

A Multicenter, Randomized, Double-Blind, Placebo-Controlled Trial of Ibuprofen Injection for Treatment of Pain in Post-Operative Adult Patients

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INTRODUCTION

Opioid medications are a mainstay of postoperative pain management and act centrally within the nervous system to provide analgesia.¹ These agents, however, can have serious, well recognized side effects. Furthermore, opioids do not interrupt the inflammatory process. It has been suggested that preempting the inflammatory response, which can begin within 20 minutes of injury, may reduce the overall need for analgesic medication, including opioids, and improve recovery following surgical procedures.²⁻⁴ Nonsteroidal anti-inflammatory drugs (NSAIDs) have been extensively used for several years as a reliable way to block pain and inflammation in a variety of settings.

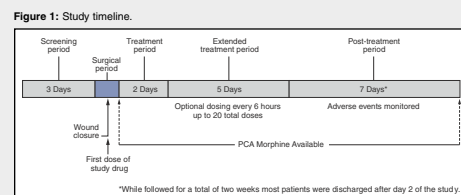
A multimodal approach to pain management has been proposed as a means of achieving comprehensive pain relief, while minimizing the potential for opioid-related adverse effects by lowering the total dose of opioid that is required.⁵ An aqueous formulation of ibuprofen, Caldolor[®], has recently been approved by the US Food and Drug Administration (FDA) for use in adults for treatment of mild to moderate pain, moderate to severe pain as an adjunct to opioid medications and reduction of fever. Oral ibuprofen is a widely used, generally well tolerated, and effective NSAID with analgesic, anti-pyretic and anti-inflammatory properties. However, oral administration is not practical during the immediate postoperative period. To provide efficacy and tolerability data for a new drug application submitted to FDA, this study was conducted to assess the tolerability and efficacy of intravenously administered ibuprofen in the management of pain control as measured by the reduction of opioid use and patients' self-assessment of pain in patients after elective abdominal surgical procedures.

ABBREVIATIONS & DEFINITIONS

ACE	Angiotensin Converting Enzyme
AE	Adverse Event
AUC	Area Under the Curve
BL	Baseline
BUN	Blood Urea Nitrogen
C	Centigrade
CPI	Cumberland Pharmaceuticals Inc.
CTM	Clinical Trial Material
dL	Deciliter
EEP	Efficacy Evaluable Population
FDA	Food and Drug Administration
ITT	Intent to Treat
IVib	Ibuprofen Injection
Kg	Kilogram
mg	milligrams
mL	Milliliter
mm	Millimeter
N/A	Not Applicable
NSAID	Non-Steroidal Anti-Inflammatory Drug
PCA	Patient Controlled Analgesia
q	Every
SAE	Serious Adverse Event

METHODS

This multicenter, randomized, double-blind, placebo-controlled trial was conducted at 10 sites within the United States between January 2007 and December 2007 enrolling a total of 319 patients. An institutional review board or independent ethics committee approved the study at each clinical study site. Patients were eligible for the study if they underwent elective abdominal hysterectomy, and were expected to require hospitalization and post-operative IV morphine analgesia for longer than 24 hours.



Study Design:

Key Inclusion Criteria

- Scheduled for elective abdominal hysterectomy surgery with anticipated need for post-operative I.V. morphine analgesia with anticipated use of > 24 hours
- Adequate IV access
- Anticipated hospital stay ≥ 24 hours

Key Exclusion Criteria

- <18 or >70 year of age
- Unable to provide informed consent or reliable self-report of pain
- Weighted <30 kg
- History of allergy or hypersensitivity to ibuprofen, aspirin, NSAIDs, or cyclooxygenase-2 inhibitors
- Anemic
- History of asthma or heart failure
- Pregnant or breastfeeding
- At increased risk for bleeding (including a platelet count < 30,000 cells/L)
- History of gastrointestinal bleeding within 6 weeks before surgery, or a history of bleeding diathesis, or were at increased risk for intra-cerebral 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
- 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)

Randomization:

Participants were randomized in a 1:1 ratio to one of two treatment groups: morphine and 800 mg IV ibuprofen, or morphine and placebo. Because morphine dosage correlates with age and weight,^{6,7} participants were stratified to two age (18-45 years, 46-70 years) and weight (<75 kg, >75 kg) groups prior to randomization.

Surgical Analgesia:

The study protocol allowed the preoperative and intraoperative administration of morphine until approximately 45 minutes prior to the end of the surgical procedure. After this time, patients could only receive fentanyl until the first dose of IV ibuprofen or placebo was administered.

Dosing:

The first dose of IV ibuprofen or placebo was administered intra-operatively at the initiation of wound closure. The IV ibuprofen or placebo was then administered every six hours for a total of eight doses over the first 48 hours of the study. After the initial eight doses, the protocol allowed for continued administration of IV ibuprofen or placebo, every six hours, at the discretion of the investigator, for control of postoperative pain for a total of up to 120 hours. However, after the first 24 hours the, study protocol mandated discontinuation of IV ibuprofen and placebo if the patient received either narcotic pain medication other than morphine or non-narcotic pain medication, including the use of another NSAID. After 24 hours and through day five, IV ibuprofen and placebo could also be discontinued if the patient was able to tolerate oral pain medication, upon resolution of pain or loss of IV access, or if the patient was discharged from the hospital.

Patients also had access to morphine throughout the treatment period. Morphine could be administered either by patient request or by patient-controlled analgesia (PCA) pump (1-2 mg every five minutes).

Objectives:

The primary objective was to determine the efficacy of IV ibuprofen compared to placebo for the treatment of post-operative pain as measured by reduction in the requirement for the narcotic analgesic, morphine, post-surgery.

Primary Endpoint

The primary endpoint of this study was a reduction in morphine administered during the immediate 24 hours following surgery.

Secondary Endpoints

- Efficacy Endpoints
 - Secondary endpoints included a reduction in pain intensity measured at rest and with movement by patient self-report using a 0-10 visual analog pain scale (VAS; 0 being no pain and 10 being intense pain).

Safety Endpoints

- comparison of treatment emergent adverse events;
- vital signs;
- clinical chemistry, hematology and coagulation measurements;
- transfusion requirements (total units of packed red blood cells, fresh frozen plasma, and platelets)

Statistical Analysis:

Statistical analyses for the efficacy endpoints were conducted on the intent-to-treat population (all patients who were randomized and received at least a

partial dose of IV ibuprofen or placebo) and the efficacy-evaluable population (EEP) (all patients who received at least 4 doses of IV ibuprofen or placebo within 60 minutes of the scheduled administration time).

Morphine usage values were analyzed with SAS[®] PROC GLM, Version 9.1.3. 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 2-sided, with $P < 0.05$ considered significant for treatment differences and $P < 0.10$ considered 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.⁸

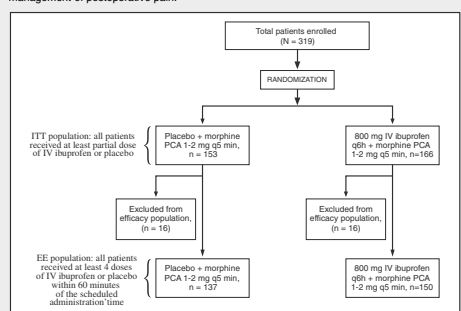
RESULTS

A total of 319 patients were enrolled, randomized, and received study medication; 166 in the 800 mg IV ibuprofen + morphine group, and 153 in the placebo + morphine group.

Table 1: Summary of Patient Demographics and Baseline Characteristics: All data are no. (%) unless otherwise indicated.

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

Figure 2: Distribution of patients randomized to receive IV ibuprofen or placebo for the management of postoperative pain.



Efficacy Outcomes:

The primary efficacy measure was reduction in the requirement for morphine use in the 24 hours following surgery. Table 2 presents morphine requirements during the first 24 hours following surgery in patients administered IV ibuprofen or placebo.

Primary Efficacy Variable:

Reduction in Morphine Requirements

Compared to placebo there was a reduction in the use of morphine through 24 hours in patients receiving 800 mg IV ibuprofen ($p < 0.001$). In the ITT population there was a 19.5% reduction and in the EEP population there was a 22% reduction in median morphine consumption in patients receiving 800 mg IV ibuprofen.

Table 2: Morphine requirements during the immediate 24 hours following surgery

	Placebo + morphine PCA	800 mg IV ibuprofen + morphine PCA
ITT population		
No. of patients included in analysis	153	166
Morphine requirement, mg		
Mean (SD)	56.0 (20.6)	47.3 (25.6)
Median	24.0	43.5
LSMeans (SE) [†]	57.03 (2.4)	48.7 (2.3)
P-value*	---	>0.001
Transformed morphine requirement*		
LSMeans (SE) [†]	13.57 (0.4)	12.08 (0.4)
P-value*	---	<0.001

[†]LS means are adjusted for age group, weight group, randomization center, and treatment group.
*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 LSMeans from the final ANOVA model.
*Data are transformed using the box-cox transformation. LS means are adjusted for age group, weight group, randomization center, and treatment group.

Figure 3: Median morphine usage in the immediate 24 hours following surgery, ITT population.

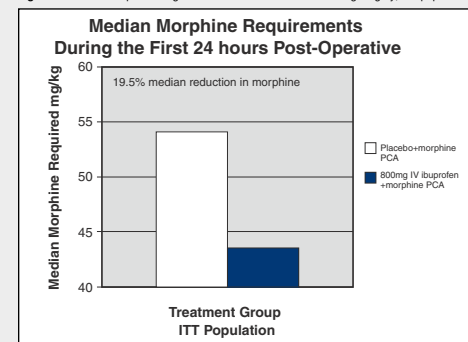
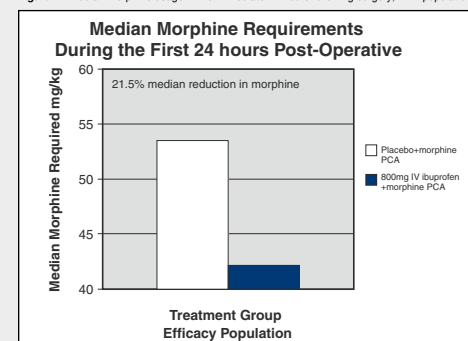


Figure 4: Median morphine usage in the immediate 24 hours following surgery, EEP population.



Secondary Efficacy Variables

Data were also analyzed to assess a reduction in pain intensity by patient self-report using a 0-10 visual analog scale (VAS; 0 being no pain and 10 being intense pain). To determine the difference in overall pain at differing time-points, the area under the VAS pain curve (AUC) was analyzed over the first 24 hours, between 6 and 24 hours, and between 12 and 24 hours.

Secondary Efficacy Variables (continued)

Patients receiving IV ibuprofen reported lower levels of both pain with movement and pain at rest for all three time segments (during the first 24 hours, 6-24 hours, and 12-24 hours), compared with patients who received placebo, as determined by the AUC for patient self-reported scores.

Figure 5: Pain Reduction Assessed at Rest Over Time with 800 mg IV ibuprofen vs. Placebo

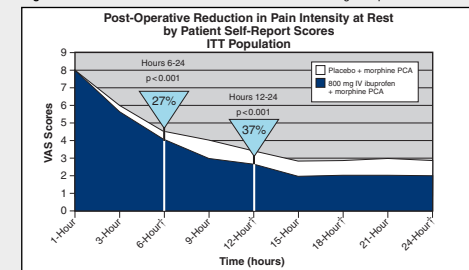
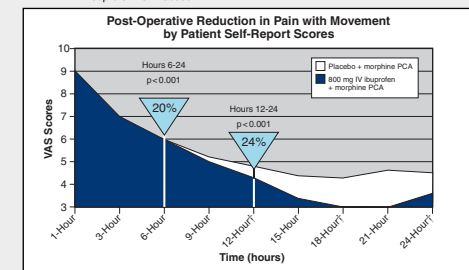


Figure 6: Pain Reduction Assessed with Movement Over Time with 800 mg IV ibuprofen vs. Placebo



In the ITT group, the 800 mg dose of IV ibuprofen significantly reduced both pain at rest and pain with movement for all three time periods (1-24 hours, 6-24 hours, 12-24 hours) when compared to placebo.

Safety Outcomes:

Adverse Events

Compared to placebo, treatment with IV ibuprofen did not result in more adverse events, serious adverse events, or abnormalities of safety lab measurements.

Table 3: Summary of Adverse Events

System Organ Class	Preferred Term	Placebo (n=153)	IV ibuprofen (n=166)	Total Safety Population (n=319)
Gastrointestinal disorders				
Nausea	107 (70%)	106 (64%)	213 (67%)	
Flatulence	34 (22%)	42 (25%)	76 (24%)	
Constipation	21 (14%)	13 (8%)	34 (11%)	
Vomiting	12 (8%)	15 (9%)	27 (8%)	
Abdominal distension	6 (4%)	2 (1%)	8 (2%)	
Itus	1 (<1%)	4 (2%)	5 (2%)	
Skin and subcutaneous tissue disorders				
Pruritus	33 (22%)	32 (19%)	65 (20%)	
Body temperature increased	7 (5%)	7 (4%)	14 (4%)	
White blood cell count increased	6 (4%)	4 (2%)	10 (3%)	
Hematocrit decreased	5 (3%)	3 (2%)	8 (2%)	
Hemoglobin decreased	2 (1%)	5 (3%)	7 (2%)	
Blood potassium decreased	3 (2%)	3 (2%)	6 (2%)	
Blood lactate dehydrogenase increased	3 (2%)	1 (<1%)	4 (1%)	
Neutrophil count increased	3 (2%)	1 (<1%)	4 (1%)	
Nervous system disorders				
Headache	11 (7%)	10 (6%)	21 (7%)	
Dizziness	3 (2%)	1 (<1%)	4 (1%)	
General disorders and administration site conditions				
Pyrexia	9 (6%)	6 (4%)	15 (5%)	
Renal and urinary disorders				
Dysuria	3 (2%)	3 (2%)	6 (2%)	
Hematuria	0	3 (2%)	3 (<1%)	
Infections and infestations				
Respiratory, thoracic and mediastinal disorders				
Metabolism and nutrition disorders				
Hypocalcemia	5 (3%)	3 (2%)	8 (2%)	
Psychiatric disorders				
Insomnia	5 (3%)	3 (2%)	8 (2%)	

Vital Signs

There were no observed differences between heart rate, respiratory rate, temperature, systolic or diastolic blood pressure between treatment groups.

Clinical Laboratory Values

Laboratory abnormalities that are commonly associated with oral ibuprofen, such as blood pressure elevations, bleeding, and bruising, were evaluated and the incidence of these events did not differ between groups.

Transfusion Requirements

The packed red blood cell transfusions between study day 0 and 5 did not differ between groups: 800 mg IVib 6 (4%); Placebo 8 (6%).

CONCLUSIONS

- Compared with placebo, IV ibuprofen had a significant reduction in patient self-reported pain intensity in addition to a morphine-sparing effect.
- Patients receiving 800 mg IV ibuprofen used less morphine than those receiving morphine alone.
- There was a 19.5% reduction in median morphine use in patients receiving 800 mg IV ibuprofen compared with those receiving morphine alone.
- Results from this trial demonstrated significant reductions in pain, assessed at rest and with movement for 800 mg IV ibuprofen compared with placebo.
- Adverse events were experienced by 82% of patients in the 800 mg IV ibuprofen group, and by 86% in the placebo group. There was no significant difference in the incidence of serious adverse events between either IV ibuprofen group when compared to placebo.

These findings indicate that intra- and postoperative administration of 800 mg IV ibuprofen is safe and effective for postoperative pain management.

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Presented at the 20th Annual American Academy of Pain Management Meeting
October 10, 2009, Phoenix, AZ