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ORIGINAL ARTICLE

A Prospective Randomized Study to Evaluate the Antipyretic Effect of the Combination of Acetaminophen and Ibuprofen in Neurological ICU Patients

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Abstract
Background To compare the antipyretic effect of simultaneously administered acetaminophen (APAP) plus ibuprofen (IBU) to either APAP or IBU alone in critically ill febrile neurological and neurosurgical patients.
Methods This is a prospective, three-armed, randomized controlled trial of 79 patients in the neurology/neurosurgery intensive care unit (NNICU) of a tertiary care academic hospital. Eligible patients who developed a temperature ≥38°C were randomized to receive either a single dose of APAP 975 mg, a single dose of IBU 800 mg, or a combination of both (APAP + IBU). Oral temperatures were measured hourly for 6 h following medication administration.
Results All three treatments decreased temperature over the 6-h period. The area under the curve (AUC) for ΔT for APAP was −3.55°C-h (95% CI −4.75 to −2.34°C-h); for IBU was −4.05°C-h (95% CI −5.16 to −2.94°C-h); and for the combination of APAP and IBU was −5.10°C-h (95% CI −6.20 to −4.01°C-h). The differences in AUC between the groups were as follows: IBU versus APAP = −0.50°C-h ($P = 0.28$), APAP + IBU versus IBU = −1.05°C-h ($P = 0.09$), and APAP + IBU versus APAP = −1.56°C-h ($P = 0.03$).
Conclusion The combination of IBU and APAP produces significantly greater fever control than APAP alone, with trends favoring the combination over IBU alone and IBU over APAP alone.

Keywords Fever · Acetaminophen · Ibuprofen

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Introduction

Fever is a common problem in patients with severe neurologic injury such as stroke, trauma, and intracranial hemorrhage. Numerous studies have reported a worse prognosis in brain-injured patients with hyperthermia [1–4]. Taking measures to control fever is recommended by guidelines for the management of ischemic stroke, subarachnoid hemorrhage, intracerebral hemorrhage, and traumatic brain injury [5–8]. Fever management is routinely employed in this patient population. Standard methods of fever control consist of antipyretic drug therapy and external physical cooling, including cooling blankets, ice packs, nasogastric or rectal lavage, or alcohol baths. Novel cooling methods such as intravascular devices have been introduced, and are being studied in the ICU population [9, 10].

The mainstay of fever management remains the use of antipyretic medication [11]. Acetaminophen (APAP) and ibuprofen (IBU) are two of the most frequently used antipyretic agents. Both antipyretic agents inhibit prostaglandin synthetase in the hypothalamus, and both have separately proven effective in reducing fever [12–14]. A meta-analysis concluded that IBU is equal or superior to APAP in reducing fever or pain in adults and children with no additional adverse effects [15]. Pediatric studies have shown that the simultaneously administered combination (APAP + IBU) to be superior to APAP alone but not statistically significant difference between APAP + IBU and IBU alone or between APAP and IBU [16, 17]. No studies have evaluated the combined efficacy when both agents are administered simultaneously in neurologic critical care patients.

We sought to determine whether APAP + IBU provided more effective fever control in patients with severe neurologic injury than either APAP or IBU alone.

Methods

The study was an IRB-approved, prospective, unblinded, randomized, controlled trial conducted in the neurological/neurosurgical intensive care unit (NNICU) of an academic tertiary care facility. The intensive care unit was selected as the site of study due to the standardized, conscientious surveillance of temperature. NNICU protocol specifies that temperature must be measured every 2 h on every patient. Data were collected from May 2003 to May 2005. Based on similar studies, we set a study goal of 120 treated patients. The Investigational Pharmacy Service prepared 120 sequentially numbered packets which contained APAP 975 mg, IBU 800 mg, or both (APAP + IBU). The packet contents were assigned in random order in blocks of 20. All medications were in tablet form.

The primary endpoints of the study were average temperature reduction and the area under the temperature–time curve during the 6 h after treatment. We pragmatically selected this interval to conform to the existing NNICU protocol indicating repeat antipyretic treatment if the temperature was elevated 6 h after the previous dose.

Secondary endpoints analyzed adverse outcomes such as worsening intracranial hemorrhage, renal failure, and liver failure. Specific endpoints measured were serum creatinine, serum AST, and new intracranial hemorrhage within 7 days of study participation.

Patients newly admitted to the NNICU were screened for consent into the study after the first 24 h in the unit. We excluded patients who met any of the following criteria: pregnant, unstable intracranial bleed for >24 h, surgery within 24 h, renal failure (creatinine >1.5), liver dysfunction (AST or ALT >50), thrombocytopenia (platelet count $<100{,}000$), history of peptic ulcer or upper gastrointestinal bleed, administration of antipyretic in past 4 h, inability to measure oral temperature, use of cooling blanket, or use of intravascular cooling device.

We approached eligible patients or their families in person for study consent. Family members were the source of consent for all but one patient. For each patient with consent, the chart was marked with a yellow sticker to indicate study participation, and a study protocol order was placed into the chart. If a consented patient later had an oral temperature >38°C, the patient received the contents of the next sequentially numbered packet. For patients who were unable to swallow, the nurse was permitted to crush the medication and administer it through a nasogastric tube. The nurse was instructed to measure oral temperature hourly for the next 6 h. A Welch-Allyn Sure Temp ® Model 678 electronic thermometer (Welch-Allyn Inc., Skaneateles Falls, NY) was used for all measurements. Laboratory and radiographic investigations into the source of fever remained at the discretion of the treating physicians.

A priori, we planned to perform pair-wise comparisons between IBU versus APAP, APAP + IBU versus APAP, and APAP + IBU versus IBU.

Results

Of the 120 pre-prepared packets, 16 were not used. We excluded 25 patients from the analysis due to protocol violations. These included one use of a Foley catheter to measure temperature, 13 subjects with concomitant use of cooling blanket or intravascular cooling device, three axillary temperatures recorded, three subjects with missing temperature data, two subjects who received antipyretics in addition to study medications, and three subjects who were enrolled twice. Of the remaining 79 subjects, 25 were in the APAP group, 28 in the IBU group, and 26 in the APAP + IBU group. The mean baseline temperatures were virtually identical (38.39, 38.44, and 38.42°C, respectively). Half of the patients had intracranial hemorrhage (including subarachnoid, subdural, epidural, intraparenchymal, and/or intraventricular hemorrhage) as the reason for NNICU admission; a variety of other diagnoses accounted for the other half (Table 1).

We calculated and graphed the mean hourly change from baseline temperature for the 6-h study period (Fig. 1). We calculated the trapezoidal area under the curve (AUC) among the three groups (Table 2). We compared the difference in AUC (Δ AUC) between groups (Table 3). Since we were evaluating fever reduction, a more negative number for Δ AUC indicates a superior treatment. In our subjects, APAP + IBU was superior to APAP alone, and this difference is statistically significant. There was a trend favoring APAP + IBU over IBU, and a smaller trend favoring the IBU over APAP, but neither of these

Table 1 Neurological diagnoses of included patients

Intracranial hemorrhage	39
Stroke	8
Closed head injury	4
Tumor	6
Spinal cord injury	5
CNS infection	5
Encephalopathy	2
Myasthenia gravis	2
Aneurysm	2
Guillain–Barre	1
Seizure	1
Laminectomy	1
Missing data	3
Total	79

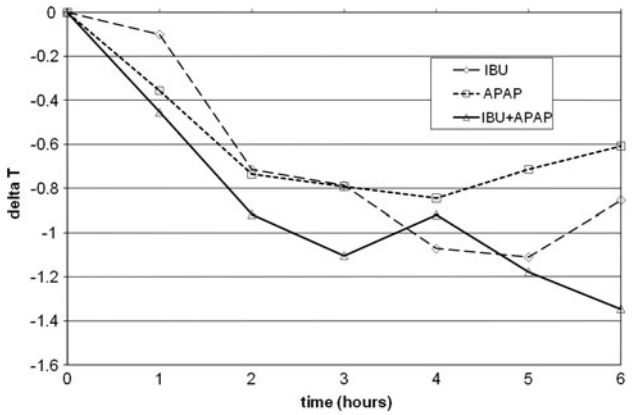

Fig. 1 Mean change from baseline temperature (Celsius) for 6 h after study medication

Table 2 Comparisons of mean temperature at time of medication administration (T0), mean temperature in hours 2–6 (T2–6) after medication administration and area under the curve (AUC) for change in temperature in degree-hours

	Mean T0 (°C)	Mean T2–6 (°C)	AUC (°C-h)	95% CI (°C-h)
APAP	38.39	37.53	−3.55	−4.75 to −2.34
IBU	38.44	37.65	−4.05	−5.16 to −2.94
APAP + IBU	38.42	37.33	−5.10	−6.20 to −4.01

Table 3 Intergroup differences in AUC in degree-hours

	Δ AUC (°C-h)	*P*
IBU vs. APAP	−0.50	0.28
APAP + IBU vs. IBU	−1.05	0.09
APAP + IBU vs. APAP	−1.55	0.03

differences achieved statistical significance. Secondary endpoints support the safety of IBU, APAP, and APAP + IBU in brain-injured patients. There was no increase in creatinine, AST, or new intracranial hemorrhage within 7 days of study participation.

Discussion

Fever is a common occurrence in critically ill neurological and neurosurgical patients. Fever sometimes heralds infection, which complicates patient care, increases length of ICU stay, and increases mortality. All febrile ICU patients should be thoroughly worked-up for infection, and treated appropriately. In the neurological ICU population, however, fever can be directly related to the CNS insult itself, in the absence of infection. This noninfectious, or "central" fever, independently increases duration of critical care, worsens neurological damage, and increases mortality [4, 9, 14, 18]. The precise mechanism of central fever is not well understood, but multiple mechanisms have been suggested. Hypoxia, ischemia, reperfusion, or the presence of blood in the central nervous system (brain parenchyma or subarachnoid space) may instigate a cascade of pyrogenic cytokines, which in turn causes prostaglandin E2 release from the hypothalamus, stimulating temperature elevation [9, 14, 18]. Under normal circumstances, body temperature is tightly regulated by the preoptic nucleus of the anterior hypothalamus (POAH) [9] Severe neurological and neurosurgical insults often result in global cerebral edema, space-occupying lesions with midline shift, or significant head trauma. Direct injury to the POAH via compression or mechanical damage can lead to temperature dysregulation and resulting fever.

There is ample evidence to indicate that hyperthermia has a detrimental effect on injured brain tissue [1–4, 9, 14]. Animal studies suggest that hyperthermia further damages injured brain tissue via multiple mechanisms [19–23]. These mechanisms include increased energy utilization, accelerated exitotoxic neurotransmitter release from injured brain, disruption of the blood–brain barrier, ischemia-induced free radical production, and activation of apoptotic signaling proteins which lead to cell death. In numerous clinical studies, fever is an independent predictor of poor outcome in patients with acute neurological disorders [1, 3, 4, 9, 14, 18, 24–27]. Unfavorable outcomes include increased hospital and ICU length of stay, increased mortality, and worse functional outcome after controlling for complications, diagnoses, severity of illness, and age. As fever contributes to worsening neurologic damage and poorer outcomes for brain-injured patients, controlling fever in the neurological ICU is an important objective.

Current methods for temperature control include antipyretic medications, external cooling devices, and endovascular cooling methods. Antipyretic medications are the most universally available methods of fever control. They are inexpensive and have few adverse effects. The aim of our study was to test the effectiveness of the two most commonly prescribed antipyretic agents, IBU or APAP versus a combination of both for treating fever in the acutely brain-injured patient.

Conclusion

The combination of APAP plus IBU provided superior fever control when compared to APAP alone. There were apparent trends favoring combination over IBU alone and

favoring IBU alone over APAP alone, but our study was underpowered to detect these differences.

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