A Prospective, Multicenter, Randomized, Double-Blind Trial of IV Ibuprofen for Treatment of Fever and Pain in Burn Patients

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This prospective study evaluated the efficacy and safety of IV ibuprofen for the reduction of fever and treatment of pain in patients with thermal burn injury. A total of 61 patients with second- and/or third-degree thermal burns covering >10% TBSA were randomly assigned in a 2:1 ratio to receive either 800 mg IV ibuprofen or placebo every 6 hours for 120 hours (5 days). Antipyretic medications were restricted during the first 24 hours of the study, but analgesics were allowed throughout. The primary efficacy endpoint was area under the curve for temperature (AUC-T°) within the first 24 hours of treatment. After 24 hours of dosing, there was a significant reduction in temperature in patients who received IV ibuprofen compared with those who received placebo ($P = .008$). The temperature remained reduced over the entire 120-hour dosing period in the patients who received IV ibuprofen, although the difference beyond 24 hours did not reach statistical significance. Because of enrollment of patients unable to perform self-assessments of pain, an inadequate number of patients were enrolled to detect differences in pain scores. There was no significant difference in the incidence of serious adverse events. Fever was reduced significantly by IV ibuprofen in burn patients over the initial 24-hour dosing period and remained reduced throughout the dosing period. Exposure to the maximum daily recommended dose of 3200 mg (800 mg every 6 hours) for a total of 120 hours (5 days) was well tolerated. (J Burn Care Res 2011;32:79–90)

More than a half a million people a year receive medical treatment for thermal burns in the United States alone, and approximately 40,000 of them require hospitalization.[1–3] In addition, the incidence of burn injury is known to climb even higher in developing countries, further demonstrating the impact of this serious medical condition and emphasizing the importance of new approaches to burn care.[4]

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In recent years, therapeutic advances in the treatment of burns have been made based on a better understanding of the pathophysiologic response after burn injury.[5] More than 30 years ago, it was first demonstrated that significant metabolic changes occur in burn patients as the body attempts to heal the wound.[6] This hypermetabolic response is known to occur in the critically ill, especially including those patients with severe burns. This response is mediated by a surge of catecholamines, corticosteroids, and cytokines and typically results in hyperthermia (high fever).[7,8] The hypermetabolic response is so pronounced and sustained that patients with large, severe burns "reset" to a baseline body temperature of ~101.3°F (~38.5°C).[9] Increased body temperature is thought to help the immune system stave off infection after serious injury, but no positive relationship between this increased body temperature and burn wound healing has ever been delineated.[10] For example, one study on burn-injured children even demonstrated that attenuation of fever results in a metabolic benefit.[11] Although only a few studies have been

completed, it is now widely accepted that modulation of the hypermetabolic response including fever/body temperature after burn injury helps to reduce morbidity and mortality.[12] In addition, reduction of fever is known to improve patient comfort.[13]

In addition to fever, burn injury results in severe and dynamic pain that is often poorly managed. Burn patients experience a wide range of pain intensity, from a lower background level at rest to extreme pain during wound cleansing and dressing changes.[14,15] Opioids are typically used to treat burn pain, but some controversy exists surrounding their efficacy and safety in burn patients.[14]

Nonsteroidal anti-inflammatory drugs (NSAIDs) such as ibuprofen have been used to treat the hypermetabolic response/fever in burn patients.[16,17] In addition, multimodal therapy involving NSAIDs as an adjunct to opioids has been proposed for the treatment of pain in burn patients.[14] However, widespread oral NSAID use in burn patients for the treatment of pain was discouraged because of a possible risk of gastrointestinal (GI) toxicity and bleeding.[15] Large studies on the efficacy and safety of NSAIDs for the treatment of pain in burn patients have not been reported, likely due to the heterogeneity of the burn patient population, nonuniversal treatment practices, and a population of patients who are often unable to communicate.[18]

It is well established that the long-standing options for the treatment of fever in burn patients are of limited efficacy.[19] In addition, administration of oral antipyretics in burn patients is not always practical for reasons due to reduced gastric motility, recent surgery, sedation, nausea, vomiting, and/or intubation. Serious burn injury is also known to alter oral drug absorption and pharmacokinetics, as the pharmacokinetics of oral ibuprofen has been shown to vary in burn patients.[20,21] These dosing and pharmacokinetic issues demonstrate the need for an IV antipyretic in burn patients. In addition, an IV formulation of an NSAID, such as ibuprofen, may provide the added benefit of an analgesic as well.

Earlier studies have demonstrated the efficacy of IV ibuprofen in the treatment of fever and pain, and recently an aqueous formulation of ibuprofen (Caldolor®, Cumberland Pharmaceuticals, Inc., Nashville, TN) was approved by the U.S. Food and Drug Administration for reduction of fever, treatment of mild to moderate pain, and as an adjunct to opioid medications in the treatment of moderate to severe pain.[22–28]

This study was conducted to assess the efficacy and safety of IV ibuprofen for the reduction of fever and pain in burn patients through measurement of temperature and visual (Visual Analog Scale [VAS]) and verbal (Verbal Response Scale [VRS]) pain assessments.

METHODS

This was a prospective, multicenter, randomized, double-blind, placebo-controlled study of the safety and efficacy of IV ibuprofen for fever and pain in patients with severe thermal burns. An institutional review board or independent ethics committee approved the study at each clinical study site.

Study Design

Patients who met all the inclusion criteria and did not meet any exclusion criteria were consented and randomized in a 2:1 ratio to one of two treatment groups: 800 mg of IV ibuprofen or placebo (saline) over 30 minutes every 6 hours for 120 hours (5 days) for a total of 20 doses. Randomization was conducted in a 2:1 (IV ibuprofen:placebo) manner to allow for increased enrollment of patients receiving active treatment and to allow for additional collection of safety information associated with a longer duration of dosing of IV ibuprofen. Sealed envelopes containing the randomization sequence were provided to each site. The study pharmacist prepared each patient's doses of study drug (IV ibuprofen or placebo) and provided these to the investigator in identical infusion bags labeled with the patient's identification number. The 800 mg dose, and the dosing schedule (every 6 hours), was selected based on results from previous clinical studies of IV ibuprofen for the management of postoperative pain in hospitalized patients.[23] The study included three distinct time periods: screening, treatment, and posttreatment. The screening period was from study hour −72 to study hour 0. Hour 0 was defined as the time of the first dose of study drug. The treatment period was from study hour 0 to study hour 120, and to allow for additional safety assessments, the posttreatment period was from study hour 120 to study hour 144.

Patient Population and Interventions

The trial was conducted at five sites; two within the United States (Orlando Regional Medical Center, Orlando, FL, and Wake Forest University Baptist Medical Center, Winston-Salem, NC) and three within India (Lokmanya Tilak Municipal General Hospital, Sion, Mumbai; Naik's Hospital, Baroda; and Surya Hospital, Pune) between September 2007 and April 2009.

Participants were required to have second- and third-degree thermal burns covering more than 10%

TBSA (including face) with anticipated hospital stay >72 hours, adequate IV access, and fever documented by temperature ≥100.4°F (38°C). Patients with >10% TBSA burns were chosen because it was thought that these patients would be experiencing significant fever and pain and would therefore require at least 3 days of hospitalized treatment for their burns to evaluate the longer-term use of IV ibuprofen.

Patients excluded from enrollment included those with electrical burns; those prospectively receiving acetaminophen, NSAIDs, or other fever-reducing medications within 4 hours before dosing with study drug; those taking warfarin or lithium; those with active, clinically significant asthma; those with a history of allergy or hypersensitivity to any component of IV ibuprofen, NSAIDs, aspirin (or related products), or COX-2 inhibitors; women who were pregnant or nursing; those with a 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 aneurysm, or CNS mass lesion. Patients with a history of congenital bleeding diathesis, any active clinically significant bleeding, any platelet dysfunction, or a platelet count <20,000 mm^3 were also excluded. Patients with GI bleeding that required medical intervention within the previous 6 weeks (unless definitive surgery had been performed), those receiving dialysis, or those receiving full-dose anticoagulation therapy or Activated Protein C within 6 hours before dosing (clopidogrel, or prophylaxis with enoxaparin or subcutaneous heparin were acceptable regimens) were also excluded.

To evaluate the antipyretic effect of IV ibuprofen, a placebo-controlled comparator study was chosen. Non-NSAID antipyretic medications (including acetaminophen) were restricted during the first 24 hours of the study but were allowed from hours 24 to 120 of the treatment period. Other than study drug, NSAIDs were restricted throughout the entire study. There were no restrictions on non-NSAID analgesics, and agents such as morphine, oxycodone, fentanyl, methadone, nalbuphine, tramadol, hydromorphone, and pentazocine were administered during the study. The use of cold packs and cooling blankets was restricted during the first 24 hours of the study. Temperatures were obtained every 2 hours during the first 24 hours of the study, every 4 to 6 hours through hour 120 during the treatment period, and twice in the posttreatment period (>hour 120 to hour 144). Core body temperature (tympanic, rectal, urinary catheter, or pulmonary artery catheter) measurements were preferred. However, the route used for screening had to be used throughout the study.

Treatment Failures

A treatment failure was declared if a patient's temperature was >103.0°F (39.4°C) during the treatment period after a minimum of 2 hours after a dose of study drug/placebo. A patient who was declared a treatment failure could then receive rescue treatment (eg, cold packs and cooling blankets). Treatment failure did not require study discontinuation.

Pain Assessments

A 100 mm VAS and an objective VRS were utilized for pain assessments. These measurements were performed at baseline, every morning, evening, and 1 to 4 hours after dressing change through the 120-hour treatment period and during the posttreatment period through hour 144. Use of the institutions' standard analgesics for pain was not restricted in the study design.

Efficacy Assessments

The primary objective of this study was to evaluate the efficacy of IV ibuprofen compared with placebo when administered every 6 hours on reducing fever as measured by the AUC-T° within the first 24 hours of treatment (as compared with a target temperature of 98.6°F [37.0°C]). This primary endpoint was selected to assess antipyretic efficacy and to minimize variability associated with inherent temperature fluctuation in this patient population. After 24 hours of dosing, concomitant use of acetaminophen and/or other antipyretics was allowed. Secondary endpoints were designed to assess safety and efficacy throughout the treatment and posttreatment periods.

The secondary objectives of this study included the following:

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

Safety Assessments

The following safety endpoints were assessed at baseline, hour 24, 96, 120, and 144.

- Vital signs (heart rate, respiratory rate, and blood pressure).
- Clinical chemistry, hematology, and coagulation measurements.
- Transfusion requirements (units of packed red blood cells [PRBC], fresh frozen plasma, and platelets administered).
- Adverse events (AEs).

Statistical Analysis

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

The type 3 sum of squares test was used to generate *P* values for antipyretic efficacy, and a modified analysis of covariance model was used to generate *P* values for analgesic efficacy. Fisher's exact test was used to generate *P* values for adverse event incidence between IV ibuprofen and placebo treatment groups.

RESULTS

A total of 61 patients were enrolled, randomized, and received study medication (intent to treat population); 40 received IV ibuprofen and 21 received placebo. Patients younger than 18 years were eligible for the study but none were enrolled. A full listing of patient demographics by treatment group is shown in Table 1. When reported, the percentage of TBSA of thermal burns ranged from 11 to 54.5%.

Table 1. Demographics of the study population

	Placebo (n = 21)	IV 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%)

By protocol, 20 doses of clinical trial material were to be administered at 6-hour intervals during the 120-hour treatment period. The number of doses administered ranged from 3 to 20, with a median of 20 doses across treatment groups and mean per treatment group of 800 mg IV ibuprofen (18 ± 5.1) or placebo (18 ± 4.3). Figure 1 describes study drug exposure by treatment group and shows that 30 of the 40 patients (75%) treated with IV ibuprofen and 17 of the 21 patients (81%) treated with placebo received all 20 scheduled doses of study medication. Of the 14 patients who did not receive all 20 doses of study medication, 12 patients were discontinued from the study for various reasons (Figure 1), and 2 patients missed doses during the conduct of the study.

Primary Endpoint

AUC-T° (0–24 hours)

The primary efficacy measure was the AUC-T° during the first 24 hours of the treatment period, as compared with a target temperature of 98.6°F (37.0°C). The AUC-T° (0–24 hours) was significantly reduced

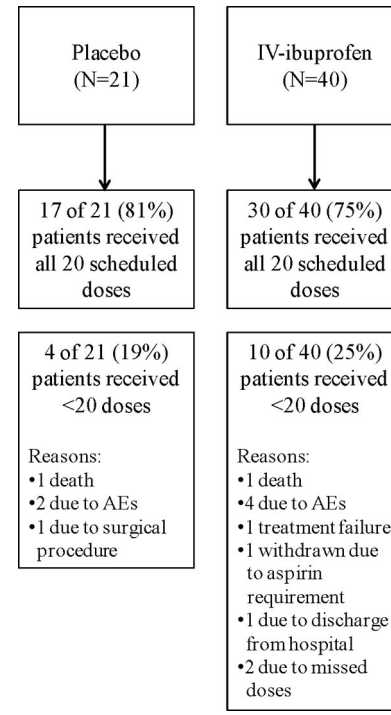

Figure 1. Study drug exposure for burn patients receiving placebo or IV ibuprofen with reasons for discontinuation (n = 61). Patients were scheduled to receive 20 doses of placebo or IV ibuprofen during the 120-hour study period (5 days). However, some patients received less than 20 doses for reasons such as death, adverse events, and treatment failure.

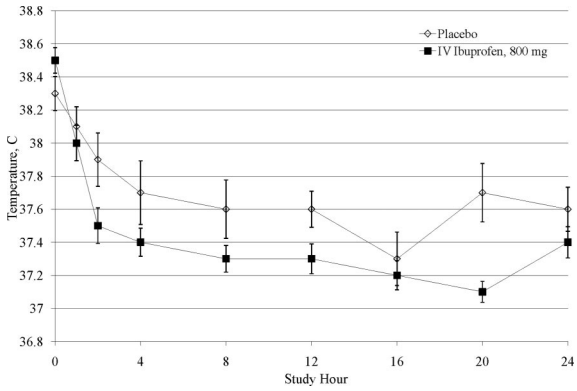

Figure 2. Body temperature in the first 24 hours in burn patients receiving placebo or IV ibuprofen (n = 61). Patients' body temperatures were recorded at baseline and then they were treated with placebo or IV ibuprofen every 6 hours with body temperature measurements every hour initially, followed by every 4 hours to complete the 24-hour time period.

(n = 61; $P = .008$) in the patients who received IV ibuprofen compared with those who received placebo (Figure 2 and Table 2).

Secondary Endpoints

AUC-T° (0–120 hours)

The temperature remained reduced over the entire 120-hour dosing period in patients who received IV ibuprofen, although the difference beyond 24 hours did not reach statistical significance (n = 61; $P = .475$; Table 3). Antipyretic therapy was not restricted after the first 24 hours of the study. Furthermore, 6 of 21 (28.6%) patients in the placebo group received acetaminophen during the treatment period compared with 6 of 40 (15%) patients in the IV ibuprofen group ($P = .309$).

Table 2. AUC-T° (0–24 hr) for placebo and IV ibuprofen-treated burn patients (n = 61)

AUC-T° (0–24 hr)	Placebo (n = 21)	IV 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 with placebo		
P		.008
LS mean difference (95% CI)		−6.09 (−10.52 to −1.65)

Min, Max is the minimum and maximum value for AUC-T° (0–24 hr) that were observed among all patients.
AUC, area under the curve; *LS*, least squares.

Table 3. AUC-T° (0–120 hr) for placebo and IV ibuprofen-treated burn patients (n = 61)

AUC-T° (0–120 hr)	Placebo (n = 21)	IV Ibuprofen (n = 40)
Mean (SD)	54.02 (40.7)	40.97 (40.4)
LS means (SE)	55.8 (10.1)	48.4 (7.7)
Median	34.4	23.2
Min, Max	6.0, 148.6	2.9, 173.7
Comparison with placebo		
P		.475
LS mean difference (95% CI)		−7.42 (−28.09 to 13.25)

Min, Max is the minimum and maximum value for AUC-T° (0–120 hr) that were observed among all patients.
AUC, area under the curve; *LS*, least squares.

Additional Secondary Endpoints

Additional secondary endpoints included frequency of treatment failure, the time to afebrility, and background and procedural pain. There was one (3%) treatment failure in the group that received IV ibuprofen and two (10%) treatment failures in the group that received placebo (n = 61; $P = .228$). There was a reduced time to patients becoming afebrile (hours) in the group that received IV ibuprofen (1.6 ± 0.4) compared with placebo (3.1 ± 1.2); however, the difference was not significant (n = 61; $P = .403$). Pain scores via patient VAS or VRS assessments did not differ between IV ibuprofen and placebo treatment groups.

Safety Outcomes

Adverse Events

The safety analysis encompassed all 61 patients who participated in the study, 38 (62%) of whom experienced AEs (serious and nonserious) (Table 4). In the adverse events experienced by at least three patients, there were no significant differences between treatment groups for all events combined or any event subgroup (n = 61; all $P > .7$). The administration of GI protective agents was not required during the study, and 14 of 61 (23%) patients (8/40 [20%] patients receiving IV ibuprofen vs 6/21 [29%] patients receiving placebo) received either famotidine, ranitidine, or metoclopramide at the discretion of the patient's attending physician.

There were eight patients (13%) for whom 12 serious adverse events (SAEs) were reported (total n = 61). In the 800 mg IV ibuprofen group, 5 of 40 (13%) participants experienced six SAEs (one acute

Table 4. Adverse events by organ system that occurred in three or more burn patients receiving placebo or IV ibuprofen

System Organ Class	Placebo (n = 21)	IV Ibuprofen (n = 40)	Total Safety Population (n = 61)	*P*
Any adverse event	15 (71%)	23 (58%)	38 (62%)	.41
Blood and lymphatic system disorders	8 (38%)	11 (28%)	19 (31%)	.40
Leukocytosis	4 (19%)	6 (15%)	10 (16%)	.73
Anemia	3 (14%)	5 (13%)	8 (13%)	>.99
Metabolism and nutrition disorders	4 (19%)	7 (18%)	11 (18%)	>.99
Hyperchloremia	1 (5%)	3 (8%)	4 (7%)	>.99
Hypernatremia	1 (5%)	3 (8%)	4 (7%)	>.99
Infections and infestations	4 (19%)	5 (13%)	9 (15%)	.71
General disorders and administration site conditions	3 (14%)	5 (13%)	8 (13%)	>.99
Vascular disorders	2 (10%)	5 (13%)	7 (11%)	>.99
Hypotension	2 (10%)	5 (13%)	7 (11%)	>.99
Renal and urinary disorders	2 (10%)	4 (10%)	6 (10%)	>.99
Gastrointestinal disorders	3 (14%)	2 (5%)	5 (8%)	.33
Respiratory, thoracic and mediastinal disorders	2 (10%)	3 (8%)	5 (8%)	>.99
Tachypnea	2 (10%)	3 (8%)	5 (8%)	>.99

respiratory distress syndrome [ARDS], one tachypnea, one severe septic shock, one septicemia, one invasive wound sepsis, and one breathlessness). In the placebo group, 3 of 21 (14%) participants experienced six SAEs (two ARDS, one cardiac arrest, one cardiopulmonary arrest, one tachypnea, and one hypotension). None of these values differed significantly between treatment groups. Five of the eight patients mentioned above died during the study: two in the placebo treatment group (two ARDS) and three in the IV ibuprofen treatment group (two sepsis and one ARDS). All deaths occurred at the study sites in India, and none of the study deaths were deemed related to the study drug by the investigator.

The first of the two placebo-treated patients who died during the study was a 30-year-old man who had 48% TBSA burns involving the back, legs, and hands, and this patient succumbed to cardiac arrest as a result of ARDS. The second placebo-treated patient who died during the study was a 33-year-old woman who had 63% TBSA burns involving the face, chest, back, and upper limbs, and this patient also succumbed to cardiac arrest as a result of ARDS.

The first of the three IV ibuprofen-treated patients who died during the study was a 32-year-old woman who had 25% TBSA burns of second- and third-degree nature and was deemed a treatment failure by the investigator due to altered sensorium and fever. This patient tested positive for infection with *Pseudomonas aeruginosa* and was treated with antibiotics and two units of PRBC but still succumbed to cardiorespiratory arrest as a result of sepsis originating from an infected burn wound. The second IV ibuprofen-treated patient was a 30-year-old woman who had 48% TBSA burns involving the face, neck, chest, hands, and legs, and this patient succumbed to cardiorespiratory arrest as a result of ARDS. The third IV ibuprofen-treated patient was a 24-year-old woman who had 25% TBSA burns involving the face, neck, chest, upper limbs, abdomen, and back, and this patient succumbed to cardiac arrest as a result of sepsis of unknown origin.

Two patients randomized to IV ibuprofen erroneously received 3200 mg IV ibuprofen per dose (every 6 hours) rather than 800 mg per dose. One of these patients who completed the study received 20 doses of 3200 mg IV ibuprofen over 120 hours (5 days) and did not experience any SAEs or significant changes in laboratory values, including platelet, hematocrit, International Normalized Ratio (INR), and creatinine. The second patient was withdrawn from the study because of an adverse event. This patient received seven 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 number, hematocrit, INR/coagulation, and creatinine. The patient received 200 ml PRBC and 200 ml fresh frozen plasma for a hematocrit of 33%.

Vital Signs and Laboratory Assessments

There were no observed differences in body temperature, heart rate, respiratory rate, or mean arterial pressure between treatment groups when comparing baseline to completion of the study (Table 5). In addition, there were no observed differences in any

Table 5. Baseline and endpoint vital signs and laboratory values in burn patients receiving placebo or IV ibuprofen (n = 61)

Parameter	Placebo (n = 21)			IV Ibuprofen (n = 40)		
Vital Signs*	**Baseline**	**Endpoint†**	**Change**	**Baseline**	**Endpoint**	**Change**
Body temperature (°C)	38.3 (0.5)	37.4 (0.8)	−0.9 (1.0)	38.5 (0.5)	37.5 (0.8)	−1.0 (0.7)
Heart rate (beats/min)	105 (10.1)	103 (17.6)	−2 (14.1)	108 (12.8)	103 (17.6)	−5 (16.0)
Respiratory rate (breaths/min)	22 (4.2)	21 (5.3)	0 (5.1)	23 (3.7)	23 (3.5)	0 (3.8)
Mean arterial pressure (mm Hg)	84 (8.5)	86 (10.2)	2 (7.7)	85 (8.7)	85 (8.8)	0 (8.0)
Laboratory Values*	Baseline	Endpoint	Change	Baseline	Endpoint	Change
Hematocrit (%)	32.2 (6.5)	29.6 (5.5)	−2.6 (5.9)	33.4 (7.2)	29.2 (7.4)	−4.1 (7.8)
Platelets ($\times 10^9$/L)	285 (162.6)	398 (204.5)	113 (179.4)	326 (180.5)	367 (173.7)	43 (187.8)
Sodium (mEq/L)	133 (5.6)	134 (6.3)	1 (5.0)	134 (5.7)	135 (7.3)	2 (5.3)
Potassium (mEq/L)	3.9 (0.5)	4.3 (0.5)	0.4 (0.6)	4 (0.6)	4.2 (0.7)	0.1 (0.9)
Blood urea nitrogen (BUN) (mg/dl)	11.1 (7.1)	12.4 (14.0)	1.3 (14.8)	13.7 (10.9)	15.2 (17.1)	1.5 (16.1)
Creatinine (mg/dl)	0.8 (0.2)	0.8 (0.2)	−0.1 (0.2)	0.9 (0.4)	1.0 (0.7)	0.1 (0.7)
Total bilirubin (mg/dl)	0.8 (0.8)	0.68 (0.6)	−0.09 (0.6)	0.63 (0.4)	0.63 (0.4)	0 (0.3)
Aspartate aminotransferase (AST) (U/L)	45 (24.0)	55 (56.1)	11 (58.1)	57 (52.0)	43 (38.6)	−13 (39.7)
Alanine aminotransferase (ALT) (U/L)	46 (30.3)	49 (23.6)	3 (31.4)	60 (45.5)	47 (28.7)	−13 (35.3)

*Data reported as mean (SD).

†Endpoint defined as the last assessment taken during the treatment period.

laboratory values between groups when comparing baseline with completion of the study (Table 5). Selected laboratory abnormalities were evaluated, and the incidence of these events did not differ significantly between groups (hematocrit [Figure 3], coagulation as measured by INR [Figure 4], serum creatinine [Figure 5], platelet count, prothrombin time/partial thromboplastin time). Line graphs were used to show the mean and SD of each of these parameters (Figures 3A, 4A, and 5A), whereas box and whisker plots were used to demonstrate the range of these parameters by showing the median, quartile, and the smallest and greatest values recorded for each treatment group (Figures 3B, 4B, and 5B). Acute kidney injury (AKI) is defined as a 0.3 mg/dl absolute increase in serum creatinine over a 48-hour period.[29] While laboratory assessments were not performed on study day 2 to 4, changes in creatinine were evaluated between baseline and study day 1 and between baseline and study day 5. From baseline to day 1, 1 of 21 (4.8%, patient range = 0.5–0.8 mg/dl) placebo-treated patients and 5 of 40 (12.5%, patient ranges = 0.7–1.0, 0.8–2.0, 0.91–1.39, 1.1–1.5, and 2.6–3.7 mg/dl) IV ibuprofen-treated patients experienced a 0.3 absolute increase in creatinine ($P = .654$). From baseline to day 5, 0 of 21 (0%) placebo-treated patients and 4 of 40 (10%, patient ranges = 0.7–2.8, 0.74–1.81, 0.8–1.1, 2.6–5.0 mg/dl) IV ibuprofen-treated patients experienced a 0.3 absolute increase in creatinine ($P = .284$). The day 6 serum creatinine levels and underlying disease state for the three IV ibuprofen-treated patients who had high creatinine levels on day 5 (defined as serum creatinine >1.5 mg/dl) were 4.1 mg/dl (severe septic shock) in the patient who had a day 5 creatinine value of 2.8 mg/dl, 2.5 mg/dl (worsening renal failure) in the patient who had a day 5 creatinine value of 5.0 mg/dl, and 1.9 mg/dl (sepsis) in the patient who had a day 5 creatinine value of 1.81 mg/dl. The PRBC transfusions between study hour 0 (day 0) and 120 (day 5) did not differ between groups: IV ibuprofen, 15 of 40 (38%) patients; placebo, 7 of 21 (33%) patients.

DISCUSSION

Acute and sustained attenuation of the hypermetabolic response including fever and pain in burn patients is critical to patient comfort and outcome.[8,9] However, oral administration of antipyretics and analgesics in hospitalized burn patients is often impossible due to reduced GI function/motility, sedation, and/or intubation.[15] An IV formulation of ibuprofen offers a convenient new route of administration for these patients and has the potential to attenuate the COX-mediated portion of the inflammatory cascade triggered by the burn injury and to thereby reduce fever and alleviate pain.[30] IV ibuprofen is the first injectable product for the treatment of pain and fever in the United States.[31] Previous studies in hospitalized critically ill patients with sepsis, hospitalized patients with malaria, and hospitalized patients with fever due to various underlying causes have demonstrated the

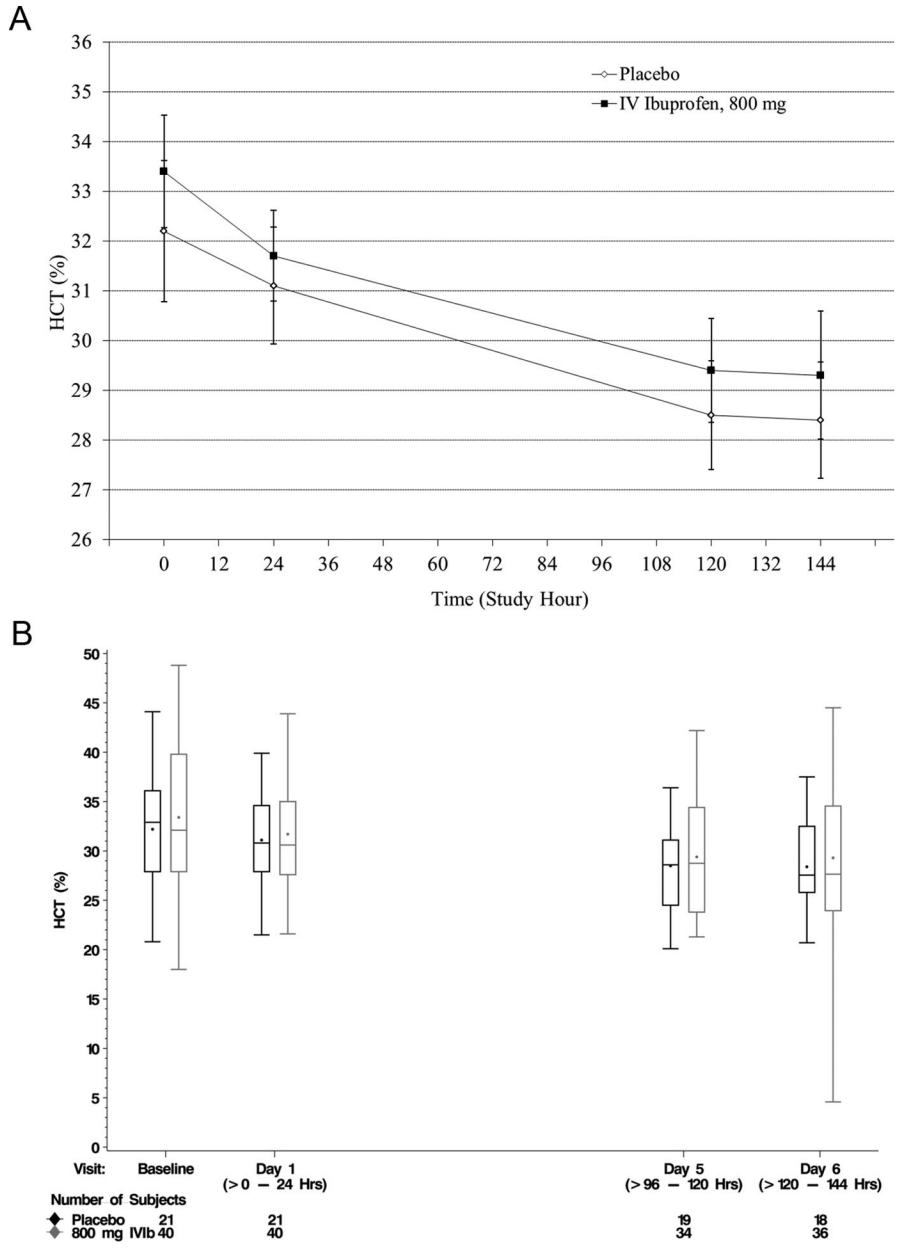

Figure 3. Hematocrit levels over time in burn patients receiving placebo or IV ibuprofen for all enrolled patients (n = 61). Patients' hematocrit levels were recorded at baseline and then they were treated with placebo or IV ibuprofen every 6 hours for up to 5 days with assessments after 24, 120, and 144 hours and presented as a line graph (A) and a box and whisker plot (B). Values in panel A are mean (SD). Values in panel B are median (smallest/greatest).

antipyretic efficacy of IV ibuprofen.[22,24,27] The current recommended dose of IV ibuprofen is 400 mg followed by 400 mg every 4 to 6 hours or 100 to 200 mg every 4 hours as necessary for the treatment of fever.[28] Interestingly, Morris et al[27] demonstrated that the magnitude of the antipyretic effect corresponded with the severity of illness of the patient. In this study, patients were stratified by severity of illness defined as critically ill (requiring mechanical ventilation for respiratory failure, pressor support for hypotension, or both) or not critically ill.[27] Both ibuprofen concentrations and the magnitude of temperature reduction in the critically ill group were on average lower at the same time points and doses as compared with the non-critically ill group.[27] The higher metabolic state of critically ill patients may account for this difference. In addition, the antipyretic efficacy of 800 mg IV ibuprofen has been observed in hospitalized

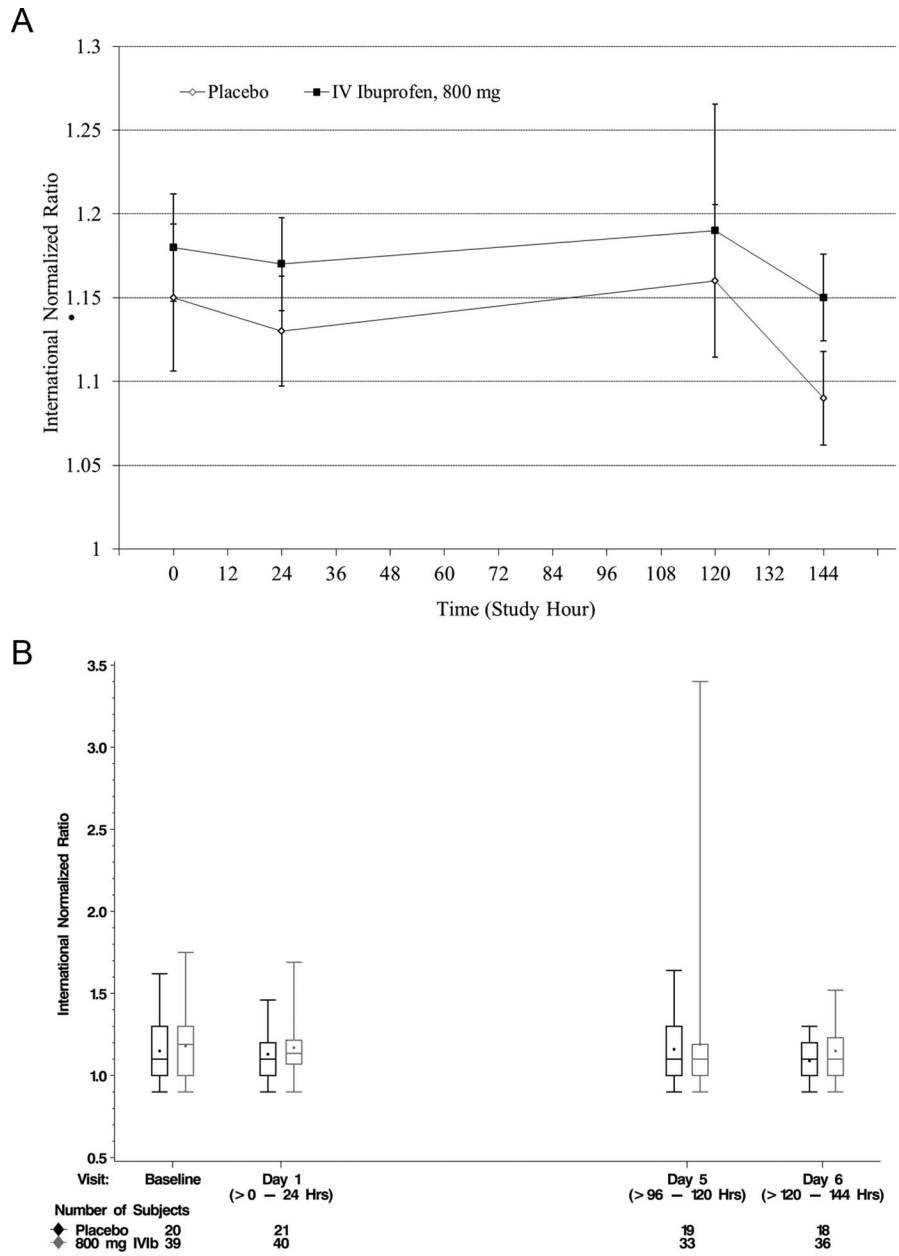

Figure 4. Coagulation (INR) over time in burn patients receiving placebo or IV ibuprofen for all enrolled patients (n = 61). Patients' ability to coagulate was recorded at baseline and then they were treated with placebo or IV ibuprofen every 6 hours for up to 5 days with assessments after 24, 120, and 144 hours and presented as a line graph (A) and a box and whisker plot (B). INR, International Normalized Ratio. Values in panel A are mean (SD). Values in panel B are median (smallest/greatest).

patients with sepsis, a patient population similar to what was defined critically ill in the study by Morris et al.[22] Finally, the analgesic efficacy of IV ibuprofen has been demonstrated in the perioperative setting where 800 mg dose of IV ibuprofen is typically given for analgesic and anti-inflammatory purposes.[23,25,26,28] In all studies mentioned of using IV ibuprofen, the doses studied did not result in differences in patient safety profiles when comparing patients receiving IV ibuprofen vs placebo. These collective findings of dose and patient severity of illness helped the investigators select the 800 mg dose of IV ibuprofen for this study on the treatment of fever and pain in hospitalized burn patients.

This study not only involves the first report of the use of an IV NSAID for the treatment of fever and pain in hospitalized thermal burn patients but also involves the longest and highest dose and duration of

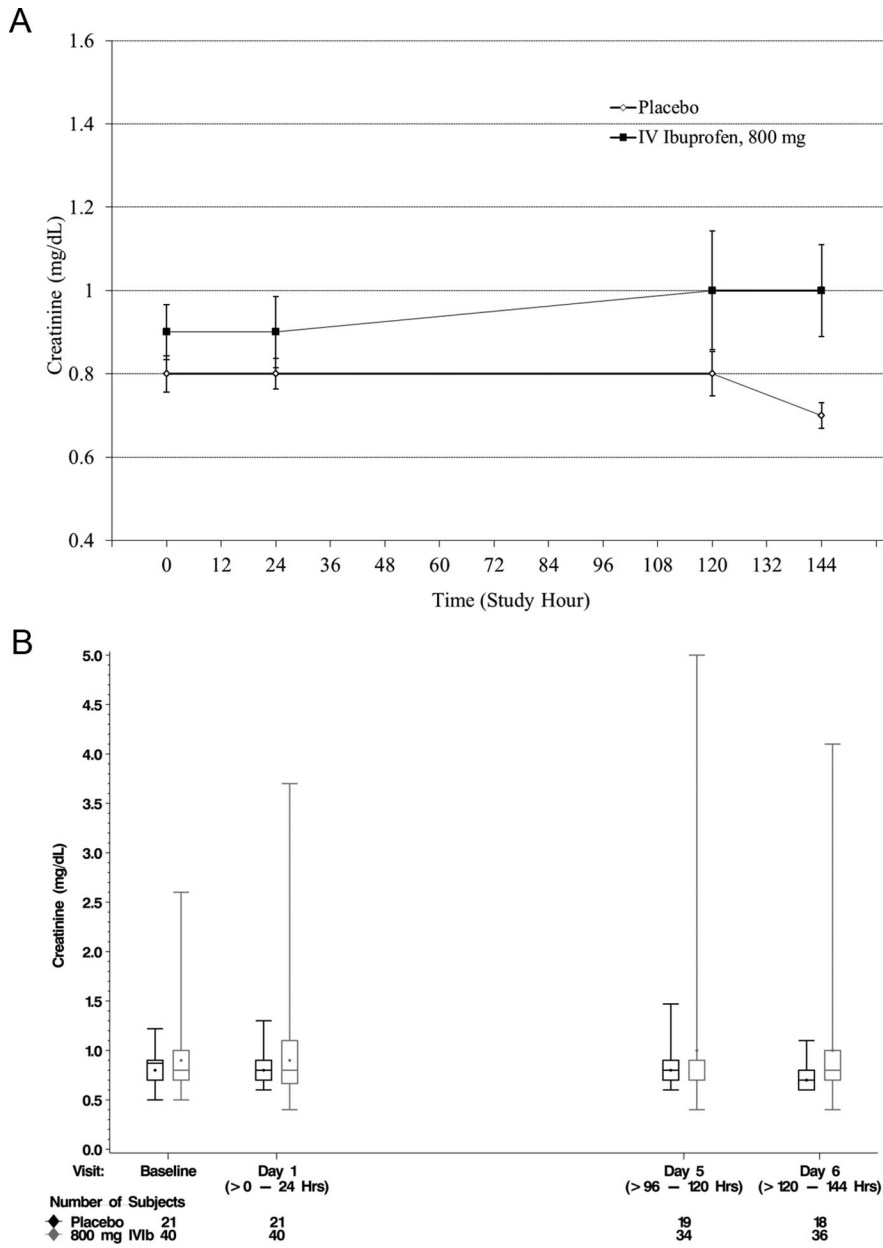

Figure 5. Creatinine levels over time in burn patients receiving placebo or IV ibuprofen for all enrolled patients (n = 61). Patients' creatinine levels were recorded at baseline and then they were treated with placebo or IV ibuprofen every 6 hours for up to 5 days with assessments after 24, 96–120, and 144 hours and presented as a line graph (A) and a box and whisker plot (B). Values in panel A are mean (SD). Values in panel B are median (smallest/greatest).

exposure to IV ibuprofen to date. In this study, exposure to the recommended maximum daily dose of 3200 mg/day IV ibuprofen (800 mg every 6 hours) for a total of 120 hours (5 days) was well tolerated, and no additional safety concerns were noted.

The pain endpoint was underpowered, as many of the patients were unable to perform self-assessments of pain due to sedation or unconsciousness. In addition, analgesics such as morphine were allowed during the study, at least partially masking the analgesic effect of IV ibuprofen when compared with placebo.

There was no statistically significant difference in the general or subgroup incidences of AEs, SAEs, vital signs, or laboratory assessments between the IV ibuprofen and placebo treatment groups. The box and whisker plots presented in Figures 3B, 4B, and 5B reveal that, for each laboratory parameter assessed, at day 1, there is no difference in the median values

between the treatment groups, and at days 5 and 6, there is a 0.1 difference in the median values between the treatment groups, demonstrating the inherent variability in laboratory assessments in this small sampling of burn patients. A few outliers did exist at baseline and after treatment (as denoted by the range bars showing the smallest and greatest values in the distribution).

Although the protocol did not include an explicit provision for renal failure or a prospective assessment of AKI, renal adverse events were captured according to Food and Drug Administration guidelines, and the investigator could discontinue clinical trial medication at any time. Retrospective assessment of AKI using serum creatinine data did not reveal any significant differences between treatment groups, but three of the IV ibuprofen-treated patients did have serum creatinine levels above the normal range at the conclusion of the study. None of these serum creatinine shifts were attributed to study medication by the investigator, as the patients were suffering from serious underlying conditions, including sepsis, septic shock, and worsening renal failure. Patients with high serum creatinine levels were allowed to remain in the study, as burn patients are often dehydrated due to burn wound exudation, and these patients were treated at the physician's discretion per institutional standards.

Previous studies did not raise safety concerns with short-term administration of IV ibuprofen, and therefore safety laboratory assessments were completed on days 1, 5, and 6 in this study.[22–27] However, a larger study would be beneficial to further evaluate the safety of 5 days of dosing of IV ibuprofen in this patient population. No particular events related to bleeding were noted, and transfusion requirements did not differ between the two groups. There were five deaths reported in this study, divided among active and placebo arms. However, all deaths were deemed unrelated to study medication by the treating physician, as all five patients were found to have succumbed to their injuries.

Limitations

The main limitation of this study is that no conclusions can be made regarding the efficacy of IV ibuprofen in the treatment of pain of thermal burn injury, as many patients were unable to provide VAS scores, and concomitant analgesic use was not restricted. Another limitation is that no conclusions can be made regarding the administration of IV ibuprofen in the pediatric or elderly populations. Pediatric patients were not enrolled in this study, as the sites participating treated only adult patients. Furthermore, only five patients older than 55 years were enrolled in this study, limiting any safety conclusions about the elderly population. A larger study including pediatric-specific sites would be needed to assess these populations.

In summary, this study demonstrates that IV ibuprofen is an effective antipyretic option for the management of fever in adult burn patients. Safety profiles in IV ibuprofen-treated patients were no different than the placebo group, and there were no serious safety concerns associated with 120 hours (5 days) of IV ibuprofen treatment with a dose of 800 mg every 6 hours (3200 mg/d).

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