

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

Neil Singla, MD<sup>a</sup>, Byron Kaelin, RN<sup>b</sup>, Leo Pavliv, RPh, MBA<sup>c</sup>, Amy Rock, PhD<sup>d</sup>

<sup>a</sup>Chief Executive Officer, Lotus Clinical Research Inc. | <sup>b</sup>Manager, Clinical Affairs, Cumberland Pharmaceuticals Inc. | <sup>c</sup>Senior Vice-President, Operations, Cumberland Pharmaceuticals Inc. | <sup>d</sup>Senior Director, Regulatory and Scientific Affairs, Cumberland Pharmaceuticals Inc.

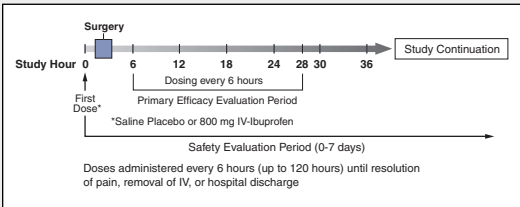
## INTRODUCTION

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.<sup>1</sup> An intravenous formulation of ibuprofen, Caldolor® (ibuprofen) Injection, 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, antipyretic and anti-inflammatory properties. However, oral administration is not practical during the immediate pre- and postoperative periods. This study was conducted to assess the tolerability and efficacy of pre- and postoperatively administered IV ibuprofen in the management of pain control as measured by the patients' self-assessment of pain and by the reduction of opioid use in patients after elective orthopedic surgical procedures.

## METHODS

This was a multi-center, randomized, double-blind, placebo-controlled study conducted at eight sites; six in the U.S. and two in South Africa between June 2007 and April 2008 enrolling a total of 198 patients with 185 of the patients randomized to receive study drug. An institutional review board or independent ethics committee approved the study at each clinical study site.

Figure 1: Study Timeline



### Study Design

#### Key Inclusion Criteria:

- Scheduled for elective hip or knee replacement, reconstruction or arthroplasty surgery with anticipated need for post-operative IV morphine analgesia with anticipated use of ≥ 28 hours and adequate IV access.

#### Key Exclusion Criteria

- <18 years of age or > 80 years of age
- Unable to provide informed consent or reliable self-report of pain
- Weighed <30 kg
- History of allergy or hypersensitivity to ibuprofen, aspirin, NSAIDs, or cyclooxygenase-2 inhibitors
- History of asthma or heart failure
- Pregnant or breastfeeding
- Anemic or at increased risk for bleeding (including a platelet count <30,000 cells/μL)

- 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 or were undergoing dialysis within 28 days before surgery
- Receiving warfarin, lithium, or a combination of angiotensin-converting enzyme inhibitors and furosemide

#### 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, participants were stratified to two age (18-45 years, 45-80 years) and weight (≤75 kg, >75 kg) groups prior to randomization.

#### Surgical Analgesia:

All patients received general anesthesia using various anesthetics such as propofol or a member of the flurane drug family along with fentanyl for intra-operative narcotic maintenance (fentanyl dose was per the discretion of the anesthesiologist). Intraoperative use of any other analgesics including non-steroidal agents was prohibited. Neuraxial anesthesia (local anesthetics and narcotics) were prohibited. Patients had access to morphine throughout the treatment period. Morphine could be administered by patient-controlled analgesia (PCA) pump (1-2 mg every five minutes) or by patient.

#### Dosing:

The first dose of IV ibuprofen or placebo was administered at the initiation of anesthesia prior to the surgical procedure. IV ibuprofen or placebo was then administered every six hours for a total of 5 doses. After the initial five doses, the protocol allowed for continued administration of study medication, every six hours, for a total of up to 120 hours. After 28 hours and through day five, study medication could 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.

#### Objectives:

The primary objective of this study was to determine the efficacy of IV ibuprofen plus morphine compared to morphine plus placebo for the treatment of post-operative pain demonstrated by patients' self-assessment of pain with movement using a 0-10 visual analog pain scale (VAS; 0 being no pain and 10 being intense pain).

#### Primary Endpoint:

- The AUC-VAS (ibuprofen plus morphine) assessed with movement during the post-operative period (study hour 6 through hour 28), as compared to morphine plus placebo.

#### Secondary Endpoints:

- Morphine use in the post-operative period (study hour 6 through hour 28).
- The AUC-VAS at rest.
- The AUC-VRS.
- The initial VAS score at the first possible post-operative assessment post-surgery.

Safety was evaluated based upon comparison of treatment emergent adverse events, vital signs, clinical chemistry, hematology and coagulation measurements, and transfusion requirements.

#### Statistical Analysis:

Analysis of the efficacy parameters was conducted on all patients randomized to receive study drug.

- The area under the curve (AUC) from 6 to 28 hours for the VAS (AUC-VAS) assessed with movement was the primary efficacy endpoint, and the analysis of variance (ANOVA) was applied. The primary model included factors for study center, treatment group, age group, weight group and their interactions. Frequency and percent of treatment failure was compared across treatment groups using a Chi-square test, while the time to treatment failure was evaluated using survival methods. Median time to treatment failure was calculated using the Kaplan-Meier approach and the treatment groups were compared with a Log-rank test.

## RESULTS

A total of 198 patients were enrolled, randomized, and 185 received study medication; 99 in the 800 mg IV ibuprofen + morphine group, and 86 in the placebo + morphine group. There were no observed differences in demographic and baseline characteristics between treatment groups. The mean age for all patients was 61 (±10.2 SD) years. Age ranged from a minimum of 24 to a maximum of 80 years. Of the 185 patients enrolled, 92 (50%) underwent a knee replacement, 40 (22%) underwent a hip replacement, 36 (19%) underwent a knee reconstruction, 16 (9%) underwent a hip reconstruction and one (<1%) underwent an "other" surgical procedure.

#### Efficacy

##### Primary Efficacy Measure:

- Patients receiving IV ibuprofen experienced a 25.8% decrease in the mean AUC-VAS with movement (p <0.001) compared to the placebo plus morphine group.

##### Secondary Efficacy Measures:

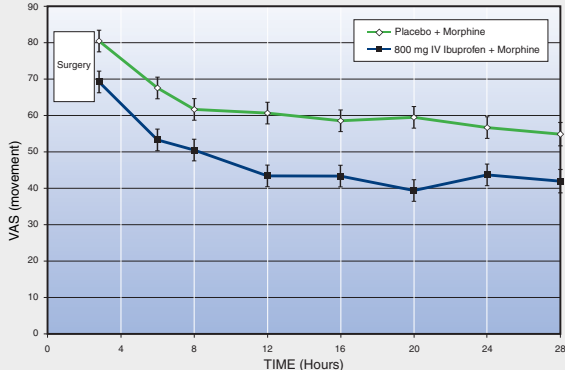
- Patients receiving IV ibuprofen experienced a 31.8% decrease in the mean AUC-VAS at rest (p <0.001) compared to the placebo plus morphine group.
- Patients receiving IV ibuprofen experienced a 20.2% decrease in the mean AUC-VRS (p <0.001) compared to the placebo plus morphine group.
- Patients receiving IV ibuprofen experienced a 15.8% decrease in the mean VAS at rest (p=0.012) and a 13.9% decrease in the mean VAS with movement (p=0.003) immediately post-surgery compared to the placebo plus morphine group.
- Patients who received IV ibuprofen had a significant reduction in mean morphine use, experiencing a 30.9% decrease in the mean morphine used in the postoperative period.

Table 1: Summary of AUC-VAS and AUC-VRS in the Post-operative Period

	Placebo + Morphine (n=86)	800 mg + Morphine (n=99)
<b>AUC-VAS</b>		
<b>With Movement</b>		
Mean (SD)	1307.8 (388.7)	970.1 (422.2)
p-value vs. Placebo <sup>1</sup>		<0.001
<b>At Rest</b>		
Mean (SD)	910.9 (424.3)	620.8 (401.0)
p-value vs. Placebo <sup>1</sup>		<0.001
<b>AUC-VRS</b>		
Mean (SD)	49.5 (18.2)	39.5 (17.1)
p-value vs. Placebo <sup>1</sup>		<0.001

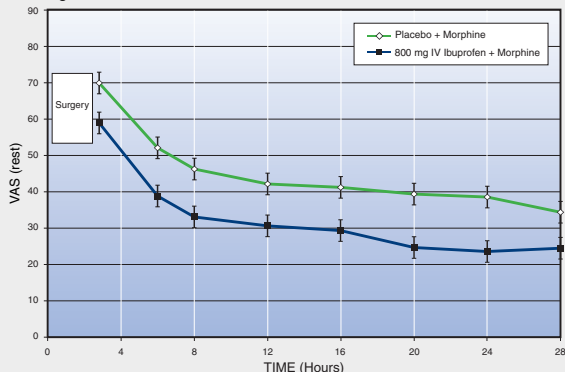
<sup>1</sup>The analysis is based on a linear ANCOVA model with fixed effects for age group, weight group, randomization center, and treatment group. The p-values and 95% confidence intervals are based on the difference in the LS Means from the final ANCOVA model.

Figure 2: VAS Assessed with Movement, Over Time



VAS was assessed with movement beginning at the first immediate post-operative opportunity (mean 2.81 hours) through study hour 28 in the IV ibuprofen and placebo treatment groups. Error bars denote SEM.

Figure 3: VAS Assessed at Rest, Over Time



VAS was assessed at rest beginning at the first immediate post-operative assessment (mean 2.81 hours) through study hour 28 in the IV ibuprofen and placebo treatment groups. Error bars denote SEM.

Table 2: Summary of Reduction of Morphine Use (mg morphine sulfate)

Morphine Requirement	Placebo (N=86)	800 mg (N=99)
N	85	97
Mean (SD)	59.5 (29.9)	41.1 (27.3)
Median	58.0	38.0
p-value vs. Placebo <sup>1</sup>		<0.001

<sup>1</sup>The analysis is based on a linear ANCOVA model with fixed effects for age group, weight group, randomization center, and treatment group. The p-values and 95% confidence intervals are based on the difference in the LS Means from the final ANCOVA model.

Additional assessments included comparisons of the incidence of treatment failure, time to GI motility, time to resumption of ambulation, time to resumption of liquid intake and solid diet, incidence of opioid related side effects and length of hospital stay. Due to the small sample size, there were no significant differences between treatment groups for the additional assessments. However, there was a numerical difference in the incidence of treatment failures between treatment groups: placebo 8/78 (9%), IV ibuprofen 4/95 (4%).

Treatment after Study Hour-28: More than 80% of the patients had dropped out of the study by the 38 hour time point making any efficacy comparisons for the later time points statistically underpowered. These patients discontinued study participation due to removal of IV access and/or being switched over to oral ibuprofen or other analgesics.

#### Safety

##### 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.

- There were 164 of the 185 patients for whom adverse events (serious and non-serious) were reported. In the 800 mg IV ibuprofen group, 90/99 (91%) patients experienced adverse events; 45 mild, 39 moderate and 6 severe. In the placebo group, 74/86 (86%) patients experienced adverse events; 36 mild, 37 moderate, and 1 severe.
- Events related to bleeding and coagulation times, and transfusion requirements, did not differ between the two groups.
- In the adverse events experienced by at least three patients, there were significantly more patients in the IV ibuprofen group that experienced vomiting and significantly more patients in the placebo group that experienced dyspepsia.
- There is no statistically significant difference in the incidence of serious adverse events between the patients receiving placebo and the patients receiving 800 mg IV ibuprofen.

Table 3: Adverse Events

	Placebo (n=86)	800 mg IVib (n=99)	Safety Population (n=185)	p-value
Number of Patients Experiencing At Least One Adverse Event	74 (86%)	90 (91%)	164 (89%)	0.356
Adverse Events That Differed Significantly Between Treatment Groups				
Type of Adverse Event	n	%	n	%
Vomiting	12	(14%)	27	(27%)
Dyspepsia	4	(5%)	0	0

## CONCLUSIONS

- Patients receiving pre- and post-operative doses of IV ibuprofen experienced significantly less pain in the post-operative period as demonstrated by AUC calculations of VAS scores assessed with movement and at rest, VRS scores, and immediate post-operative assessments (all tests significant).
- Patients receiving pre- and post-operative doses of IV ibuprofen used 31% less morphine (p<0.001) in the post-operative period.
- There was no significant difference in the incidence of adverse events between the patients receiving placebo and the patients receiving IV ibuprofen.

## REFERENCES

1. Kehlet H, Dahl JB. The value of "multimodal" or "balanced analgesia" in post-operative pain treatment. *Anesth Analg*. 1993;77:1048-1056.

CALDOLOR®  
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