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## ORIGINAL ARTICLE

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# A Multicenter, Randomized, Double-Blind, Placebo-Controlled Trial of Intravenous Ibuprofen (IV-Ibuprofen) in the Management of Postoperative Pain Following Abdominal Hysterectomy

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### ■ Abstract

**Background:** Ibuprofen and other nonsteroidal anti-inflammatory drugs are widely used to block pain and inflammation in a variety of settings. Contrarily, opioid analgesia does not block the inflammatory component of pain and the use of these agents can be accompanied by serious side effects. We conducted a multicenter, randomized, double-blind, placebo-controlled trial to evaluate the safety and efficacy of intravenous ibuprofen (IV-ibuprofen) as a postoperative analgesic.

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**Methods:** A total of 319 patients were randomly assigned in a 1:1 ratio to receive 800 IV-ibuprofen or placebo every 6 hours; in addition patients had access to morphine at a dose of 1–2 mg every 5 minutes. The primary outcome measure was median morphine consumption within the first 24 hours following surgery.

**Results:** During the first 24 hours of treatment, the median morphine requirement was reduced by 19% ( $P \leq 0.001$ ) and resulted in a significant reduction in pain at rest (AUC, 6 to 24 hours and 12 to 24 hours,  $P < 0.001$ ) and pain with movement (AUC, 6 to 24 hours,  $P = 0.010$  and 12 to 24 hours,  $P \leq 0.001$ ) as measured by the visual analog scale (VAS) in patients receiving 800 mg IV-ibuprofen compared to placebo. Time to ambulation was significantly faster ( $P = 0.018$ ) in the IV-ibuprofen treated group, as well. Similar treatment-emergent adverse events occurred across both study groups and there was no difference in the overall incidence of these events.

**Conclusion:** This study demonstrated that IV-ibuprofen is an effective analgesic medication that is safe and well tolerated when administered as an 800 mg dose every 6 hours in patients undergoing total abdominal hysterectomy surgery. ■

**Key Words:** analgesia, postoperative pain, nonsteroidal anti-inflammatory drugs, intravenous ibuprofen, hysterectomy

## INTRODUCTION

The importance of effective postoperative analgesia is now widely accepted,<sup>1</sup> and during the last decade there have been a number of organized efforts to improve the overall management of acute pain.<sup>2-4</sup> Nevertheless, the majority of patients undergoing surgical procedures rate their pain as *moderate* to *severe*.<sup>5,6</sup> Overlooking the need for effective postoperative pain control in the short term can evolve into a longer-term clinical problem: if acute postoperative pain is not promptly and adequately controlled, neurohumoral changes and neuronal remodeling can occur, and, as a result, the acute pain may evolve into a prolonged, persistent pain state lasting several months.<sup>7-10</sup>

Several factors have been reported to contribute to suboptimal pain management in patients undergoing a surgical procedure, including both patient and physician concerns about opioid side effects.<sup>11-13</sup> Consequently, over recent years there has been a high degree of interest in the development of opioid-sparing analgesic regimens.<sup>14-16</sup>

One solution to this medical conundrum may lie in a multimodal approach to postoperative analgesia. Multiple mechanisms are now known to be involved in the perception of surgical pain, and although opioids have become the mainstay of postoperative analgesia, these agents alone do not address the inflammatory cascade that occurs during surgical procedures. Uncontrolled inflammation may contribute to inadequate pain control and to the subsequent progression of acute pain to more persistent pain.<sup>17-20</sup> Thus, following a surgical procedure, pre-empting the inflammatory response may reduce the need for opioid analgesics and improve recovery.<sup>21-23</sup>

Nonsteroidal anti-inflammatory drugs (NSAIDs) can provide effective management of mild to moderate postoperative pain, and these medications have also been shown to be effective adjuncts to opioid analgesia. American Pain Society guidelines recommend that opioids and NSAIDs should be provided in an around-the-clock dosing schedule during the first several days after major surgery to prevent and control moderate to severe acute pain.<sup>4</sup>

Ibuprofen is an effective and generally well tolerated NSAID with analgesic, antipyretic, and anti-inflammatory properties.<sup>24-28</sup> Oral administration of ibuprofen, however, is not practical just prior to or

during the immediate postoperative period and at least not until normal bowel function returns. In a recent clinical trial of patients undergoing orthopedic or abdominal surgery, administration of an aqueous ibuprofen formulation at a dosage of 800 mg IV once every 6 hours was associated with a significant reduction in morphine use compared with placebo, as well as reductions in pain severity at rest and with movement.<sup>29</sup> The present study examined reduction in opioid requirements, pain relief, and tolerability when IV ibuprofen was administered to women undergoing elective abdominal hysterectomy.

## METHODS

This was a multicenter, randomized, double-blind, placebo-controlled trial conducted at 10 sites throughout the U.S.A., and approved by an institutional review board or independent ethics committee at all sites (<http://www.Clinicaltrials.gov> registration: NCT00225732).

### Participants

The study population consisted of female patients scheduled for an elective abdominal hysterectomy, who were expected to require postoperative hospitalization and IV morphine analgesia lasting at least 24 hours. Patients requiring hysterectomy were enrolled in this study, and both benign and malignant uterine conditions were eligible. Total abdominal hysterectomy, with either a midline or transverse incision, was the required procedure. Transvaginal and laparoscopic procedures were excluded. Eligible participants ranged in age from 18 to 70 years and were able to reliably provide self-report of pain. All participants provided written informed consent.

Patients were excluded from the study if they had a history of allergy or hypersensitivity to ibuprofen, aspirin, NSAIDs, or COX-2 inhibitors, or if they had a history of tolerance or dependence to narcotics or opioids. Those who were anemic, weighed less than 30 kg, had a history of asthma or heart failure, or were pregnant or nursing were also excluded. Patients were not eligible if they had a platelet count less than 30,000 per mm<sup>3</sup>, gastrointestinal bleeding within 6 weeks of the study, history of bleeding diathesis, or those with a recent history of or increased risk for intracerebral hemorrhage. In addition, patients with renal creatinine clearance less than 70 mL/min, oliguria, or on dialysis within 28 days prior to surgery were also not eligible. Finally, patients were excluded if they were taking warfarin, lithium, or a combination of ACE-

inhibitor and furosemide, or if they received any analgesic, muscle relaxant, or sedative medications within 24 hours of administration of the study medication, excluding sedatives or muscle relaxants used during the surgical procedure. Participants were allowed to take acetaminophen up until 6 hours or NSAIDs up until 12 hours prior to receiving study medication. Local anesthetics were not allowed prior to or during the surgical procedure. Epidural anesthesia and nerve blocks (pre- and intraoperative) were also prohibited.

### Study Design

Patients who met all the inclusion and exclusion criteria during the Screening/Baseline Period were randomized in a 1:1 ratio to receive either IV-ibuprofen or placebo. It has been demonstrated in the literature that morphine use directly correlates with patient age and weight.<sup>30,31</sup> Therefore, before randomization took place, patients were stratified according to two age groups (<45 and >45 to 70 years of age) and two weight groups (<75 kg and >75 kg of weight). Patients greater than 70 years of age were not enrolled in this study because the literature has shown these patients require significantly less morphine for pain treatment, therefore significantly increasing variability in the results. Within each stratum, patients were then randomized to placebo or an 800 mg dose of IV-ibuprofen. In either case, study medication was administered every 6 hours for up to 5 days, in addition to morphine.

The first dose of study medication was administered upon initiation of skin closure (Figure 1). Intraoperatively, patients could receive morphine until approximately 45 minutes prior to completion of the surgical procedure and fentanyl until initiation of study medication. The study medication was administered every 6

hours for a total of eight doses over the first 48 hours. Those patients who received the initial eight doses could continue to receive study medication as needed through the end of the treatment period (day 5). Throughout the treatment period, patients also had access to morphine (1–2 mg every 5 minutes) via patient-controlled analgesia or by patient request.

Study protocol mandated discontinuation of study medication if the patient required the use of additional pain medication, including a narcotic other than morphine or any other non-narcotic pain medication including NSAIDs due to the inability to manage pain. These cases were classified as treatment failures. After 24 hours (four doses of study medication), study medication could be discontinued upon resolution of pain, loss of IV access, or discharge from the hospital.

### Efficacy Endpoints

The primary efficacy endpoint was a reduction in the requirement for morphine during the first 24 hours following surgery as measured by total morphine usage compared with placebo. Secondary efficacy endpoints included: reduction in pain intensity, time to first subsequent narcotic analgesia for breakthrough pain, incidence of opioid-related side effects, resumption of ambulation, resumption of liquid intake and solid diet, and length of hospital stay.

Pain intensity was measured by patient self-assessment using a visual analog scale (VAS) of 0–10. These assessments were made at 1, 3, 6, 9, 12, 15, 18, 21, 24, 30, 36, 42, and 48 hours for both pain at rest and pain with movement. Assessment of pain continued in this way from hour 48 through day 5 (or discontinuation of study medication). To determine the difference in overall pain at differing time-points, the area under

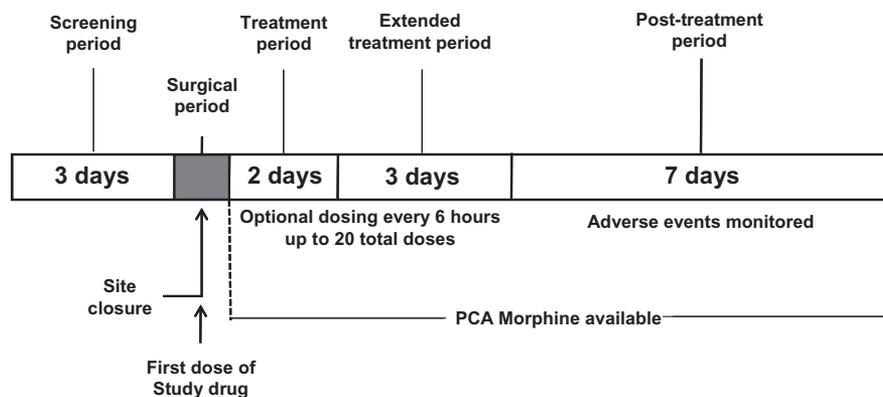


Figure 1. Study timeline.

the VAS pain curve (AUC) was analyzed during the first 24 hours, between 6 and 24 hours, and between 12 and 24 hours.

Evaluation of the incidence of opioid-related side effects was made by measuring multiple endpoints including: gastrointestinal motility, resumption of ambulation, resumption of liquid intake and solid diet, length of hospital stay. A combined safety assessment also included the incidence of diffuse pruritis, overt respiratory depression requiring treatment, need for a postoperative urinary indwelling catheter (after removal of the surgical catheter), postoperative vomiting or need for an anti-emetic medication, and score on the Richmond Agitation Sedation Scale less than or equal to -3.

### Safety Assessment

At baseline entry to the study, vital signs were recorded; a physical examination was conducted; blood samples were drawn for clinical chemistry, hematology, and coagulation analysis; and concomitant medications were reviewed. Baseline signs and symptoms, and transfusion requirements were recorded for each patient. Adverse events, vital signs, concomitant medications, and transfusion requirements were monitored throughout the 5-day treatment period.

After day 5, participants were observed during a post-treatment period from day 6 through day 14. Monitoring for adverse events continued through the post-treatment period. Patients discharged before day 14 either returned to the hospital or were contacted by telephone to obtain reports of any adverse events that occurred following their discharge through day 14. Upon discharge, or on day 7, blood samples were drawn for final measurement of clinical chemistry, hematology, and coagulation variables.

### Statistical Analysis

A predefined statistical analysis plan was utilized for this study and the power calculations contained therein indicated that a sample size of 290 (145 per group) was needed to show a 20% reduction in morphine use (alpha level of 0.05 and power of 90%).

Case report forms were identical for all sites and contained a "manual of operations," providing detailed instructions for each data item. Special instructions required for procedures were included within the manual. This information supplemented instructions in the clinical protocol. Additionally, the principal investigators and their staff were trained on the data collection procedures required for the study, including how to

conduct the patient-completed VAS assessment. The VAS was presented as a 100-mm horizontal line anchored by the words "no pain" and "worst possible pain" at each end. The patient was instructed to mark on the line the point that they felt represented their perception of their current pain.

Statistical analyses for the efficacy endpoints were conducted on the intent-to-treat (ITT) population, which comprised all patients who were randomized and received at least a partial dose of IV-ibuprofen or placebo.

Morphine usage values were analyzed with SAS<sup>®</sup> PROC GLM, Version 9.1.3 (SAS Institute, Inc., Cary, NC, U.S.A.). 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. 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.

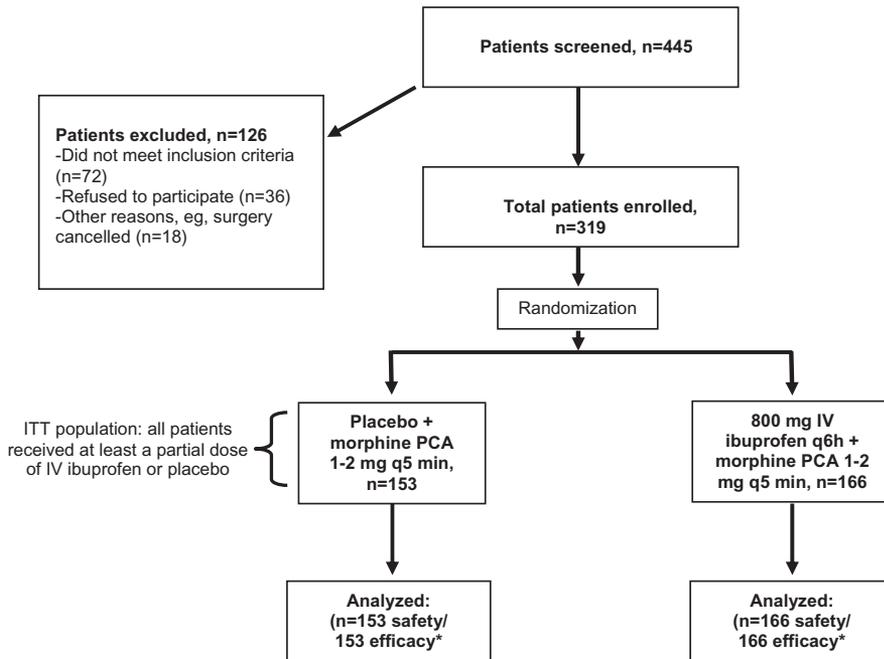
Among the methods that were used were logarithm (log) and Box-Cox transformations and nonparametric testing (rank transformation). It was determined that the Box-Cox transformation method was most appropriate and therefore was used for this analysis. Mean, median, and least squares means (transformed) data are presented.

All statistical tests were two-sided, with  $P < 0.05$  considered to be significant for treatment differences and  $P \leq 0.10$  considered to be significant for interaction effects. Analysis of variance and covariance procedures were used to compare the reduction in the requirement for morphine use in the 24 hours following surgery among the treatment groups. Dunnett's test was used as a multiple comparison test to compare active dose groups with the placebo group.<sup>32</sup>

## RESULTS

### Patient Population

A total of 319 female patients were randomized into the two treatment groups, with 153 patients in the placebo group and 166 patients in the IV-ibuprofen group (Figure 2). There were no observed differences in demographic and baseline characteristics between the treat-



**Figure 2.** Distribution of patients randomized to receive IV-ibuprofen or placebo for the management of pain following abdominal hysterectomy. \* All 319 patients were eligible for analysis of the primary endpoint (morphine use in the 24 hours following surgery). However, all 319 patients had study medication discontinued prior to treatment day 5. The primary reason for discontinuation was due to intravenous access being discontinued: IV-ibuprofen 148 (89%); Placebo 127 (83%).

**Table 1. Summary of Baseline Demographics and Patient Characteristics**

	IV-Ibuprofen + Morphine PCA (n = 166)	Placebo + Morphine PCA (n = 153)	Total (n = 319)
Age, years			
Mean (SD)	42 (7.0)	42 (7.2)	42 (7.1)
Age category			
< 45 years	110 (66%)	104 (68%)	214 (67%)
45–70 years	56 (34%)	49 (32%)	105 (33%)
Gender			
Male	0 (0%)	0 (0%)	0 (0%)
Female	166 (100%)	153 (100%)	319 (100%)
Race			
Caucasian	71 (43%)	52 (34%)	123 (39%)
Black	84 (51%)	91 (59%)	175 (55%)
Hispanic	11 (7%)	8 (5%)	19 (6%)
Asian	0 (0%)	0 (0%)	0 (0%)
Other	0 (0%)	2 (1%)	2 (< 1%)
Height, cm			
Mean (SD)	163.8 (8.22)	163.0 (7.56)	163.4 (7.91)
Weight, kg			
Mean (SD)	83.9 (18.67)	83.0 (19.07)	83.5 (18.83)
Weight category			
< 75 kg	61 (37%)	57 (37%)	118 (37%)
> 75 kg	105 (63%)	96 (63%)	201 (63%)
Age and weight stratum			
Age < 75 years, weight < 75 kg	43 (26%)	41 (27%)	84 (26%)
Age < 75 years, weight > 75 kg	67 (40%)	63 (41%)	130 (41%)
Age 45–70 years, weight < 75 kg	18 (11%)	16 (10%)	34 (11%)
Age 45–70 years, weight > 75 kg	38 (23%)	33 (22%)	71 (22%)

Differences between placebo and IV-ibuprofen groups were not statistically significant for all categories. SD, standard deviation.

ment groups (Table 1). Twenty-four patients in the placebo treatment group and 16 patients in the IV-ibuprofen treatment group discontinued the study intervention/dropped out of the study. The reasons for

study discontinuation were initiated by both physicians and patients, and they included discontinuation secondary to an AE or discontinuation due to treatment failure.

There was no difference between treatment groups with respect to the number of doses of study medication that were administered. All 319 patients who met the inclusion criteria, and who were randomized to one of the two treatment groups, received at least one dose of study medication, with a median of five doses administered across treatment groups.

### Primary Efficacy Variable

Patients who received IV-ibuprofen required significantly less morphine in the first 24 hours following surgery, compared with patients who received placebo (Table 2). Patients who received IV-ibuprofen used a median of 43.5 mg morphine, whereas patients in the placebo group used a median of 54.0 mg morphine, representing a 19% reduction in median morphine use for those receiving IV-ibuprofen ( $P < 0.001$ ).

### Secondary Efficacy Variables

Compared with patients receiving placebo, those receiving IV-ibuprofen reported statistically significantly lower pain assessment scores, both at rest and with movement, for all three time segments (during the first 24 hours, 6 to 24 hours, and 12 to 24 hours), as determined by the AUC for patient self-reported scores (Figure 3). In addition to the morphine sparing-effect, patients receiving 800 mg IV-ibuprofen experienced a significant reduction in pain as measured by the VAS at rest AUC for the first 24 hours (21%,  $P = 0.011$ ), from 6 through 24 hours (27%,  $P < 0.001$ ), and from 12 through 24 hours (37%,  $P < 0.001$ ) and pain with movement for the first 24 hours (14%,  $P = 0.010$ ), from 6 through 24 hours (20%,  $P = 0.001$ ), and from 12

through 24 hours (24%,  $P < 0.001$ ) after surgery. In addition, the time to ambulation was significantly shorter in the IV-ibuprofen group than in the placebo group (23.4 hours vs. 25.3 hours,  $P = 0.009$ ).

The incidence of treatment failure was numerically lower in the group of patients receiving IV-ibuprofen compared to those in the placebo group (4% vs. 7%); this difference, however, was not statistically significant ( $P = 0.250$ ). Statistically significant differences were not observed in the other secondary efficacy variables.

### Safety Analysis

All patients who were enrolled in the study and received at least one dose of medication were included in the safety analysis population. Treatment-emergent adverse events were reported in 268 of the 319 patients. In the IV-ibuprofen group, 136/166 (82%) patients experienced treatment-emergent adverse events compared with 132/153 (86%) patients in the placebo group. This difference did not reach statistical significance.

Similar treatment-emergent adverse events were reported in both study groups (Table 3). The most common adverse events experienced by three or more patients were nausea, flatulence, pruritis, constipation, vomiting, pyrexia, headache, and increase in body temperature and white blood cell count. All of these effects are commonly observed in postoperative patients receiving morphine. There was no difference between the two groups with respect to blood pressure, bleeding, or bruising, which are commonly associated with oral ibuprofen use.

There was no statistically significant difference in the number of patients experiencing serious adverse events when comparing the IV-ibuprofen group with the placebo group (placebo  $n = 5$ , IV-ibuprofen  $n = 12$ ;  $P = 0.136$ ). There were no observed differences between the treatment groups with respect to heart rate, respiratory rate, temperature, or systolic or diastolic blood pressure, and there were no patient deaths during the 14-day study.

## DISCUSSION

There is now an abundance of evidence supporting the effectiveness of multimodal analgesic regimens for the management of acute postoperative pain,<sup>4,16,21,33</sup> and the findings of this study add further to that body of evidence. Using IV-ibuprofen at a dosage of 800 mg every 6 hours to alleviate postoperative pain was found to be significantly morphine-sparing, with a

**Table 2. Morphine Requirements During the Immediate 24 Hours Following Surgery**

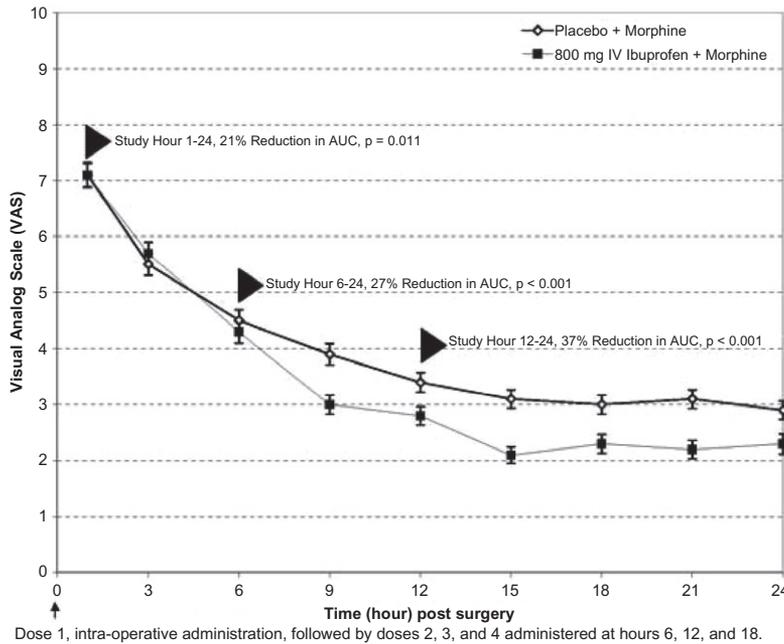
	IV-Ibuprofen + Morphine PCA ( $n = 166$ )	Placebo + Morphine PCA ( $n = 153$ )
Morphine requirement		
Mean (SD), mg	47.3 (25.6)	55.9 (20.6)
Median, mg	43.5	54.0
LS Means* (SE), mg	48.7 (2.3)	57.0 (2.4)
$P$ -value <sup>†</sup>	< 0.001	—
Transformed morphine requirement <sup>‡</sup>		
LS Means (SE),* mg	12.08 (0.4)	13.6 (0.4)
$P$ -value <sup>†</sup>	< 0.001	—

\* LS means are adjusted for age group, weight group, randomization center, and treatment group.

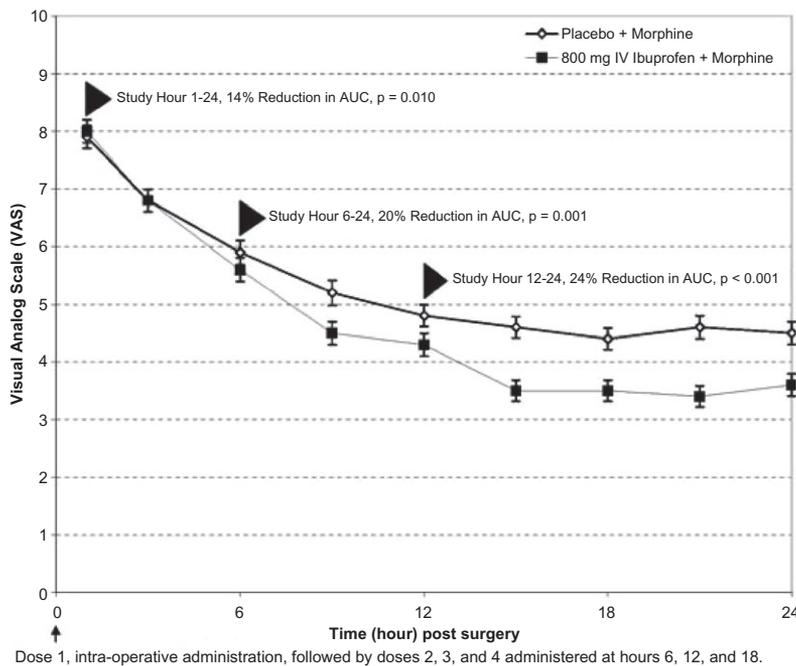
<sup>†</sup> The analysis is based on a linear 4-way ANOVA model with fixed effects for age group, weight group, randomization center, and treatment group. The  $P$ -value is based on the difference in LS Means from the final ANOVA model.

<sup>‡</sup> Data are transformed using the Box-Cox transformation. LS means are adjusted for age group, weight group, randomization center, and treatment group.

(A)



(B)



**Figure 3.** Postoperative pain reduction over time at rest (A) and with movement (B). The patient self-reported pain scores at rest and with movement during the immediate 24 hour postsurgery period were plotted for the IV-ibuprofen and placebo treatment groups. The AUC was then calculated for each treatment group.

19.5% reduction in median morphine use in patients receiving IV-ibuprofen compared with those receiving placebo.

Results from this trial also demonstrated significant reductions in pain, assessed at rest and with movement, for IV-ibuprofen compared with placebo. Because both treatment groups received morphine, the lower pain

intensity reported by patients who received IV-ibuprofen vs. placebo suggests that a synergistic benefit may have been conferred in these patients. This observation is not surprising, given that multiple mechanisms are known to be involved in the perception of postoperative pain, further underscoring the potential value of multimodal analgesia in this setting. Additional

**Table 3. Summary of Adverse Events Occurring in 3 or More Patients**

	IV-Ibuprofen + Morphine PCA <i>n</i> = 166 (%)	Placebo + Morphine PCA <i>n</i> = 153 (%)	Total <i>n</i> = 319 (%)	<i>P</i> value
Overall	136 (82)	132 (86)	268 (84)	—
Gastrointestinal disorders	106 (64)	107 (70)	213 (67)	0.285
Nausea	79 (48)	85 (56)	164 (51)	0.179
Flatulence	42 (25)	34 (22)	76 (24)	0.599
Constipation	13 (8)	21 (14)	34 (11)	0.103
Vomiting	15 (9)	12 (8)	27 (8)	0.841
Abdominal distension	2 (1)	6 (4)	8 (3)	0.159
Ileus	4 (2)	1 (< 1)	5 (2)	0.373
Skin and subcutaneous tissue disorders	33 (20)	34 (22)	67 (21)	0.680
Pruritus	32 (19)	33 (22)	65 (20)	0.677
Investigations	22 (13)	23 (15)	45 (14)	0.748
Body temperature increased	7 (4)	7 (5)	14 (4)	> 0.999
While blood cell count increased	4 (2)	6 (4)	10 (3)	0.529
Hematocrit decreased	3 (2)	5 (3)	8 (3)	0.487
Hemoglobin decreased	5 (3)	2 (1)	7 (2)	0.451
Blood potassium decreased	3 (2)	3 (2)	6 (2)	> 0.999
Blood lactate dehydrogenase increased	1 (< 1)	3 (2)	4 (1)	0.353
Neutrophil count increased	1 (< 1)	3 (2)	4 (1)	0.353
Nervous system disorders	14 (8)	15 (10)	29 (9)	0.701
Headache	10 (6)	11 (7)	21 (7)	0.822
Dizziness	1 (< 1)	3 (2)	4 (1)	0.353
General disorders and administration site conditions	12 (7)	11 (7)	23 (7)	> 0.999
Pyrexia	6 (4)	9 (6)	15 (5)	0.430
Renal and urinary disorders	9 (5)	5 (3)	14 (4)	0.419
Dysuria	3 (2)	3 (2)	6 (2)	> 0.999
Hematuria	3 (2)	0 (0)	3 (< 1)	0.249
Infections and infestations	6 (4)	4 (3)	10 (3)	0.752
Respiratory, thoracic, and mediastinal disorders	7 (4)	3 (2)	10 (3)	0.340
Metabolism and nutrition disorders	3 (2)	5 (3)	8 (3)	0.487
Hypokalemia	3 (2)	5 (3)	8 (3)	0.487
Psychiatric disorders	3 (2)	5 (3)	8 (3)	0.487

evidence from recent epidemiologic studies suggests that women undergoing hysterectomy may be particularly at risk for adverse pain experiences. These studies have found that, in general, postoperative pain may be more severe among women than men,<sup>34</sup> and the new multimodal approach presented in this study involving IV ibuprofen as an adjunct to morphine may prove beneficial to these patients.

Oral ibuprofen has been widely used as a safe and effective treatment of pain, fever, and inflammation for more than 30 years.<sup>35,36</sup> However, there are some safety concerns for the NSAID drug class as a whole, most of these effects are associated with longer-term use.<sup>37</sup> These concerns resulted in the FDA adding a black box warning to all NSAID containing products in 2005.<sup>38</sup> This warning specifically outlines the gastrointestinal and renal toxicity and general bleeding risks associated with NSAID use.<sup>38</sup>

An IV-ibuprofen preparation would most likely be used on a short-term basis in hospitalized patients and in out-patient surgical procedures, likely decreasing the incidence of these safety concerns. IV-ibuprofen has

been modestly studied in pain and fever, although several studies have been done with a low dose preparation of the lysine salt that is used to treat patent ductus arteriosus in neonates.<sup>39</sup>

Three studies have been completed on investigational formulations of IV-ibuprofen and none have demonstrated any safety concerns.<sup>40–42</sup> These studies used a range of doses up to 800 mg and found: no renal issues in terms of the number of days of renal failure, serial creatinine levels, serial urinary output, or the need for dialysis; no GI toxicity or bleeding issues; and no effect on transfusion requirements or hemoglobin levels.<sup>40–42</sup> These results are pertinent considering that the studies involved critically ill hospitalized patients. Additionally, Southworth et al. did not find an increased incidence of bleeding in their IV-ibuprofen in surgical procedures study,<sup>29</sup> and Brinkmann et al. found no adverse effects of IV-ibuprofen on renal function in critically ill patients undergoing renal surgery.<sup>43</sup> In the present study, adverse events were experienced by 82% of patients in the 800 mg IV-ibuprofen group, and by 86% of patients in the placebo group. There was no significant difference

in the incidence of serious adverse events with IV-ibuprofen compared with placebo, as well. Gastrointestinal bleeding and/or toxicity, renal toxicity, and generalized bleeding did not arise in the present study. Taken together, these data suggest that IV-ibuprofen is a safe treatment option for surgical patients.

## CONCLUSIONS

These findings indicate that intraoperative and postoperative administration of 800 mg IV-ibuprofen for the management of postoperative pain has a significant morphine-sparing effect, reduces the severity of pain as determined by patient self-reported scores using a VAS, and is generally well tolerated. These results are consistent with and support the findings from another recent clinical trial that evaluated IV-ibuprofen in patients undergoing orthopedic or abdominal surgery.<sup>29</sup>

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