution was infused over 3–5 min. The randomization code was kept concealed in the operating room pharmacy.

Sample Size

The study was powered (500 patients/group) to detect a 10% intergroup difference in the proportion of patients who achieved at least 50% decrease in initial pain intensity, with an α level of 0.05 (two tailed) and a β level of 0.9. We assumed, based on a published meta-analysis,[3] that 46% of the subjects in the morphine group would achieve at least a 50% decrease in pain intensity, and we hypothesized that 36% of subjects in the NSAID group would achieve this degree of relief.

The enrollment of 500 patients/group also permitted us to detect, with 80% power, a 5% difference in the incidence of a side effect with prevalence as low as 10%, such as would be the case with pruritus.[19] For more common side effects such as sedation, nausea, vomiting, and dizziness, the study was overpowered.

Assessment of Outcomes and Study Procedure

The primary outcome was the proportion of subjects who reported a 50% decrease in pain intensity 30 min after the initiation of the intravenous infusion.

We chose a threshold pain intensity decrement of 50% because this value has been extensively applied to evaluate pain treatments and to estimate NNTs[2] and represents a clinically meaningful decrease in pain intensity from the patients' point of view.[8]

We chose to evaluate the analgesic response at 30 min because ketorolac and morphine not only have a similar onset of analgesic action—time to peak plasma concen-

tration for 30 mg intravenous ketorolac is around 5 min# and that for morphine is 10 min[20]—but also a similar first-order rate constant K_{eo} (15–20 min for both ketorolac[21] and morphine[22]). K_{eo} determines the equilibration of drug between plasma and effect site; the effect site concentrations determine the pharmacodynamic effects. This pharmacokinetic similarity is confirmed by the fact that the analgesic effects of both ketorolac#[21] and morphine are observed at this time period.[11,22] In addition, the evaluation at 30 min is clinically relevant and reflects clinical judgment—that it would be unethical and impractical to delay supplemental analgesic therapy by more than 30 min after patients have received an initial therapeutic dose of an analgesic.

Evaluation of Side Effects

Simultaneously with pain intensity, patients evaluated the presence and severity of sedation, nausea, vomiting, pruritus, and dizziness as absent, mild, moderate, or severe. We recorded the number of episodes of vomiting and instances of antiemetic therapy.

Statistical Analysis

We conducted an intention-to-treat analysis. For analgesic effectiveness, we calculated the proportion of subjects who reported a 50% or greater decrease in pain intensity 30 min after the initiation of the intravenous analgesic infusion. The percentage of pain reduction was calculated as 100 times the difference between pretreatment and posttreatment pain intensity, divided by the pretreatment pain intensity.[23] In addition, we calculated risk differences and the NNT for analgesia,[24] along with 95% CIs.

To evaluate the effects of sex and baseline pain intensity on the odds of having 50% or greater decrease in the numerical rating scale, we applied a logistic regression model. This model included these variables as well as the interaction between treatment and baseline pain intensity to determine which of the two analgesics was more efficacious in relation to baseline pain intensity.

In addition to pain relief, we assessed whether pain intensity differed between the morphine and ketorolac–morphine groups, using a linear regression. Because each patient had multiple evaluations (until pain intensity was $\leq$ 4 out of 10) and these measures were not independent, we used an analysis of repeated measures using generalized estimating equations. That method takes this lack of independence into consideration by adjusting the standard errors.[25]

To determine whether there was a difference in opioid requirements between the groups, we used a robust linear regression, because the total dose of morphine

had outliers (patients with unusually high requirements). Robust regression does not assume normality and minimizes the impact of influential observations; it produces valid and more efficient estimates than the traditional linear regression.[26] It assigns less weight to observations that have larger residuals or observations that are very influential.[27] This technique has been previously used in the analysis of analgesic studies.[28,29]

To determine whether opioid requirements were different in men and women, we estimated the dose of morphine in milligrams per kilogram according to sex and performed a robust linear regression.

To evaluate side effects, we created a variable that summarized the presence of *any* side effect during the duration of the study and estimated the 95% CI for the difference in proportions. Because the overall incidence of any adverse effect differed significantly between the groups, we compared each side effect. We also estimated the number needed to harm as an index of the safety and tolerability of a medication and the 95% CI.

The sample size calculations, randomization, and analyses were performed with STATA® software version 7SE (College Station, TX). *P* values less than 0.05 were considered statistically significant.

Results

We followed the CONSORT guidance for reporting results.[30] We randomized 1,003 patients. Five hundred subjects received morphine, and 503 received ketorolac. There were no protocol violations, and all patients were included in the analyses (fig. 1).

Demographic characteristics, duration and type of surgery, type of anesthesia, intraoperative fentanyl, and baseline pain intensity were similar in both groups. Fifty-eight percent of patients had severe pain at the start of the infusion (table 1).

Pain Relief

Fifty-nine percent of all subjects did not achieve a 50% or greater decrease in pain intensity. The probability of not achieving 50% or more of pain relief increased when the initial pain intensity was severe (table 2).

Morphine provided a superior analgesic effect to ketorolac for patients with both moderate and severe pain (table 2). Fifty percent of the subjects in the morphine group achieved a 50% or greater decrease in pain intensity *versus* 31% in the ketorolac group. Therefore, the difference in the proportion of patients who achieved a 50% decrease in pain intensity was 19% (95% CI, 13–25%), which corresponds to an NNT of 5 (95% CI, 4–10).

The degree of pain relief was also higher in the morphine group. Forty-nine percent of the subjects in the morphine group reported at least "much improvement," in contrast with the ketorolac group, in which 39%
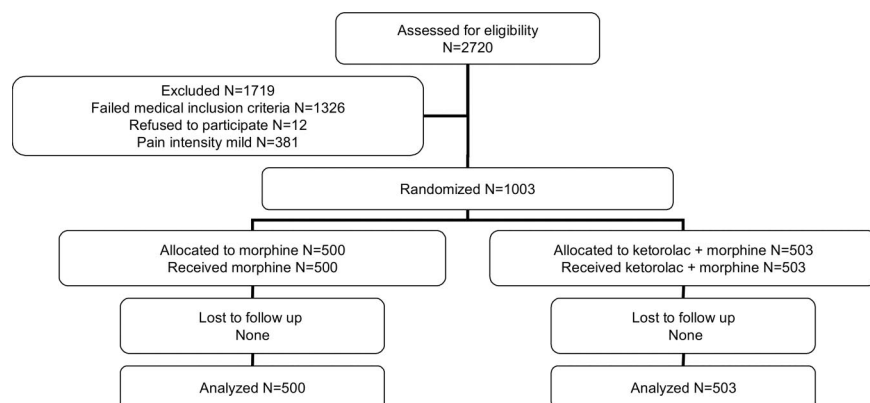
Fig. 1. Flow diagram of the phases of the study.

of the subjects reported at least "much improvement" ($P = 0.005$).

Effect of Sex and Baseline Pain Intensity

Patient sex did not affect the odds of having adequate pain relief (odds ratio = 1.0; 95% CI, 0.7–1.3). Baseline pain intensity was a good inverse predictor of having at least a 50% or greater decrease in pain intensity. That is, if the baseline pain intensity was severe, the odds of having a 50% decrease in pain intensity were lower than when the pain was moderate (odds ratio = 0.4; 95% CI, 0.3–0.5). The interaction between baseline pain intensity and analgesic treatment was not significant ($P = 0.2$).

Pain Intensity throughout the Duration of the Study

Pain intensity was higher in the ketorolac–morphine group during the first 30 min after analgesic administration (when patients in this group had received only

ketorolac). The difference was 1.0 unit (95% CI, 0.5–1.6). Afterward, pain intensity was similar in both groups (intergroup difference = 0.1 units; 95% CI, −0.4 to 0.2]) (fig. 2).

Opioid Requirements

Opioid requirements in each group are displayed in table 3. The morphine group required more morphine to achieve the desired pain intensity levels than did the ketorolac–morphine group (table 3). This estimate includes the 0.1-mg/kg dose given at the outset of the protocol for the morphine group. The intergroup difference in morphine requirements was 6.5 mg (95% CI, 5.8–7.2).

Dose Response

As morphine consumption increased, the risk of development of any side effects also increased (fig. 3). For

Table 1. Characteristics of the Subjects Evaluated

Characteristic	Ketorolac–Morphine (n = 503)	Morphine (n = 500)
Age, mean ± SD, yr	37.4 ± 11.0	38.2 ± 11.6
Weight, mean ± SD, kg	65.8 ± 11.5	65.4 ± 12.3
Height, mean ± SD, cm	164.0 ± 8.6	163.5 ± 8.8
Sex, % male	52.8	47.2
Dose of fentanyl, mean ± SD, μg	167.1 ± 65.2	165.9 ± 67.9
Type of anesthesia, %		
General anesthesia	92.2	92.8
Regional anesthesia	5.8	5.6
General plus regional	2.0	1.6
Duration of surgery, mean ± SD, min	113.8 ± 72.3	108.6 ± 70.8
ASA I or II, %	96.6	97.2
ASA III, %	3.4	2.8
Type of surgery, %		
Abdominal surgery	48.5	48.8
Orthopedic surgery	22.3	22.4
Craniofacial surgery	15.5	14.4
Thoracic surgery	9.7	10.4
Spinal surgery	3.9	4.0
Baseline numerical rating scale pain intensity (0–10), mean ± SD	7.9 ± 2.0	7.9 ± 1.9
Median numerical rating scale score for self-rated "moderate pain"	6	6
Moderate pain, %	41.8	41.9
Median numerical rating scale score for self-rated "severe pain"	9	9.5
Severe pain, %	58.2	58.1

ASA = American Society of Anesthesiologists (physical status classification).

Table 2. Pain Relief in the Morphine and Ketorolac Groups by Pain Intensity

Baseline Pain Intensity		Morphine	Ketorolac–Morphine	Total (%)
All patients	Pain relief	250	156	406 (40.5)
	No pain relief	250	347	597 (59.5)
	Total	500	503	1003
	Risk of having pain relief	0.5	0.31	0.40
	Risk difference		0.19 (95% CI, 0.13–0.25)	
Moderate	Pain relief	131	88	219 (52.1)
	No pain relief	79	122	201 (47.9)
	Total	210	210	420
	Risk of having pain relief	0.62	0.42	0.52
	Risk difference		0.2 (95% CI, 0.11–0.30)	
Severe	Pain relief	119	68	187 (32.1)
	No pain relief	171	225	396 (67.9)
	Total	290	293	583
	Risk of having pain relief	0.41	0.23	0.32
	Risk difference		0.18 (95% CI, 0.10–0.25)	

CI = confidence interval; pain relief = at least a 50% decrease in initial pain intensity.

each 1-mg increment of morphine consumed, the risk of development of side effects increased 1.3% (95% CI, 1.3–1.4).

Sex Effect on Opioid Requirements and Side Effects

Women required more morphine than men to achieve a similar degree of pain relief. On average, women required 20% more morphine in milligrams per kilogram (95% CI, 8–34%). Women also had a 6% higher risk of development of side effects than men (relative risk = 1.06); however, this difference did not achieve statistical significance (95% CI, 0.97–1.16).

Side Effects at 30 Minutes of Evaluation (before Any Rescue Medication)

The proportion of patients who experienced any side effect by 30 min after the start of the initial analgesic infusion was 54% in the ketorolac–morphine group and 68% in the morphine group. Therefore, the difference in the proportion of subjects who exhibited any side effect

was 14% (95% CI, 8–20), which corresponds to a number needed to harm for morphine of 7 (95% CI, 5–12).

Side Effects throughout the Study

The incidence and severity of side effects was higher in the morphine group. The proportions of patients who experienced any side effect were 63% in the ketorolac–morphine group and 74% in the morphine group, so the absolute risk difference for development of any side effect was 11% lower in the ketorolac–morphine group than in the morphine group (95% CI, 5–16) (table 4). This difference corresponds to a number needed to harm for morphine compared with the combination of ketorolac–morphine of 9 (95% CI, 6–20).

Looking at each side effect, the morphine group had a higher incidence of sedation, dizziness, and pruritus. The occurrence of nausea/vomiting was similar in both groups (table 4).

Discussion

We found that morphine is a more efficacious analgesic than ketorolac. Our results showed that the NNT of ketorolac compared with morphine is 5, meaning that of 5 patients treated with ketorolac, 1 did not obtain adequate pain relief who would have experienced it had he or she received morphine.

How can we explain that morphine provided superior analgesia compared with ketorolac despite the fact that published NNTs for morphine and NSAIDs suggest sim-
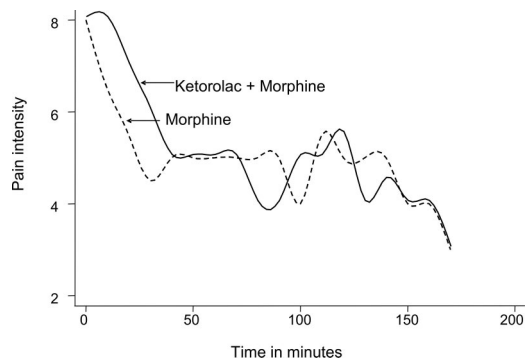

Fig. 2. Pain intensity throughout the duration of the study. Pain intensity was higher in the ketorolac–morphine group during the first 30 min after analgesic administration (when this group had received only ketorolac); the difference was 1.0 unit (95% confidence interval, 0.5–1.6). Afterward, pain intensity was similar in both groups; the difference was 0.1 units (95% confidence interval, −0.4 to 0.2).

Table 3. Morphine Requirements in the Two Experimental Groups

	Ketorolac–Morphine	Morphine	P Value
Mean ± SD, mg	4.5 ± 5.3	11.1 ± 6.2	0.00001
Median, mg	2.5	8.9	
Range, mg	0–27.5	0–42	

ilar analgesic efficacy? First, ketorolac and morphine were not directly compared in earlier calculations of NNT.[3,31,32] Arithmetically, the NNT is the inverse of the absolute risk reduction; therefore, changes in the baseline risk yield different NNTs.[33] In analgesic studies, the intensity of baseline pain could be analogous to the baseline risk. We found that if pain is severe, the probability of having pain relief is lower than when pain is moderate. Therefore, systematic differences in the baseline pain intensity among studies that evaluated NSAIDs and opioids could explain the discrepancy.

Second, the sample size of the trials included in the meta-analysis could also be a contributor. The calculation of the NNT for ketorolac was based on a total of only 176 patients.[2] Discrepancies in the results between small and larger trials are not uncommon[34,35] and can be explained by inclusion of patients with diverse baseline risks of experiencing the event of interest[34,36] or by the uneven allocation of these subjects in the small trials.[36,37] In the current study, we directly compared ketorolac and morphine, and included more than 1,000 subjects.

Third, the moment of evaluation also could explain why morphine was more efficacious than ketorolac. We evaluated pain intensity and pain relief 30 min after analgesic administration, not 4–6 h, as the studies that served for the NNT calculations did. Although the onset of action of ketorolac and morphine is similar, ketorolac has a longer half-life, 5–6 h, than morphine, 2–3 h. Last, we administered the medication intravenously, and many studies from which the NNTs were obtained used the intramuscular route. The evaluation at 30 min and the intravenous administration of analgesics are more appropriate for the treatment of acute postoperative pain of moderate or severe magnitude.

Various studies have compared ketorolac with strong opioids with conflicting results. The findings range from ketorolac being less effective than strong opioids[5,38–47] to being equally effective[13–16,18,48–54] or to being more effective than opioids.[55–58]

The studies that have reported no difference in the degree of analgesia have at most one fifth the number of subjects we studied, so differences between ketorolac and morphine could have been missed; in addition, very small doses of opioids (2–4 mg morphine or morphine equivalent) were used.[59–62] Of the studies in which ketorolac was more effective than morphine, two evaluated analgesia for renal colic.[55,56] Opioids produce tonic contraction of smooth muscle[57] and so may have a spasmogenic effect on ureteric activity,[63] possibly by inhibiting the release of nitric oxide.[64] On the contrary, NSAIDs have a spasmolytic effect[63] and therefore may be a superior choice for this kind of pain. The study that found ketorolac to be superior to morphine[58] included a total of 119 patients undergoing major surgery and allocated to three groups (10 and 30 mg ketorolac, and morphine). It is difficult to reconcile these varied findings with those of the current study.

The superior analgesic effect of morphine in our trial was balanced by an increased occurrence of side effects. The number needed to harm of morphine at 30 min of observation indicates that for seven patients treated with morphine, one will experience an adverse effect that would not have occurred if that patient had received ketorolac.

Nonetheless, to limit analgesics in the ambulatory setting only to NSAIDs, as has been suggested,[65] could result in inadequate pain relief, and pain by itself may produce nausea.[66] We found that adding an opioid to an NSAID regimen, if pain is not adequately controlled, led to a much lower opioid consumption. Although some authors have suggested that the opioid-sparing effect of NSAIDs does not have clinical importance,[67,68] we found that the reduction in opioid requirements was marked: 4.5 mg *versus* 11.1 mg. The confidence interval of this estimate indicates that the smallest decrease in opioid requirements that one could expect would be 48%, which is still a considerable reduction. A very recent systematic review that evaluated the morphine-sparing effect of acetaminophen combined with morphine patient-controlled analgesia found a 20% (9-mg) reduction in morphine requirement in 24 h.[69]

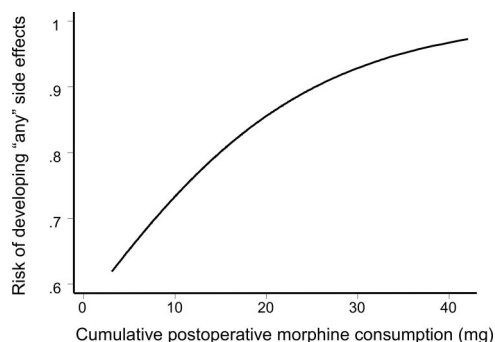As the dose of morphine increased, the risk of side

Fig. 3. As the dose of morphine increases, the risk of developing any side effect increases. For each 1-mg increment of postoperative morphine consumption, the risk of side effects increased by 1.3% (95% confidence interval, 1.3–1.4).

Table 4. Proportion of Subjects with Side Effects in the Two Groups throughout Follow-up

	Ketorolac–Morphine	Morphine	P Value
No side effects	36.4	26.2	0.007
Any side effect of mild intensity	45.9	53	
Any side effect of moderate intensity	9.5	11.2	
Any side effect of severe intensity	8.1	9.6	
Sedation	46.3	58.0	0.0001
Dizziness	28.2	35.2	0.018
Nausea	19.4	19.8	0.8
Vomiting	3.6	4.2	0.6
Pruritus	3.3	6.6	0.019
Antiemetic use	16.0	15.0	0.4

effects increased, a finding that echoes many (but not all) of the conclusions of a recent meta-analysis by Marret *et al.*[70] that assessed the morphine-sparing effect of NSAIDs in 22 trials enrolling 2,307 patients. Other research largely confirms these findings and likewise supports the existence of a dose–response relation for postoperative opioid adverse effects.[9] Therefore, it is not surprising that the reduction in opioid requirements was associated with a clinically important reduction in opioid side effects. Such a finding is a principal benefit of multimodal analgesia,[71] which is now advocated in numerous clinical practice guidelines on acute pain management.[72]

We found that the combination of ketorolac and morphine decreased the occurrence of opioid-related side effects, including pruritus. However, we did not find any difference in the incidence of nausea/vomiting between the groups. This last finding contrasts with the meta-analysis by Marret *et al.*[70] Possible explanations for this difference are the short window of observation and that our patients were not yet mobilized. It is believed that movement increases the likelihood of nausea/vomiting after opioid exposure. In addition, patients received antiemetic therapy if, at arrival in the postanesthesia care unit, they reported moderate or severe nausea or were vomiting. The prescription of antiemetics could have hindered detection of any difference, but we, as others, considered it inappropriate to withhold routine symptomatic treatment because patients were participating in the study.[73,74]

We found that women required more morphine to achieve a similar degree of analgesia than did men. This result confirms previous findings.[29] However, women did not exhibit more side effects than men, as has also been reported.[9] Still, the confidence interval of our estimate is wide, and so we cannot rule out the presence of sex differences.

The duration of follow-up in the current study was short, and this limitation deserves discussion. We do not know whether the magnitude of the opioid-sparing effect and the decrease in opioid side effects are persistent. In addition, we did not consider the toxicity of repeated NSAID administration, such as gastrointestinal toxicity, operative site bleeding, or renal dysfunction, which are major clinical concerns during postoperative pain management.[75]

Although the use of broad inclusion criteria and unrestricted use of anesthetic techniques in this trial could be criticized, we see this inclusiveness as a strength. We designed a pragmatic trial that emulated the conditions in which the results would be applied.[76] A trial with these characteristics assures the generalizability and usefulness of the results, and it does so without compromising scientific rigor. The randomization, masked allocation, and large sample size of this study assure group balance so that risk factors for greater or lesser analgesic

responses or for development of side effects are similarly distributed and therefore would not bias the results.

In summary, clinicians should be aware of the superior analgesic properties of morphine compared with ketorolac, despite the fact that historic data for these two drugs yield similar NNTs. There is a trade-off, however, in that one of seven patients treated with morphine will experience an adverse effect that would not have occurred if that patient had received ketorolac. The addition of a strong opioid to an NSAID decreases the risk of opioid side effects in the early postoperative period due to a considerable reduction in opioid requirements. Given the safety of short-term (less than 5 days) administration of NSAIDs such as ketorolac after major operations,[77] we encourage the use of this combination when there is no contraindication to NSAID therapy.

References

1. Collins SL, Moore RA, McQuay HJ, Wiffen PJ, Edwards JE: Single dose oral ibuprofen and diclofenac for postoperative pain. Cochrane Database Syst Rev 2000; (2):CD001548

2. Smith LA, Carroll D, Edwards JE, Moore RA, McQuay HJ: Single-dose ketorolac and pethidine in acute postoperative pain: Systematic review with meta-analysis. Br J Anaesth 2000; 84:48-58

3. McQuay HJ, Carroll D, Moore RA: Injected morphine in postoperative pain: A quantitative systematic review. J Pain Symptom Manage 1999; 17:164-74

4. McQuay HJ, Moore RA: Using numerical results from systematic reviews in clinical practice. Ann Intern Med 1997; 126:712-20

5. Cepeda MS, Vargas L, Ortegon G, Sanchez M, Carr DB: Comparative analgesic efficacy of patient-controlled analgesia with ketorolac versus morphine after elective intra-abdominal operations. Anesth Analg 1995; 80:1150-3

6. Carr DB, Jacox AK, Chapman CR, Fields HL, Heidrich G, Hester NK: Acute pain management: Operative or medical procedures and trauma, Clinical Practice Guideline, AHCPR Pub. No. 950034 edition. Rockville, Agency for Health Care Policy and Research, 1992

7. Song F, Altman DG, Glenny AM, Deeks JJ: Validity of indirect comparison for estimating efficacy of competing interventions: Empirical evidence from published meta-analyses. BMJ 2003; 326:472-7

8. Cepeda MS, Africano JM, Polo R, Alcala R, Carr DB: What is the change in the pain intensity levels that is meaningful to the patients? Pain 2003; 105:151-7

9. Cepeda MS, Farrar JT, Baumgarten M, Boston R, Carr DB, Strom BL: Side effects of opioids during short-term administration: Effect of age, gender, and race. Clin Pharmacol Ther 2003; 74:102-12

10. Cepeda MS, Meng QC, Roa JH, Boston R, Meng QC, Ruiz F, Carr DB, Strom BL: Ethnicity influences morphine pharmacokinetics and pharmacodynamics. Clin Pharmacol Ther 2001; 70:351-61

11. Sarton E, Olofsen E, Romberg R, den H, Kest B, Nieuwenhuijs D, Burm A, Teppema L, Dahan A: Sex differences in morphine analgesia: An experimental study in healthy volunteers. ANESTHESIOLOGY 2000; 93:1245-54

12. Dahan A, Sarton E, Teppema L, Olievier C: Sex-related differences in the influence of morphine on ventilatory control in humans. ANESTHESIOLOGY 1998; 88:903-13

13. Yee JP, Koshiver JE, Allbon C, Brown CR: Comparison of intramuscular ketorolac tromethamine and morphine sulfate for analgesia of pain after major surgery. Pharmacotherapy 1986; 6:253-61

14. O'Hara DA, Fragen RJ, Kinzer M, Pemberton D: Ketorolac tromethamine as compared with morphine sulfate for treatment of postoperative pain. Clin Pharmacol Ther 1987; 41:556-61

15. Brown CR, Mazzulla JP, Mok MS, Nussdorf RT, Rubin PD, Schwesinger WH: Comparison of repeat doses of intramuscular ketorolac tromethamine and morphine sulfate for analgesia after major surgery. Pharmacotherapy 1990; 10: 45S-50S

16. Rice AS, Lloyd J, Miller CG, Bullingham RE, O'sullivan GM: A double-blind study of the speed of onset of analgesia following intramuscular administration of ketorolac tromethamine in comparison to intramuscular morphine and placebo. Anaesthesia 1991; 46:541- 4

17. deAndrade JR, Maslanka M, Reines HD, Howe D, Rasmussen GL, Cardea J, Brown J, Bynum L, Shefrin A, Chang YL, Maneatis T: Ketorolac versus meperidine for pain relief after orthopaedic surgery. Clin Orthop Relat Res 1996; 325:301-12

18. Lieh-Lai MW, Kauffman RE, Uy HG, Danjin M, Simpson PM: A randomized comparison of ketorolac tromethamine and morphine for postoperative analgesia in critically ill children. Crit Care Med 1999; 27:2786-91

19. Cepeda MS, Alvarez H, Morales O, Carr DB: Addition of ultralow dose naloxone to postoperative morphine PCA: Unchanged analgesia and opioid requirement but decreased incidence of opioid side effects. Pain 2004; 107:41–6

20. Hain RD, Hardcastle A, Pinkerton CR, Aherne GW: Morphine and morphine-6-glucuronide in the plasma and cerebrospinal fluid of children. Br J Clin Pharmacol 1999; 48:37–42

21. Mandema JW, Stanski DR: Population pharmacodynamic model for ketorolac analgesia. Clin Pharmacol Ther 1996; 60:619–35

22. Peng PW, Sandler AN: A review of the use of fentanyl analgesia in the management of acute pain in adults. ANESTHESIOLOGY 1999; 90:576–99

23. Cepeda MS, Africano JM, Polo R, Alcala R, Carr DB: Agreement between percentage pain reductions calculated from numeric rating scores of pain intensity and those reported by patients. Pain 2003; 106:439–42

24. Cook RJ, Sackett DL: The number needed to treat: A clinically useful measure of treatment effect. BMJ 1995; 310:452–4

25. Zeger SL, Liang KY, Albert PS: Models for longitudinal data: A generalized estimating equation approach. Biometrics 1988; 44:1049–60

26. Fox J: Outlying and influential data, Regression Diagnostics. Edited by Lewis-Beck MS. Newbury Park, Sage University Papers, 1991, pp 21–39

27. Mosteller F, Tukey JW: A class of mechanisms for fitting, Data Analysis and Regression. Edited by Mosteller F, Tukey JW. Reading, Addison-Wesley, 1997, pp 333–80

28. Akerman N, Saxena S, Wilson R, Columb M, Lyons G: Effect of intrathecal diamorphine on block height during spinal anaesthesia for caesarean section with bupivacaine. Br J Anaesth 2005; 94:843–7

29. Cepeda MS, Carr DB: Women experience more pain and require more morphine than men to achieve a similar degree of postoperative analgesia. Anesth Analg 2003; 97:1464–8

30. Moher D, Schulz KF, Altman DG: The CONSORT statement: Revised recommendations for improving the quality of reports of parallel group randomized trials. BMC Med Res Methodol 2001; 1:2–8

31. Edwards JE, Loke YK, Moore RA, McQuay HJ: Single dose piroxicam for acute postoperative pain. Cochrane Database Syst Rev 2001; (4):CD002762

32. Edwards JE, Meseguer F, Faura CC, Moore RA, McQuay HJ: Single-dose dipyrone for acute postoperative pain. Cochrane Database Syst Rev 2001; (3):CD003227

33. Dans A, McAlister F, Dans L, Richardson WS, Straus S, Guyatt G: Therapy and applying results: Applying results to individual patient, Example number needed to treat, Users' Guides to the Medical Literature. Edited by Guyatt G, Rennie D. Chicago, AMA Press, 2002, pp 369–433

34. Lau J, Ioannidis JP, Schmid CH: Summing up evidence: One answer is not always enough. Lancet 1998; 351:123–7

35. LeLorier J, Gregoire G, Benhaddad A, Lapierre J, Derderian F: Discrepancies between meta-analyses and subsequent large randomized, controlled trials. N Engl J Med 1997; 337:536–42

36. Ioannidis JPA, Lau J: The impact of high-risk patients on the results of clinical trials. J Clin Epidemiol 1997; 50:1089–98

37. Moore RA, Gavaghan D, Tramer MR, Collins SL, McQuay HJ: Size is everything–large amounts of information are needed to overcome random effects in estimating direction and magnitude of treatment effects. Pain 1998; 78:209–16

38. Powell H, Smallman JM, Morgan M: Comparison of intramuscular ketorolac and morphine in pain control after laparotomy. Anaesthesia 1990; 45:538–42

39. Folsland B, Skulberg A, Halvorsen P, Helgesen KG: Placebo-controlled comparison of single intramuscular doses of ketorolac tromethamine and pethidine for post-operative analgesia. J Int Med Res 1990; 18:305–14

40. Power I, Noble DW, Douglas E, Spence AA: Comparison of i.m. ketorolac trometamol and morphine sulphate for pain relief after cholecystectomy. Br J Anaesth 1990; 65:448–55

41. Spindler JS, Mehlisch D, Brown CR: Intramuscular ketorolac and morphine in the treatment of moderate to severe pain after major surgery. Pharmacotherapy 1990; 10:51S– 8S

42. Larkin GL, Prescott JE: A randomized, double-blind, comparative study of the efficacy of ketorolac tromethamine versus meperidine in the treatment of severe migraine. Ann Emerg Med 1992; 21:919–24

43. Maunuksela EL, Kokki H, Bullingham RE: Comparison of intravenous ketorolac with morphine for postoperative pain in children. Clin Pharmacol Ther 1992; 52:436–43

44. Twersky RS, Lebovits A, Williams C, Sexton TR: Ketorolac versus fentanyl for postoperative pain management in outpatients. Clin J Pain 1995; 11:127–33

45. O'Hara DA, Fanciullo G, Hubbard L, Maneatis T, Seuffert P, Bynum L, Shefrin A: Evaluation of the safety and efficacy of ketorolac versus morphine by patient-controlled analgesia for postoperative pain. Pharmacotherapy 1997; 17:891–9

46. Chiaretti A, Simeone E, Langer A, Butera G, Piastra M, Tortorolo L, Polidori G: Analgesic efficacy of ketorolac and fentanyl in pediatric intensive care. Pediatr Med Chir 1997; 19:419–24

47. Veenema KR, Leahey N, Schneider S: Ketorolac versus meperidine: ED treatment of severe musculoskeletal low back pain. Am J Emerg Med 2000; 18:404–7

48. Oosterlinck W, Philp NH, Charig C, Gillies G, Hetherington JW, Lloyd J: A double-blind single dose comparison of intramuscular ketorolac tromethamine and pethidine in the treatment of renal colic. J Clin Pharmacol 1990; 30:336–41

49. Stahlgren LR, Trierweiler M, Tommeraasen M, Mehlisch D, Otterson W, Maneatis T, Bynum L, DiGiorgio E: Comparison of ketorolac and meperidine in patients with postoperative pain: Impact on health care utilization. Clin Ther 1993; 15:571–80

50. Munro HM, Riegger LQ, Reynolds PI, Wilton NC, Lewis IH: Comparison of the analgesic and emetic properties of ketorolac and morphine for paediatric outpatient strabismus surgery. Br J Anaesth 1994; 72:624–8

51. Koenig KL, Hodgson L, Kozak R, Jordan K, Sexton TR, Leiken AM: Ketorolac vs meperidine for the management of pain in the emergency department. Acad Emerg Med 1994; 1:544–9

52. Popp JE, Sanko WA, Sinha AK, Kaeding CC: A comparison of ketorolac tromethamine/oxycodone versus patient-controlled analgesia with morphine in anterior cruciate ligament reconstruction patients. Arthroscopy 1998; 14:816–9

53. Dula DJ, Anderson R, Wood GC: A prospective study comparing i.m. ketorolac with i.m. meperidine in the treatment of acute biliary colic. J Emerg Med 2001; 20:121–4

54. Henderson SO, Swadron S, Newton E: Comparison of intravenous ketorolac and meperidine in the treatment of biliary colic. J Emerg Med 2002; 23:237–41

55. Larkin GL, Peacock WF, Pearl SM, Blair GA, D'Amico F: Efficacy of ketorolac tromethamine versus meperidine in the ED treatment of acute renal colic. Am J Emerg Med 1999; 17:6–10

56. Sandhu DP, Iacovou JW, Fletcher MS, Kaisary AV, Philip NH, Arkell DG: A comparison of intramuscular ketorolac and pethidine in the alleviation of renal colic. Br J Urol 1994; 74:690–3

57. Kusama T, Murakoshi Y, Murakami H: Contractile response of guinea pig ileum by repetitive application of morphine. Gen Pharmac 1992; 23:391–6

58. Stouten EM, Armbruster S, Houmes RJ, Prakash O, Erdmann W, Lachmann B: Comparison of ketorolac and morphine for postoperative pain after major surgery. Acta Anaesthesiol Scand 1992; 36:716–21

59. Brown CR, Moodie JE, Wild VM, Bynum LJ: Comparison of intravenous ketorolac tromethamine and morphine sulfate in the treatment of postoperative pain. Pharmacotherapy 1990; 10:116S– 21S

60. Peirce RJ, Fragen RJ, Pemberton DM: Intravenous ketorolac tromethamine versus morphine sulfate in the treatment of immediate postoperative pain. Pharmacotherapy 1990; 10:111S– 5S

61. Stanski DR, Cherry C, Bradley R, Sarnquist FH, Yee JP: Efficacy and safety of single doses of intramuscular ketorolac tromethamine compared with meperidine for postoperative pain. Pharmacotherapy 1990; 10:40S– 4S

62. Davis CP, Torre PR, Williams C, Gray C, Barrett K, Krucke G, Peake D, Bass BJ: Ketorolac versus meperidine-plus-promethazine treatment of migraine headache: Evaluations by patients. Am J Emerg Med 1995; 13:146–50

63. Lennon GM, Bourke J, Ryan PC, Fitzpatrick JM: Pharmacological options for the treatment of acute ureteric colic: An in vitro experimental study. Br J Urol 1993; 71:401–7

64. Lenard LJ, Halmai V, Bartho L: Morphine contracts the guinea pig ileal circular muscle by interfering with a nitric oxide mediated tonic inhibition. Digestion 1999; 60:562–6

65. Gan TJ, Meyer T, Apfel CC, Chung F, Davis PJ, Eubanks S, Kovac A, Philip BK, Sessler DI, Temo J, Tramer MR, Watcha M: Consensus guidelines for managing postoperative nausea and vomiting. Anesth Analg 2003; 97:62–71

66. Cepeda MS, Gonzales F, Granados V, Cuervo R, Carr DB: Incidence of nausea and vomiting in outpatients undergoing general anesthesia in relation to selection of intraoperative opioid. J Clin Anesth 1996; 8:324–8

67. Wright SW, Norris RL, Mitchell TR: Ketorolac for sickle cell vaso-occlusive crisis pain in the emergency department: lack of a narcotic-sparing effect. Ann Emerg Med 1992; 21:925–8

68. Green CR, Pandit SK, Levy L, Kothary SP, Tait AR, Schork MA: Intraoperative ketorolac has an opioid-sparing effect in women after diagnostic laparoscopy but not after laparoscopic tubal ligation. Anesth Analg 1996; 82:732–7

69. Remy C, Marret E, Bonnet F: Effects of acetaminophen on morphine side-effects and consumption after major surgery: meta-analysis of randomized controlled trials. Br J Anaesth 2005; 94:505–13

70. Marret E, Kurdi O, Zufferey P, Bonnet F: Effects of nonsteroidal antiinflammatory drugs on patient-controlled analgesia morphine side effects: Meta-analysis of randomized controlled trials. ANESTHESIOLOGY 2005; 102:1249–60

71. Kehlet H, Dahl J: The value of "multimodal" or "balanced analgesia" in postoperative pain treatment. Anesth Analg 1993; 77:1048–56

72. Ashburn MA, Caplan RA, Carr DB, Connis RT, Ginsberg B, Green CR, Lema MJ, Nickinovich DG, Rice LJ: Practice guidelines for acute pain management in the perioperative setting: An updated report by the American Society of Anesthesiologists Task Force on Pain Management. ANESTHESIOLOGY 2004; 100:1573–81

73. Rothman KJ: Placebo mania. BMJ 1996; 313:3–4

74. Rothman KJ: Declaration of Helsinki should be strengthened. BMJ 2000; 321:442–5

75. Strom BL, Berlin JA, Kinman JL, Spitz PW, Hennessy S, Feldman H, Kimmel S, Carson JL: Parenteral ketorolac and risk of gastrointestinal and operative site bleeding: A postmarketing surveillance study. JAMA 1996; 275:376–82

76. Schwartz D, Lellouch J: Explanatory and pragmatic attitudes in therapeutical trials. J Chronic Dis 1967; 20:637–48

77. Forrest JB, Camu F, Greer IA, Kehlet H, Abdalla M, Bonnet F, Ebrahim S, Escolar G, Jage J, Pocock S, Velo G, Langman MJ, Bianchi PG, Samama MM, Heitlinger E: Ketorolac, diclofenac, and ketoprofen are equally safe for pain relief after major surgery. Br J Anaesth 2002; 88:227–33