

A Multi-Center, Randomized, Double-Blind Trial of Ibuprofen Injection for Treatment of Fever and Pain in Burn Patients

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INTRODUCTION

Each year in the United States, 1.1 million burn injuries require medical attention. Of these, approximately 50,000 burn injuries require hospitalization.¹ These hospitalized burn patients are often in a hypermetabolic state and suffering from both fever and pain. Oral ibuprofen is often used in hospitals to treat patients with fever or pain. However, oral administration in patients suffering from 2nd and 3rd degree burns is not always practical for reasons due to reduced gastric motility, recent surgery, nausea, and vomiting. Recently, Cumberland Pharmaceuticals Inc. developed an aqueous formulation of ibuprofen for treatment in reduction of fever, mild to moderate pain, and as an adjunct to opioid medications in moderate to severe pain. This study was conducted to assess the efficacy and safety of intravenous (IV) ibuprofen for the reduction of fever and pain in burn patients through the measurement of temperature and visual (VAS) and verbal pain (VRS) assessments.

Primary Objective

To evaluate the efficacy of intravenous ibuprofen compared to placebo when administered every 6 hours on reducing fever as measured by the AUC-T^o within the first 24 hours of treatment (as compared to a target temperature of 37.0°C [98.6°F]).

Secondary Objectives

Efficacy Endpoints:

- The AUC-T^o over 120 hours of the Treatment Period, as compared to a target temperature of 37.0°C (98.6°F)
- The number and percentage of patients who were considered treatment failures
- The first time at which each patient became afebrile (temperature less than 38.0°C [100.4°F])
- Pain assessment using VAS and VRS during the Treatment Period, as compared to placebo treatment

Safety Endpoints:

- Vital signs (heart rate, respiratory rate, blood pressure)
- Clinical chemistry, hematology, and coagulation measurements
- Transfusion requirements (units of packed red blood cells, fresh frozen plasma, and platelets administered)
- Treatment-emergent adverse events (TEAEs)

METHODS

This multi-center, randomized, double-blind, placebo-controlled trial was conducted at 5 sites; 2 within the United States and 3 within India between September 2007 and April 2009 enrolling a total of 61 patients. An institutional review board or independent ethics committee approved the study at each clinical study site.

Inclusion Criteria

- Patients with 2nd and 3rd degree thermal burns covering more than 10 percent of the total body surface area (including face) with anticipated hospital stay greater than 72 hours
- Adequate IV access
- A fever documented by temperature greater than or equal to 38°C or (100.4°F)

Exclusion Criteria

- Electrical burns
- Use of acetaminophen, NSAIDs or other fever reducing medications within 4 hours prior to dosing
- Patients taking warfarin or lithium
- Active, clinically significant asthma
- History of allergy or hypersensitivity to any component of intravenous ibuprofen, NSAIDs, aspirin (or related products), or COX-2 inhibitors
- Pregnant or nursing
- History of severe head trauma that required current hospitalization, intracranial surgery or stroke within the previous 30 days, or any history of intracerebral arteriovenous malformation, cerebral aneurism or CNS mass lesion
- History of congenital bleeding diathesis, any active clinically significant bleeding, any platelet dysfunction
- GI bleeding that required medical intervention within the previous 6 weeks (unless definitive surgery has been performed)
- A platelet count less than 20,000 mm³
- Receiving dialysis
- Receiving full dose anticoagulation therapy or Activated Protein C within 6 hours before dosing (clopidogrel, or prophylaxis with enoxaparin or subcutaneous heparin are acceptable)

Participants were randomized in a 2:1 ratio to one of two treatment groups: placebo or 800 mg IV ibuprofen (patients > 12 years of age) or 10 mg/kg (patients < 12 years; maximum of 400 mg) over 30 minutes every 6 hours for 5 days (120 hours) for a total of 20 doses.

Other than trial medication, antipyretic medications for fever were restricted during the first 24 hours of the study and NSAIDs were restricted throughout the entire study. Temperatures were obtained every 2 hours during the first 24 hours and then every 4 - 6 hours until Day 5. The primary efficacy endpoint was area under the curve for temperature (AUC-T^o) within the first 24 hours of treatment (as compared to a target temperature of 38.0°C).

Visual (VAS) and verbal pain (VRS) assessments were performed at baseline and every morning, evening, and 1 - 4 hours post-dressing change for 5 days. Use of the institutions' standard analgesics for pain was not restricted in the study design.

Safety evaluation included laboratory values (baseline, and hours 24, 96, and 124) and adverse event (AE) monitoring.

All statistical computations were performed and data appendices created using the SPSS® system or NCSS®. Statistical tests are two-sided, with alpha levels less than or equal to 0.05 for treatment differences and less than or equal to 0.10 for interaction effects considered significant.

RESULTS

A total of 61 patients were enrolled, randomized, and received study medication (intent to treat population, ITT); 40 receiving IV ibuprofen and 21 receiving placebo. Patient demographics by treatment group are shown in Table 1.

By protocol, 20 doses of clinical trial material were to be administered at 6-hour intervals during the 120-hours Treatment Period. The number of doses administered ranged from 3 - 20 with a median of 20 doses across treatment groups and mean of treatment group of: 800 mg IV ibuprofen 18 (± 5.1); Placebo 18 (± 4.3).

Forty-seven (77%) patients received all 20 doses of study medication and 14 (23%) patients received fewer than the scheduled 20 doses. Of the 14 patients that did not receive all 20 doses, 12 patients were discontinued from the study and 2 patients missed doses during the conduct of the study.

No patient was less than 18 years of age.

Table 1: Patient Demographics by Treatment Group

	Placebo n=21	Intravenous ibuprofen n=40	Total n=61
Age			
Mean (SD)	30 (11.9)	33 (10.8)	32 (11.2)
Gender			
Male	10 (48%)	15 (38%)	25 (41%)
Female	11 (52%)	25 (63%)	36 (59%)
Race			
Caucasian	5 (24%)	6 (15%)	11 (18%)
Black	1 (5%)	3 (8%)	4 (7%)
Hispanic	1 (5%)	0	1 (2%)
Asian	14 (67%)	31 (78%)	45 (74%)
Height (cm)			
Mean (SD)	166.3 (13.6)	162.1 (14.1)	163.6 (13.9)
Weight (kg)			
Mean (SD)	61.2 (20.3)	61.8 (18.3)	61.6 (18.8)
Geographic Region			
India	14 (67%)	31 (78%)	45 (74%)
USA	7 (33%)	9 (23%)	16 (26%)

Primary Efficacy Objective

The primary efficacy measure was the AUC-T^o during the first 24 hours of the Treatment Period, as compared to a target temperature of 37.0°C (98.6°F). The AUC-T^o (0-24 hours) was significantly reduced (p = 0.008) in the patients receiving IV ibuprofen compared to those receiving placebo (Figure 1 and Table 2).

Figure 1: Temperature over 24 hours by Treatment Group

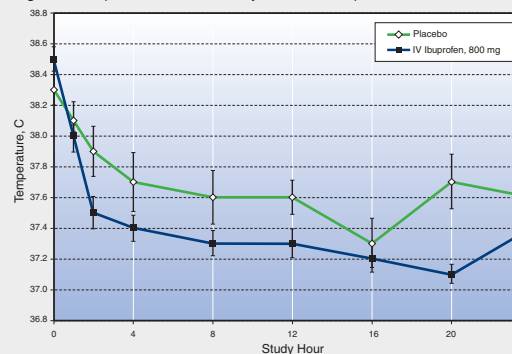


Table 2: Summary of AUC-T^o (0-24 hours) by Treatment Group

AUC-T ^o (0-24 hours)	Placebo (n=21)	Intravenous ibuprofen (n=40)
Mean (SD)	16.09 (11.5)	9.19 (7.6)
LS Means (SE)	18.29 (2.2)	12.21 (1.7)
Median	13.02	5.65
Min, Max	1.1, 46.3	0.9, 28.8
Comparison to Placebo		
p-value	-	0.008
LS Mean Difference (95% CI)	-	-6.09 (-10.52, -1.65)

Secondary Objectives

Efficacy Endpoints:

■ AUC-T^o (0-120 hours)

A reduction was observed in AUC-T^o (0-120 hours) in the patients receiving IV ibuprofen, however the difference was not significant (p = 0.475). Antipyretic therapy was not restricted after the first 24 hours of the study.

■ Treatment Failure

There was one (3%) treatment failure in the group receiving IV ibuprofen and two (10%) treatment failures in the group receiving placebo (p = 0.228).

■ Time to Patients Becoming Afebrile

There was a reduced time to patients becoming afebrile (hours) in the group receiving IV ibuprofen (1.6 ± 0.4) compared to placebo (3.1 ± 1.2); however the difference was not significant (p = 0.403).

■ Background Pain and Procedural Pain

Because enrollment was not dependent upon the ability to provide VAS or VRS assessments, many patients were unable to provide VAS scores (more than half for each treatment group). Combined with the fact that concomitant analgesic use was not restricted during the treatment period, no conclusions can be made regarding the efficacy of IV ibuprofen to treat pain in patients with burns.

Safety Endpoints:

■ In the treatment-emergent adverse events experienced by at least 3 patients, there were no significant differences between treatment groups (all p>0.7).

■ There were 8 subjects (13%) for whom 12 serious adverse events were reported. In the 800 mg IV ibuprofen group, 5/40 (13%) participants experienced 6 serious adverse events. In the placebo group, 3/21 (14%) participants experienced 6 serious adverse events. None of these values differed significantly between treatment groups.

■ There were no observed differences between heart rate, respiratory rate, or mean arterial pressure between treatment groups. Laboratory abnormalities were evaluated and the incidence of these events did not differ between groups (hematocrit, platelet count, PT/PTT, serum creatinine). The packed red blood cell transfusions between study day 0 and 5 did not differ between groups: IV ibuprofen 15/40 (38%); Placebo 7/21 (33%) (Figures 2-4).

■ Five patients died during this study: 2 placebo group (ARDS) and 3 IV ibuprofen (2 sepsis; 1 ARDS).

Table 3: Treatment Emergent Adverse Events by System Organ Classification and Preferred Term that Occurred in 3 or more Patients*

System Organ Class	Preferred Term	Placebo (n=21)	Intravenous ibuprofen (n=40)	Total Safety Population (n=61)
Any Treatment-Emergent Adverse Event		15 (71%)	23 (58%)	38 (62%)
Blood and lymphatic system disorders		8 (38%)	11 (28%)	19 (31%)
Leukocytosis		1 (5%)	6 (15%)	7 (11%)
Anemia		3 (14%)	5 (13%)	8 (13%)
Metabolism and nutrition disorders		4 (19%)	7 (18%)	11 (18%)
Hyperchloremia		1 (5%)	3 (8%)	4 (7%)
Hypernatremia		1 (5%)	3 (8%)	4 (7%)
Infections and infestations		4 (19%)	5 (13%)	9 (15%)
General disorders and administration site conditions		3 (14%)	5 (13%)	8 (13%)
Vascular disorders		2 (10%)	5 (13%)	7 (11%)
Hypotension		2 (10%)	5 (13%)	7 (11%)
Renal and urinary disorders		2 (10%)	4 (10%)	6 (10%)
Gastrointestinal disorders		3 (14%)	2 (5%)	5 (8%)
Respiratory, thoracic and mediastinal disorders		2 (10%)	3 (8%)	5 (8%)
Tachypnea		2 (10%)	3 (8%)	5 (8%)

*Treatment emergent adverse events by preferred term are only presented for those that occurred in 3 or more patients, therefore preferred term incidence does not necessarily reflect every TEAE occurring in the corresponding system organ class.

Two patients randomized to IV ibuprofen erroneously received 3200 mg IV ibuprofen per dose (every 6 hours) rather than 800 mg per dose. One patient completed the study, received 20 doses of 3200 mg IV ibuprofen over 5 days, and did not experience any serious adverse events or significant changes in laboratory values including platelet, hematocrit, INR and creatinine.

The second patient was withdrawn from the study due to an adverse event. This patient received 7 doses of 3200 mg IV ibuprofen over 2 days. The patient experienced breathlessness (serious), tachypnea (serious), and hypotension. However, the patients' laboratory tests did not demonstrate any significant changes in laboratory values including platelet, hematocrit, INR and creatinine. The patient received 200ml PRBC and 200ml FFP for a hematocrit of 33%.

Figure 2: Hematocrit Over Time, All Enrolled Patients

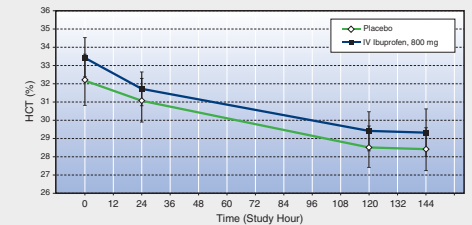


Figure 3: Coagulation (INR) Over Time, All Enrolled Patients

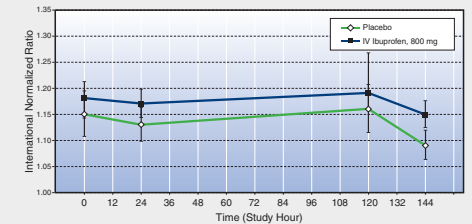
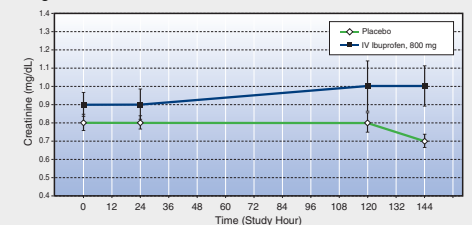


Figure 4: Creatinine Over Time, All Enrolled Patients



Limitations

■ Because many patients were unable to provide VAS scores and concomitant analgesic use was not restricted, no conclusions could be made regarding the efficacy to treat pain in patients with burns.

■ No patient under the age of 18 years was enrolled, and therefore, no conclusions can be made regarding the administration of IV ibuprofen in the pediatric population at this time.

CONCLUSIONS

The results from this study demonstrate that IV ibuprofen is a safe and effective antipyretic option for management of fever in the adult burn patient. Safety profiles in treated patients were similar to the placebo group and there were no serious safety concerns associated with up to 5 days of treatment with a dose of 800 mg every 6 hours (3200mg/day).

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REFERENCES

1. American Burn Association (2002). Burn Incidence Fact Sheet.



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