A Multicenter, Randomized, Double-Blind, Placebo-Controlled Trial of Intravenous Ibuprofen 400 and 800 mg Every 6 Hours in the Management of Postoperative Pain

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ABSTRACT

Background: Although opioids are the mainstay of inpatient postoperative pain management, they do not block inflammation. The NSAID ibuprofen has anti-inflammatory and analgesic properties, and a multimodal approach may reduce opioid requirements.

Objective: This study was conducted to assess the effects of intravenously administered ibuprofen 400 and 800 mg q6h in postoperative pain management.

Methods: This multicenter, randomized, double-blind, placebo-controlled trial was conducted in 406 patients scheduled to undergo elective, single-site orthopedic or abdominal surgery. All patients received morphine administered by patient-controlled analgesia pump, or by hospital staff at the request of the patient, after surgery and were randomly assigned in a 1:1:1 ratio to receive ibuprofen 400 mg IV, ibuprofen 800 mg IV, or inactive vehicle (placebo). The first dose of study drug was administered intraoperatively at the initiation of wound closure, then every 6 hours for a total of 8 doses over the first 48 hours of the study. After the initial 8 doses, the protocol allowed for continued administration of IV ibuprofen or placebo every 6 hours, at the discretion of the investigator, for control of postoperative pain for a total of up to 120 hours (5 days). The ibuprofen and placebo were administered while patients had access to morphine throughout the duration of the study. The primary outcome measure was morphine use in the first 24 hours after surgery. Secondary measures were patient self-reports of pain scores at rest and with movement. Pain intensity was measured before (baseline) and at 1, 2, 3, 6, 9, 12, 15, 18, 24, 27, 30, 33, 36, 39, 42, 45, and 48 hours after the first administration of study medication, and then once daily through day 5 if the patient continued to receive study medication. Patients were assessed by study personnel for treatment-emergent adverse events (AEs).

Results: A total of 406 patients were enrolled (319 women, 87 men; mean [SD] age, 45 [12] years; weight, 83.8 [19.1] kg; ibuprofen 400 mg IV, 134 patients; ibuprofen 800 mg IV, 138; and placebo, 134). In the intent-to-treat population, median morphine use was significantly reduced during the first 24 hours after administration of the study drug in patients who received ibuprofen 800 mg IV q6h (by 22% vs placebo; $P = 0.030$). The use of ibuprofen 800 mg IV q6h was associated with significant reductions in pain at rest and with movement across 3 time periods (1–24, 6–24, 12–24 hours) compared with placebo. Ibuprofen 400 mg IV q6h was associated with significant reductions in pain at rest and with movement during the 6- to 24-hour and 12- to 24-hour time periods compared with placebo. The prevalences of AEs and abnormalities in laboratory measurements were not significantly different between patients who received IV ibuprofen and those who received placebo. Treatment-emergent AEs were reported in 368 of 406 patients (91%). With respect to the number of patients who experienced serious AEs, the differences in the 400-mg IV ibuprofen group (118/134 [88%]) and the 800-mg IV ibuprofen group (124/138 [90%]) compared with the placebo group (126/134 [94%]) were not statistically significant. There were significant reductions in the proportions of patients who experienced gastrointestinal disorders in the 400- and 800-mg IV ibuprofen groups compared with the placebo group (99/134 [74%] and 98/138 [71%],

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respectively, vs 113/134 [84%]; $P = 0.05$ and $P = 0.009$). There were significant reductions in the numbers of patients experiencing pyrexia in the 400- and 800-mg IV ibuprofen groups compared with the placebo group (9/134 [7%] and 10/138 [7%] vs 23/134 [17%]; $P = 0.013$ and $P = 0.015$). Dizziness occurred in a significantly greater proportion of patients in the ibuprofen 800-mg q6h group compared with the placebo group ($P = 0.011$).

Conclusions: In these patients undergoing postoperative pain management, ibuprofen 800 mg IV q6h was associated with significant reductions in morphine use and pain at rest and with movement compared with placebo. Ibuprofen IV was not associated with significant increases in AEs compared with placebo, with the exception of dizziness with the 800-mg dose. These findings suggest that ibuprofen 800 mg IV q6h was effective for postoperative pain management and was generally well tolerated. ClinicalTrials.gov identifier: NCT00225732. (*Clin Ther.* 2009;31:1922–1935) © 2009 Excerpta Medica Inc.

Key words: ibuprofen, pain, analgesic, anti-inflammatory, NSAID, opioid, clinical trial, intravenous.

INTRODUCTION

In the United States, ~80% of patients experience postoperative pain; of these, 86% report moderate to severe pain.[1,2] Undertreated postoperative pain may have physiologic and psychological effects, and moderate to severe pain has been associated with an increased risk for progression to a chronic painful state.[1,3]

Opioids are a mainstay of postoperative pain management and act within the central nervous system to provide analgesia.[4] However, these agents do not interrupt the inflammatory component of pain.[5] Preempting the inflammatory response may reduce the overall need for opioid analgesics and improve recovery after surgical procedures.[5–7] NSAIDs have long been used for the blockage of pain and inflammation in a variety of settings. These agents inhibit the conversion of arachidonic acid to prostaglandins, thereby preventing the sensitization of pain receptors in response to injury.[8]

A multimodal approach to pain management, using combinations of analgesics with different mechanisms of action, may decrease the total dose of opioid needed, thus minimizing the potential for opioid-related adverse events (AEs), including gastrointestinal disorders and central nervous system effects.[9] In a consensus statement,[10] the American Society for Pain Management Nursing and the American Pain Society noted that combinations of analgesics with different mechanisms of action might provide better pain control with a lower risk for AEs. The combination of less morphine use with ibuprofen could result in better pain control compared with maximally allowed amounts of morphine alone. Oral ibuprofen is a widely used, generally well tolerated, and effective NSAID with analgesic, antipyretic, and anti-inflammatory properties.[11–14] However, oral ibuprofen administration is not practical during the immediate postoperative period.

To provide efficacy and tolerability data for a new drug application submitted to the US Food and Drug Administration, this study was conducted to assess the tolerability and efficacy of intravenously administered ibuprofen in the improvement of pain control (as measured using patients' self-assessment) and in the reduction of opioid use in patients after elective orthopedic or abdominal surgical procedures.

PATIENTS AND METHODS

This randomized, double-blind, placebo-controlled trial was conducted at 17 sites within the United States, Australia, and the Republic of South Africa between February 2005 and September 2006. The institutional review board or independent ethics committee at each study site approved the study protocol. Patients were eligible for the study if they were scheduled to undergo elective, single-site orthopedic or abdominal surgery and were expected to require hospitalization and postoperative analgesia with intravenously administered morphine for >24 hours after surgery. Orthopedic surgeries included replacement or reconstruction of the knee, hip, or shoulder joint; abdominal surgeries included gallbladder, bowel, or lower abdominal general investigative surgery, as well as gynecologic surgery (including hysterectomy).

Patients were excluded if they were <18 or >70 years of age; were unable to provide informed consent or reliable self-report of pain; weighed <30 kg; had a history of allergy or hypersensitivity to ibuprofen, aspirin, NSAIDs, or cyclooxygenase-2 inhibitors; were anemic; had a history of asthma or heart failure; were pregnant or breastfeeding; had an increased risk for bleeding (including a platelet count <30,000 cells/μL), a history of gastrointestinal bleeding within 6 weeks before

surgery, or a history of bleeding diathesis, or were at increased risk for intracerebral hemorrhage; or had renal insufficiency (creatinine clearance <60 mL/min or oliguria defined as urine output <500 mL/24 h) or were undergoing dialysis within 28 days before surgery. Patients were also excluded if they were receiving warfarin, lithium, or a combination of angiotensin-converting enzyme inhibitors and furosemide, or if they received any analgesic, muscle relaxant, or sedative within 24 hours before administration of the study medication (other than acetaminophen up until 6 hours, or NSAIDs up until 12 hours, before the first administration of study drug).

Informed-consent forms and all amendments were reviewed and approved by an appropriate independent ethics committee or institutional review board at each clinical study site before any study-specific screening procedures were conducted and before any preoperative medications were administered.

Study Design

After surgery, all patients received morphine by hospital staff on patient request or patient-controlled analgesia (PCA) pump (1–2 mg every 5 minutes) and were assigned in a 1:1:1 ratio using a stratified, blinded by site, randomization scheme to receive ibuprofen 400 mg IV, ibuprofen 800 mg IV, or inactive vehicle (placebo), every 6 hours for a total of 8 doses over the first 48 hours of the study. After the initial 8 doses, the protocol allowed for continued administration of IV ibuprofen or placebo every 6 hours, at the discretion of the investigator, for control of postoperative pain for a total of up to 120 hours (5 days). The ibuprofen and placebo were administered while patients had access to morphine throughout the duration of the study. Because pain intensity has been correlated with age and weight,[15,16] participants were stratified by age (≤45 or >45 years) and weight (≤75 or >75 kg) before randomization.

The first dose of intravenous ibuprofen or placebo was administered intraoperatively at the initiation of wound closure (**Figure 1**). After the first 24 hours, the study protocol mandated discontinuation of intravenous ibuprofen or placebo if the patient received either narcotic pain medication (other than morphine) or nonnarcotic pain medication (including another NSAID). After 24 hours and through day 5, intravenous ibuprofen or placebo could also be discontinued if a patient was able to tolerate oral pain medication, on resolution of pain or loss of intravenous access, or if the patient was discharged from the hospital.

The study protocol allowed preoperative and intraoperative administration of morphine until ~45 minutes before the end of the surgical procedure. After this time, the protocol allowed (but did not require) the administration of only fentanyl until the first dose of intravenous ibuprofen or placebo was administered, after which patients had access to morphine throughout the study period.

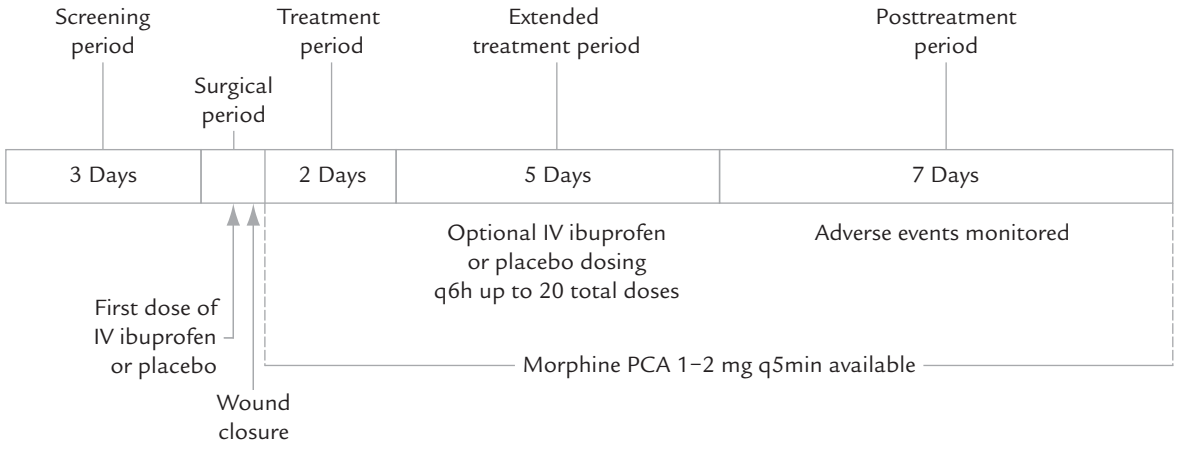

Figure 1. Study timeline. PCA = patient-controlled analgesia.

Efficacy Assessment

The primary end point of this study was the mean amount of morphine administered during the first 24 hours after surgery. Secondary end points included the mean changes in pain intensity at rest and with movement, as assessed using patient self-reporting with a 100-mm visual analog scale (VAS) (0 = no pain to 100 = intense pain). Pain intensity was measured before (baseline) and at 1, 2, 3, 6, 9, 12, 15, 18, 24, 27, 30, 33, 36, 39, 42, 45, and 48 hours after the administration of the first dose of study medication, and then once daily through day 5 in patients who continued to require study medication. To determine the differences in overall pain at differing time points, the area under the VAS pain curve (AUC) was analyzed from 1 to 24 hours, 6 to 24 hours, and 12 to 24 hours. Although the study was not powered to detect significant treatment differences, additional secondary end points were examined, including the rate of treatment failure (defined as the requirement of additional nonmorphine analgesia in the first 24 hours of the study period), time to resumption of gastrointestinal motility (defined as the return of bowel sounds, flatulence, and/or bowel movement), mean number of nocturnal awakenings due to pain, the prevalences of opioid-related AEs (and mean time to return of gastrointestinal motility), time to resumption of ambulation, time to resumption of liquid intake and solid diet, and hospital length of stay (LOS).

Tolerability Assessment

The tolerability profiles of ibuprofen 400 and 800 mg IV q6h were assessed using comparisons of the prevalences of treatment-emergent AEs; vital signs; clinical chemistry, hematology, and coagulation measurements; and transfusion requirements (total units of packed red blood cells, fresh frozen plasma, and platelets administered). Vital signs, including heart rate, respiratory rate, temperature, and blood pressure, were measured during screening and before and at 1, 3, 6, 9, 12, and 24 hours after administration of the first dose of study drug, then daily through day 5 or hospital discharge. Clinical laboratory assessments included biochemistry (sodium, potassium, chloride, total carbon dioxide, glucose, blood urea nitrogen, creatinine, total bilirubin, albumin, total protein, aspartate and alanine aminotransferases, and lactate dehydrogenase), hematology, coagulation (white blood cell count and differential, hematocrit, hemoglobin, platelets, prothrombin time, and partial thromboplastin time), and urinalysis. Laboratory values were assessed at the laboratory at each study site at screening, before the administration of the first dose of study drug, and on study days 1, 2, 3, and 5 or hospital discharge. Patients were also monitored for gastrointestinal events, which were defined using Medical Dictionary for Regulatory Activites (MedDRA) System Organ Class 10017947 AE coding.[17] Tolerability was assessed through day 14. If a patient was discharged before the end of study day 5, posttreatment assessments were conducted at follow-up visits or using telephone contacts. The severity of each AE was assessed by a blinded investigator at each site.

Statistical Analysis

Data analyses were conducted by the sponsor using widely accepted statistical methodology.[18] Initial power calculations indicated that 75 patients per group would provide 80% power for the study to show a treatment difference in morphine use at an α level of 0.05. During the study, an independent statistician performed a preplanned blinded administrative assessment of the SD of the primary efficacy parameter, morphine use. Based on this assessment, the sample size was increased to ~120 patients per group.

Statistical analyses of the efficacy end points were conducted on the intent-to-treat (ITT) population (all patients who were randomized and received at least a partial dose of IV ibuprofen or placebo) and (because the primary end point was assessed after 24 hours of dosing) the efficacy-evaluable (EE) population (all patients who received at least 4 doses of IV ibuprofen or placebo within 60 minutes of the scheduled administration time). Use of fentanyl was not addressed in the statistical analyses. Tolerability was assessed in the ITT population.

Morphine use was analyzed using SAS PROC GLM version 9.1.3 (SAS Institute Inc., Cary, North Carolina). Factors for treatment, age group, weight group, and center were included in the model. The assumptions of ANCOVA were examined. The residual plot showed that the assumption of homogeneity of variance was violated. In addition to the normal probability plot, a histogram of the data, the Kolmogorov-Smirnov test for normality, and the kurtosis value all showed that the assumption of normality was violated. The normal probability plot and histogram of the data showed that the data were highly skewed to the

right. The Kolmogorov-Smirnov test for normality was significant ($P = 0.010$), and the kurtosis value was 4.82. It was concluded that the data severely violated the assumption of normality based on the curved shape of the normal probability plot and the large kurtosis value (a value >2 indicates severe departure from normality).

Because the model assumptions for normality were violated, additional techniques were applied to test the difference between the study groups and to investigate the robustness of the conclusions. Among the methods that were used were logarithm (log) and Box-Cox transformations and nonparametric testing (rank transformation). Log transformation was performed first. The assumptions of ANCOVA were assessed for the log-transformed data, and it was determined, based on the noticeably curved shape of the normal probability plot and the large kurtosis value (74.15), that the log-transformed data severely violated the assumption of normality. The Box-Cox transformation was performed next. The assumptions of ANCOVA were assessed for the Box-Cox–transformed data, and it was determined, based on the Kolmogorov-Smirnov test for normality ($P = 0.012$), that the data violated the assumption of normality. The rank transformation was then performed to produce nonparametric tests for the treatment differences. Because the normality assumptions were severely violated for the morphine data and the log-transformed morphine data and the assumptions were violated for the Box-Cox–transformed morphine data, it was determined that the rank-transformation method was most appropriate and therefore was used for this analysis. Mean, median, and least squares means (transformed) data are presented. Due to the severe violation of the normality assumption for the morphine data and the log-transformed morphine data, the results of the statistical testing are not interpretable. The Box-Cox–transformed data violation of the normality assumption was not severe. The same inference (regarding comparisons of the study groups) is drawn from the parametric tests on the Box-Cox–transformed data and the nonparametric tests on the rank-transformed data. Because the same inference can be drawn from a parametric model with slight departure from normality and the nonparametric model, the statistical conclusions presented are robust.

All statistical tests were 2-sided, with $P \leq 0.05$ considered significant for treatment differences and $P \leq 0.10$ considered significant for interaction effects. ANOVA and ANCOVA procedures were used to compare the differences versus placebo in morphine use in the 24 hours after surgery in the ibuprofen groups. The Dunnett test was used as a multiple comparison test to compare ibuprofen groups with the placebo group.[19]

RESULTS

A total of 406 patients were enrolled (319 women, 87 men; mean [SD] age, 45 [12] years; weight, 83.8 [19.1] kg; Caucasian 348 [86%], black 45 [11%], Asian 7 [2%], Hispanic 1 [<1%], and other 5 [1%]; ibuprofen 400 mg IV, 134 patients; ibuprofen 800 mg IV, 138; and placebo, 134). Of these, 295 (73%) patients underwent abdominal surgical procedures and 111 patients (27%) underwent orthopedic procedures (**Table I**). Fifty-five percent of abdominal procedures were hysterectomies.

The baseline demographic and clinical characteristics were not significantly different between the 3 study groups, and the differences between study groups with respect to the mean number of doses of intravenous ibuprofen or placebo administered were not significant.

All 406 patients who were enrolled in the study were included in the ITT population (**Figure 2**). A total of 342 patients who received the first 4 doses of study medication (during the 24-hour time frame of the primary end point) were included in the EE population (ibuprofen 400 mg IV, 111 patients; ibuprofen 800 mg IV, 116; placebo, 115).

Efficacy

In the ITT population, median morphine use was significantly reduced during the first 24 hours of administration of study drug in patients who received ibuprofen 800 mg IV q6h (by 22% vs placebo; $P = 0.030$) (**Table II**). In the EE population, median morphine use was significantly reduced with ibuprofen 800 mg IV q6h (by 26% vs placebo; $P = 0.026$); the difference in morphine use between the ibuprofen 400-mg IV and placebo groups was not significant.

In the ITT population, the use of ibuprofen 800 mg IV q6h was associated with significant reductions in pain at rest across all 3 time periods ($P = 0.001$, $P < 0.001$, and $P < 0.001$ for 1–24, 6–24, and 12–24 hours, respectively) compared with placebo (**Table III**). Ibuprofen 400 mg IV q6h was associated with significant reductions in pain at rest during the periods of 6 to

Table I. Characteristics of study participants and study groups. All data are no. (%) unless otherwise indicated.*

Characteristic	Ibuprofen 400 mg IV + Morphine PCA (n = 134)	Ibuprofen 800 mg IV + Morphine PCA (n = 138)	Placebo + Morphine PCA (n = 134)	All Patients (n = 406)
Age, mean (SD), y	45 (13)	46 (12)	45 (11)	45 (12)
Age group				
18–45 y	80 (60)	76 (55)	77 (57)	233 (57)
46–70 y	54 (40)	62 (45)	57 (43)	173 (43)
Sex				
Female	99 (74)	111 (80)	109 (81)	319 (79)
Male	35 (26)	27 (20)	25 (19)	87 (21)
Race†				
Caucasian	112 (84)	118 (86)	118 (88)	348 (86)
Black	16 (12)	15 (11)	14 (10)	45 (11)
Asian	2 (1)	3 (2)	2 (1)	7 (2)
Hispanic	1 (1)	0	0	1 (<1)
Other	3 (2)	2 (1)	0	5 (1)
Geographic region†				
Australia	41 (31)	43 (31)	41 (31)	125 (31)
Republic of South Africa	52 (39)	52 (38)	51 (38)	155 (38)
United States	41 (31)	43 (31)	42 (31)	126 (31)
Weight, kg				
Mean (SD)	83.0 (18.2)	84.9 (20.8)	83.4 (18.2)	83.8 (19.1)
Range	44.0–140.5	50.9–150.0	54.0–160.0	44.0–160.0
Weight category				
≤75 kg	50 (37)	52 (38)	51 (38)	153 (38)
>75 kg	84 (63)	86 (62)	83 (62)	253 (62)
Type of surgery				
Orthopedic	39 (29)	40 (29)	32 (24)	111 (27)
Abdominal	95 (71)	98 (71)	102 (76)	295 (73)
Abdominal hysterectomy	50 (37)	53 (38)	58 (43)	161 (40)

PCA = patient-controlled analgesia.
*No significant between-group differences were found.
†Percentages might not total 100% due to rounding.

24 hours ($P = 0.013$) and 12 to 24 hours ($P = 0.005$) compared with placebo. The use of ibuprofen 800 mg IV q6h was associated with significant reductions in pain with movement across all 3 time periods compared with placebo ($P = 0.002$, $P < 0.001$, and $P < 0.001$ for 1–24, 6–24, and 12–24 hours, respectively). The use of ibuprofen 400 mg IV q6h was also associated with significant reductions in pain with movement across all 3 time periods compared with placebo ($P = 0.021$, $P = 0.004$, and $P = 0.003$).

In the EE population, ibuprofen 800 mg IV q6h was associated with significant reductions in pain at rest during the time periods of 6 to 24 hours ($P = 0.011$) and 12 to 24 hours ($P = 0.004$) compared with placebo, whereas the use of ibuprofen 400 mg IV q6h was not associated with any significant reductions in pain at rest (**Table IV**). Ibuprofen 800 mg IV q6h was associated with significant reductions in pain with movement during the time periods of 6 to 24 hours ($P = 0.011$) and 12 to 24 hours ($P = 0.002$) compared with placebo. Ibupro-

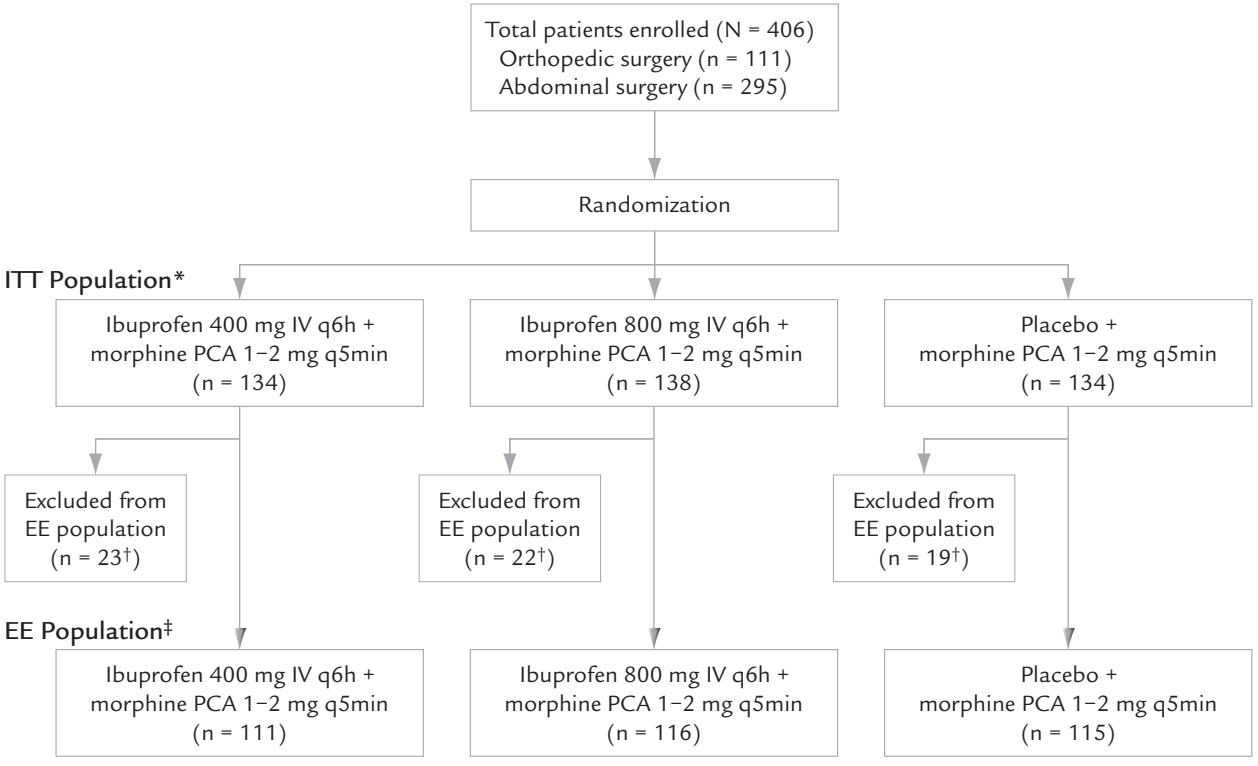

Figure 2. Distribution of orthopedic or abdominal surgery patients randomized to receive IV ibuprofen or placebo for the management of postoperative pain. PCA = patient-controlled analgesia. *ITT = intent-to-treat; all patients who received at least a partial dose of IV ibuprofen or placebo. †Reasons for exclusion from the efficacy population included adverse events, noncompliance, lack of efficacy, and withdrawn consent. These resulted in the failure to receive at least 4 doses of IV ibuprofen or placebo as required by the study protocol. ‡EE = efficacy-evaluable; all patients who received at least 4 doses of IV ibuprofen or placebo within 60 minutes of the scheduled administration time.

fen 400 mg IV q6h was also associated with significant reductions in pain with movement during the periods of 6 to 24 hours (P = 0.047) and 12 to 24 hours (P = 0.020) compared with placebo.

The rates of treatment failure were not statistically significant between study groups. No significant differences between study groups were noted with respect to time to gastrointestinal motility, mean number of nocturnal awakenings due to pain, time to resumption of ambulation, resumption of liquid intake and solid diet, or hospital LOS.

Tolerability

Treatment-emergent AEs were reported in 368 of 406 patients (91%) (**Table V**). The most common AEs experienced by ≥3 patients were nausea (77/134 [57%], 82/138 [59%], and 74/134 [70%] patients in the ibuprofen 400-mg IV q6h, 800-mg IV q6h, and placebo groups, respectively), vomiting (30/134 [22%], 31/138 [22%], and 38/134 [28%]), and constipation (23/134 [17%], 25/138 [18%], and 28/134 [21%]) (**Table VI**). Reported severe AEs included calf pain and peritoneal hematoma (1 patient each; ibuprofen 400 mg) and elevated hepatic enzymes and postoperative infection (1 patient each; ibuprofen 800 mg). It is unknown whether these AEs were related to study drug. Severe AEs considered not related to study drug included postoperative abdominal pain, pulmonary edema, and pulmonary embolism (1 patient each; ibuprofen 400 mg); ileus, hematoma, transient ischemic attack, and vagi-

Table II. Morphine requirements during the first 24 hours after surgery in patients who received intravenously administered ibuprofen or placebo.

Parameter	Ibuprofen 400 mg IV + Morphine PCA	Ibuprofen 800 mg IV + Morphine PCA	Placebo + Morphine PCA
ITT population			
No. of patients included in analysis	134	138	134
Morphine requirement, mg			
Mean (SD)	46.3 (29.4)	43.8 (33.7)	48.9 (27.7)
Median	44.0	35.5	45.3
Untransformed morphine requirement			
LS mean (SE)*	46.3 (3.5)	43.8 (3.4)	48.9 (3.6)
P†	NS	NS	–
Transformed morphine requirement‡			
LS mean (SE)*	208.5 (13.6)	190.6 (13.1)	223.0 (13.8)
P†	0.458	0.030	–
EE population			
No. of patients included in analysis	111	116	115
Morphine requirement, mg			
Mean (SD)	44.7 (27.0)	42.1 (32.0)	48.8 (28.3)
Median	43.0	33.5	45.0
Untransformed morphine requirement			
LS mean (SE)*	42.8 (3.7)	41.0 (3.5)	47.8 (3.6)
P†	NS	NS	–
Transformed morphine requirement‡			
LS mean (SE)*	168.3 (12.6)	154.5 (11.9)	184.4 (12.3)
P†	0.318	0.026	–

PCA = patient-controlled analgesia; ITT = intent-to-treat; EE = efficacy-evaluable.

*Least squares (LS) means were adjusted for age group, weight group, randomization center, and study group.

†Versus placebo, based on a linear 4-way ANOVA model with fixed effects for age group, weight group, randomization center, and study group.

‡Data were transformed using rank transformation.

nal hematoma (1 patient each; ibuprofen 800 mg); and hematoma and vomiting (1 patient each; placebo).

Patients treated with either dose of IV ibuprofen experienced statistically fewer gastrointestinal AEs compared with patients who received placebo (ibuprofen 400 mg IV, 74% [$P = 0.05$]; ibuprofen 800 mg IV, 71% [$P = 0.009$]; placebo, 84%). There were significant reductions in the proportions of patients who experienced gastrointestinal AEs in the 400- and 800-mg IV ibuprofen groups (99/134 [74%] and 98/138 [71%], respectively, vs 113/134 [84%] with placebo; $P = 0.05$ and $P = 0.009$). Gastrointestinal AEs that occurred in >1% of patients included nausea (77/134 [57%], 82/138 [59%], and 94/134 [70%]), vomiting (30/134 [22%], 31/138 [22%], and 38/134 [28%]), and constipation (23/134 [17%], 25/138 [18%], and 28/134 [21%]).

Of the most common AEs, nausea occurred in a significantly smaller proportion of patients treated with ibuprofen 400 and 800 mg IV compared with placebo ($P = 0.042$). The proportions of patients who experienced pyrexia were significantly reduced in both the 400- and 800-mg IV ibuprofen groups compared with the placebo group (9/134 [7%] and 10/138 [7%], respectively, vs 23/134 [17%]; $P = 0.013$ and $P = 0.015$). In addition to pyrexia, dizziness was the only AE experienced in a significantly larger proportion of patients in the 800-mg IV ibuprofen group compared

Table III. Patients' self-assessment of pain at rest and with movement (intent-to-treat population).

Score	Morphine PCA + Ibuprofen 400 mg IV (n = 134)	Morphine PCA + Ibuprofen 800 mg IV (n = 138)	Morphine PCA + Placebo (n = 134)
Pain at rest (VAS*-AUC, mm-h)			
1–24 hours			
Mean (SD)	81.7 (41.7)	73.9 (39.6)	91.0 (46.0)
Median	82.1	70.6	88.1
LS mean (SE)†	88.5 (4.6)	82.3 (4.4)	97.3 (4.7)
P‡	0.057	0.001	–
6–24 hours			
Mean (SD)	55.6 (32.6)	49.8 (31.4)	65.3 (37.1)
Median	55.6	48.0	65.0
LS mean (SE)†	59.6 (3.7)	54.9 (3.6)	68.8 (3.8)
P‡	0.013	<0.001	–
12–24 hours			
Mean (SD)	34.3 (21.3)	30.6 (21.5)	41.7 (24.7)
Median	34.0	29.3	41.1
LS mean (SE)†	35.5 (2.5)	32.6 (2.4)	42.5 (2.6)
P‡	0.005	<0.001	–
Pain with movement (VAS*-AUC, mm-h)			
1–24 hours			
Mean (SD)	111.9 (40.7)	106.3 (43.9)	123.3 (46.0)
Median	113.1	107.5	124.8
LS mean (SE)†	116.4 (4.9)	112.6 (4.7)	127.7 (5.0)
P‡	0.021	0.002	–
6–24 hours			
Mean (SD)	80.0 (32.7)	76.2 (35.5)	91.5 (37.6)
Median	80.0	76.2	91.5
LS mean (SE)†	81.9 (4.0)	79.4 (3.9)	93.4 (4.1)
P‡	0.004	<0.001	–
12–24 hours			
Mean (SD)	51.0 (22.2)	47.9 (24.0)	59.2 (25.3)
Median	50.7	47.9	59.1
LS mean (SE)†	50.6 (2.7)	48.6 (2.6)	58.8 (2.8)
P‡	0.003	<0.001	–

PCA = patient-controlled analgesia.
*As measured using a visual analog scale (VAS) (scale: 0 = no pain to 100 = intense pain).
†Least squares (LS) means adjusted for age group, weight group, randomization center, and study group.
‡Versus placebo, based on a linear 4-way ANOVA model with fixed effects for age group, weight group, randomization center, and study group.

with the placebo group (12/138 [9%] vs 2/134 [1%]; $P = 0.011$).

There were no significant between-group differences in the prevalences of abnormal laboratory values or vital sign measurements over the course of the study. The prevalences of AEs and clinical abnormalities, such as blood pressure elevations, bleeding, and bruising, did not differ significantly between groups. There were no significant differences between study groups in the proportions of patients with renal function abnormalities or the mean number of units of blood products transfused.

Table IV. Patients' self-assessment of pain at rest and with movement (efficacy-evaluable population).

Score	Ibuprofen 400 mg IV + Morphine PCA (n = 111)	Ibuprofen 800 mg IV + Morphine PCA (n = 116)	Placebo + Morphine PCA (n = 115)
Pain at rest (VAS*-AUC, mm-h)			
1–24 hours			
Mean (SD)	81.9 (44.6)	76.9 (41.0)	90.2 (45.5)
Median	74.4	76.2	87.0
LS mean (SE)†	90.0 (5.3)	84.6 (5.0)	94.5 (5.1)
P‡	0.383	0.051	–
6–24 hours			
Mean (SD)	56.0 (35.0)	51.7 (32.5)	64.6 (36.8)
Median	48.0	48.0	61.5
LS mean (SE)†	60.7 (4.3)	56.1 (4.0)	66.6 (4.2)
P‡	0.157	0.011	–
12–24 hours			
Mean (SD)	34.5 (22.9)	31.6 (22.1)	41.3 (24.6)
Median	31.5	28.9	40.5
LS mean (SE)†	36.3 (2.9)	33.3 (2.7)	41.5 (2.8)
P‡	0.065	0.004	–
Pain with movement (VAS*-AUC, mm-h)			
1–24 hours			
Mean (SD)	111.8 (44.1)	108.5 (45.0)	122.1 (47.3)
Median	112.7	109.8	120.5
LS mean (SE)†	117.5 (5.7)	114.5 (5.4)	125.2 (5.5)
P‡	0.166	0.053	–
6–24 hours			
Mean (SD)	80.1 (35.7)	77.2 (36.2)	90.7 (38.8)
Median	80.3	77.7	90.0
LS mean (SE)†	82.6 (4.7)	80.1 (4.4)	91.6 (4.5)
P‡	0.047	0.011	–
12–24 hours			
Mean (SD)	51.0 (24.3)	48.2 (24.3)	58.9 (26.2)
Median	50.6	48.0	58.8
LS mean (SE)†	51.0 (3.2)	48.7 (3.0)	58.1 (3.1)
P‡	0.020	0.002	–

PCA = patient-controlled analgesia.
*As measured using a visual analog scale (VAS) (scale: 0 = no pain to 100 = intense pain).
†Least squares (LS) means adjusted for age group, weight group, randomization center, and study group.
‡Versus placebo, based on a linear 4-way ANOVA model with fixed effects for age group, weight group, randomization center, and study group.

With respect to the number of patients who experienced serious AEs (**Table VII**), the differences in the 400-mg IV ibuprofen group (118/134 [88%]) and the 800-mg IV ibuprofen group (124/138 [90%]) compared with the placebo group (126/134 [94%]) were not statistically significant. There were no deaths reported during the 14-day study period.

The study drug was discontinued in all 406 patients prior to study day 5. Discontinuation was primarily due to the tolerability of oral pain medication in 89/134 (66%), 101/138 (73%), and 91/134 (68%) of patients in the ibuprofen 400-mg IV q6h, ibuprofen 800-mg IV q6h, and placebo groups, respectively. Other reasons for discontinuation of study medication

Table V. Adverse events reported in patients undergoing orthopedic or abdominal surgery who received at least a partial dose of IV ibuprofen or placebo, in addition to morphine. Values are no. (%) of patients.*

Parameter	Ibuprofen 400 mg IV + Morphine PCA (n = 134)	Ibuprofen 800 mg IV + Morphine PCA (n = 138)	Placebo + Morphine PCA (n = 134)
Mild	74 (55)	71 (51)	70 (52)
Moderate	33 (25)	44 (32)	46 (34)
Severe	11 (8)	9 (7)	10 (7)
Total	118 (88)	124 (90)	126 (94)

PCA = patient-controlled analgesia.
*Severity was determined by the blinded investigator during conduct of the study.

Table VI. The most common adverse events reported in ≥3 patients undergoing orthopedic or abdominal surgery who received at least a partial dose of IV ibuprofen or placebo, in addition to morphine. Values are no. (%) of patients.

Event	Ibuprofen 400 mg IV + Morphine PCA (n = 134)	Ibuprofen 800 mg IV + Morphine PCA (n = 138)	Placebo + Morphine PCA (n = 134)
Nausea	77 (57)*	82 (59)	94 (70)
Vomiting	30 (22)	31 (22)	38 (28)
Constipation	23 (17)	25 (18)	28 (21)
Vaginal hemorrhage	13 (10)	12 (9)	16 (12)
Headache	12 (9)	25 (18)	20 (15)
Flatulence	10 (7)	7 (5)	10 (7)
Pruritus	10 (7)	14 (10)	14 (10)
Pyrexia	9 (7)†	10 (7)‡	23 (17)
Dizziness	8 (6)	12 (9)§	2 (1)
Urinary retention	7 (5)	8 (6)	8 (6)

PCA = patient-controlled analgesia.
* $P = 0.042$ versus placebo (Fisher exact test).
† $P = 0.013$ versus placebo (Fisher exact test).
‡ $P = 0.015$ versus placebo (Fisher exact test).
§ $P = 0.011$ versus placebo (Fisher exact test).

included resolution of pain in 10/134 (7%), 12/138 (9%), and 9/134 (7%) patients in the ibuprofen 400-mg, ibuprofen 800-mg, and placebo groups, respectively; no intravenous access in 1/134 (1%), 2/138 (1%), and 3/134 (2%); request by the physician in 0%, 1/138 (1%), and 1/134 (1%); request by the patient in 5/134 (4%), 0%, and 4/134 (3%); secondary to an AE in 8/134 (6%), 6/138 (4%), and 9/134 (7%); and treatment failure in 7/134 (5%), 4/138 (3%), and 11/134 (8%).

DISCUSSION

Pain is the greatest concern of patients before surgery.[2] However, despite advances in the understanding

Table VII. Serious adverse events reported in patients undergoing orthopedic or abdominal surgery who received at least a partial dose of IV ibuprofen or placebo, in addition to morphine.

Event	Severity	Treatment Relationship*
Ibuprofen 400 mg IV + morphine PCA (n = 6/134 [4%])		
Calf pain	Severe	Unknown
Peritoneal hematoma	Severe	Unknown
Postoperative abdominal pain	Severe	Not related
Pulmonary edema	Severe	Not related
Pulmonary embolism	Severe	Not related
Ileus	Mild	Not related
Ibuprofen 800 mg IV + morphine PCA (n = 9/138 [7%])†		
Elevated hepatic enzymes	Severe	Unknown
Postoperative infection	Severe	Unknown
Ileus	Severe	Not related
Hematoma	Severe	Not related
Transient ischemic attack	Severe	Not related
Vaginal hematoma	Severe	Not related
Infection	Moderate	Unknown
Knee pain	Moderate	Unknown
Postoperative abdominal pain	Moderate	Not related
Postoperative ileus	Mild	Not related
Placebo + morphine PCA (n = 3/134 [2%])		
Hematoma	Severe	Unknown
Vomiting	Severe	Unknown
Pyrexia	Mild	Not related

PCA = patient-controlled analgesia.
* Determined by the investigator at each study site.
† One patient experienced both elevated hepatic enzymes and postoperative infection.

of the mechanisms involved, postoperative pain continues to be a considerable problem. One reason for inadequate pain relief might be patients' unwillingness to use opioids, and concern about AEs has been reported to be a main contributor to that reluctance.[20,21] The use of additional medications that might reduce the need for opioids, therefore, is an approach that has been widely endorsed.[9,10,22,23]

Administered orally, the NSAID ibuprofen is effective in blocking pain and inflammation, in part by preventing the production of prostaglandins.[24] An intravenous formulation of ibuprofen has the potential to arrest the inflammatory cascade triggered by invasive procedures, to reduce or prevent the development of postoperative pain, and to avert the sensitization of pain receptors. The package insert for prescription-strength orally administered ibuprofen carries cardiovascular and gastrointestinal risk warnings. Ibuprofen should be used with caution in patients with congestive heart failure, renal impairment, a risk for blood clots, and/or a history of ulcers or gastrointestinal bleeding.[24] While opioids such as morphine offer a high degree of pain relief, their use might result in serious gastrointestinal AEs, such as intractable nausea and vomiting.[4]

The findings from this study suggest that this intravenous formulation of ibuprofen 800 mg q6h was associated with significant reductions in the amount of morphine required for pain management, which may in turn help to reduce some of the well-established AEs associated with opioid analgesia. An intravenous formulation would allow precise dosing, especially in patients who cannot use oral medication due to intubation or unconsciousness.

In the present study, the administration of intravenous ibuprofen 800 but not 400 mg q6h in the management of postoperative pain was associated with a significant reduction in morphine consumption in the first 24 hours after surgery compared with placebo. Patients treated with ibuprofen 800 mg IV q6h required a median of 22% less morphine than did patients treated with placebo.

In addition to the morphine-sparing effect, the 800-mg dose administered every 6 hours was associated with less pain at rest and with movement compared with placebo. Because patients had the option to self-administer morphine, it might have been expected that their pain would be well controlled and that there would be no incremental pain reduction with addition of intravenous ibuprofen. However, opioids block only the perception of pain, whereas the anti-inflammatory activity of ibuprofen helps to prevent and alleviate the tissue inflammation that causes pain. The dose-dependent reduction in pain observed in this population may add to the body of evidence supporting multimodal analgesia with agents that have different mechanisms of action.[9] A meta-analysis of 17 randomized controlled trials, comprising 400 patients who received opioid analgesia plus an NSAID for the management of postoperative pain and 389 patients who received monotherapy with opioid analgesia, also found that patients who received both types of medication consumed fewer opioids and had lower pain scores than did those who received opioid monotherapy.[22]

Fewer patients in the intravenous ibuprofen–treated groups experienced pyrexia compared with patients who received placebo. This finding is consistent with the antipyretic effects of ibuprofen. Although, the antipyretic effect may improve patient comfort; it may mask an early sign of a postoperative infection.

This study was not powered to detect a significant difference in the secondary efficacy variables—gastrointestinal motility, nocturnal awakenings due to pain, resumption of ambulation, resumption of liquid intake and solid diet, and hospital LOS; there were no significant differences observed in the incidence of these variables between either dose of intravenous ibuprofen compared with placebo.

Strengths of this study include the large-scale, multinational, blinded, randomized, controlled design and the inclusion of both men and women. The randomization method accounted for the inherent variability in response to pain due to the influences of age and weight. Extensive tolerability monitoring was continued for the 7 days after the administration of the first dose of study drug.

Weaknesses of this study were the inclusion of a wide variety of surgical procedures from 3 international regions, which might have increased the variability in pain intensity resulting in abnormal distribution of morphine use. While most sites used a PCA pump to administer morphine, some sites used study personnel–administered morphine injections (patient requested), increasing the variability in the measure of the primary end point. The inclusion/exclusion criteria limited the ability to extrapolate tolerability results beyond this relatively healthy population that underwent elective surgery.

The present study found similar prevalences of treatment-emergent AEs among patients who received ibuprofen 400 or 800 mg IV or placebo every 6 hours, with the most common AEs being consistent with surgical procedures and morphine analgesia. The study also found no significant difference between study groups with respect to the proportions of patients who experienced serious AEs, gastrointestinal toxicity, or bleeding. Fewer cases of nausea—a well-established AE of opioid analgesics—were observed in patients treated with either the 400- or 800-mg dose of ibuprofen than with placebo.

CONCLUSIONS

In this study in patients undergoing elective, single-site orthopedic or abdominal surgery, ibuprofen 800 mg IV q6h was associated with a significant morphine-sparing effect and with significant reductions in pain at rest and with movement compared with placebo. Ibuprofen was associated with lower prevalences of certain AEs, including gastrointestinal AEs and pyrexia, at both the 400- and 800-mg doses. Based on these findings, a multimodal approach with morphine and ibuprofen 800 mg IV q6h might be more effective

and better tolerated compared with morphine alone in the management of postoperative pain.

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