Paracetamol therapy for septic critically ill patients: a retrospective observational study

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ABSTRACT

Background: There is little information on the use of paracetamol for septic critically ill patients. We hypothesised that paracetamol use is common in such patients, but its administration is not predictably related to body temperature.

Objective: To study the epidemiology and associations of paracetamol use in a cohort of septic critically ill patients.

Design: Retrospective observational study.

Patients and setting: Cohort of 106 patients admitted with a sepsis-related diagnostic code to the intensive care unit of a tertiary hospital, 14 December 2009 – 8 August 2010.

Methods: Using the ICU database, we identified all patients admitted with sepsis during the study period. We audited their electronic medical records to identify paracetamol administration and body temperature. The paracetamol administered and tympanic temperature at 00:00, 06:00, 12:00 and 18:00 hours for the first 7 days of admission were recorded. The reason for paracetamol administration was not documented.

Results: 73/106 (69%) patients received paracetamol at least once; 10% of all patients and 23% of postoperative patients had paracetamol for every temperature measurement. The median length of stay was 3 days and the mean total ICU paracetamol dose per patient was 6.4 g. Overall, 44% of patients received paracetamol for their peak temperature (56% in the fever group v 37% in the non-fever group; $P = 0.07$). Only 36/106 patients had a fever and 88% in the fever group had paracetamol at least once in the first 7 days, compared with 60% in the non-fever group ($P = 0.004$). After adjustment for key variables, patients with fever were more likely to receive paracetamol (odds ratio, 6.8 [95% CI, 1.9–24.7]; $P = 0.004$). Patients with fever were more likely to die in ICU than patients without fever ($P < 0.001$), although those who died in ICU did not receive more paracetamol.

Conclusions: Paracetamol administration is common among septic critically ill patients with or without fever, and more likely to occur when fever is present. However, paracetamol is not predictably given for the highest temperature in febrile patients. Future investigations are needed to understand under what circumstances and why paracetamol is given or not given to febrile or afebrile septic ICU patients.

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Clinical observation suggests that fever is a common occurrence among critically ill patients. Its incidence among patients admitted to the intensive care unit with a diagnosis of sepsis has been reported as greater than 90%.[1] Fever may cause discomfort and increase metabolic demand among patients with limited physiological reserve. These effects often lead clinicians to prescribe antipyretic medications, such as paracetamol, in the hope that attenuation of these physiological changes will increase patient comfort and prove beneficial to patient outcome.

The benefit of treating fever in patients with neurological impairment is well recognised.[2] However, the benefits of treating fever with paracetamol in non-neurological septic patients remains unclear. In particular, paracetamol administration for the treatment of fever may be deleterious because fever may be an evolutionarily selected, survival-enhancing response in sepsis.[3] Furthermore, paracetamol can cause liver toxicity and hypotension.[4,5]

Despite the uncertainty surrounding the relative advantages and risks of paracetamol administration as an antipyretic, there are only small studies of its use and effects in critically ill humans.[6-11] However, none of these studies addressed the use of paracetamol to treat fever in septic ICU patients. This is unfortunate, because a better understanding of the current use of paracetamol for septic patients is desirable and a necessary first step to the design and conduct of future observational or interventional studies of paracetamol use and patient outcome.

Accordingly, we aimed to investigate the epidemiology and associations of paracetamol administration in a cohort of septic critically ill patients. In particular, we wished to test the hypothesis that paracetamol use is common among such patients and that its administration is unpredictably related to body temperature.

Methods

This was a retrospective observational study. The data collection and data analysis were approved by the Austin Hospital Human Research Ethics Committee (approval no. H2010/04198); as this study was deemed to be low risk, the need for informed consent was waived.

All patients (medical and surgical) admitted to the ICU of the Austin Hospital over an 8-month period (14 December 2009 to 8 August 2010) with an Acute Physiology and

Chronic Health Evaluation (APACHE) III diagnosis of a sepsis-related condition were included. Coding for admission diagnosis was by means of a modified APACHE III system used by the Australian and New Zealand Intensive Care Society. Paediatric patients and patients admitted after cardiac surgery, neurosurgery and liver transplant were excluded.

Patients' temperatures (as part of routine patient observation) and use of paracetamol were collected electronically via the Austin Hospital's scanned medical record (SMR) database. Demographic, clinical, diagnostic and outcome data were obtained from electronic ICU repositories.

Patients' temperatures and paracetamol

We obtained patient temperatures documented as part of the routine observations at times 00:00, 06:00, 12:00 and 18:00 hours (or the temperature recorded nearest to that time) for the patient's time in ICU or until 7 days after admission, whichever came first. Temperature data were obtained from the intensive care observation chart electronically via an SMR database. Fever was defined as a tympanic temperature > 38.0° C.

Use of paracetamol at 00:00, 06:00, 12:00 and 18:00 hours (or that administered nearest to that time) was obtained from the medication chart electronically via the hospital's SMR database.

Statistical analysis

All analysis was performed using SAS, version 9.2 (SAS Institute Inc, Cary, NC, USA). Data on patient characteristics, temperature and paracetamol therapy are presented with descriptive statistics. Comparisons between patients with and without fever were performed using χ^2 tests for equal proportions, Student *t* tests were used for normally distributed data and Wilcoxon rank–sum tests otherwise. Continuously normally distributed data are presented as mean (SD) or mean (SE), and non-normal data are presented as median (interquartile range [IQR]). Multivariable logistic regression analysis was used to study the relationship between patient variables and outcome. A two-sided $P < 0.05$ was considered statistically significant.

Results

We studied 106 septic critically ill patients admitted to our ICU. Their mean age was 63.8 years, 59% were male and the median APACHE III score was 59 (IQR, 48–74). The most common sources of sepsis were pneumonia, peritonitis, skin infections and neurological infection. Patient demographics are shown in Table 1.

Overall, 36 (34%) of patients experienced at least one episode of fever during their ICU admission. No patient had a temperature < 36.0° C. The maximum documented temperature was reached on Day 2 after admission (Figure 1). Figure 2 illustrates the lack of relationship between peak temperature and paracetamol administration. Patients who had fever had a wider variation in temperature ($P < 0.001$), higher APACHE risk of death ($P = 0.01$) and were more likely to die in ICU ($P = 0.001$). Temperature variability, time to peak temperature, and APACHE III risk of death were independently associated with fever on multivariable analysis.

Overall, 73 (69%) patients received paracetamol while in ICU and 11 (10%) had paracetamol for every temperature measurement. The mean total paracetamol dose per patient was 6.4 g. However, only 47 (44%) had paracetamol for their peak temperature (Table 2). In total, 30 patients in the fever group (88%) compared with 40 in the non-fever group (60%) received paracetamol ($P = 0.004$). The mean and total paracetamol dose was higher among patients with fever.

Patients who had a fever were more likely to die in the ICU compared with afebrile patients ($P < 0.001$) (Table 3). They also had greater temperature variability, more sustained elevations of temperature, and were more likely to receive paracetamol and a larger dose of it (Table 3).

Patients who died in ICU had a significantly higher temperature, variability in temperature and peak temperature (Table 4). Although there were many differences in temperature-related variables between survivors and non-survivors, there were no differences in paracetamol use between the two groups (Table 4).

Table 5 compares the use of paracetamol among postoperative and non-postoperative patients. There were no significant differences in frequency of paracetamol treatment or dose when comparing patients admitted to ICU from the operating theatre with medical patients. Overall, 23% of postoperative patients had paracetamol for every temperature measurement, compared with 6% in the non-postoperative group ($P = 0.02$). Additionally, 37% of postoperative patients had a fever compared with 23% in the non-postoperative group ($P = 0.2$). Finally, 68% of postoperative patients had paracetamol at least once during the postoperative period, compared with 70% in the non-postoperative group ($P = 0.90$).

We applied multivariable logistic regression with the dependent variable being whether a patient had a temperature > 38.0° C at any point during their ICU stay. After adjustment for diagnosis, operative status and APACHE III risk of death, if a patient received paracetamol, the risk of their temperature exceeding 38.0° C was seven times greater (odds ratio [OR], 7.0 [95% CI, 1.9–26]; $P = 0.004$). Similarly, their risk of exceeding 38.0° C increased by 15% for each additional dose of paracetamol received (OR, 1.15

Table 1. Demographics of study patients

Characteristic	
Mean age, years (SD)	63.8 (16.2)
Sex	
Male	63
Female	43
Median APACHE III score (IQR)	59 (48–74)
Median APACHE III risk of death, % (IQR)	19% (10%–32%)
No. of mechanically ventilated patients	47
No. of renal replacement therapy patients	4
Source of sepsis	
Abdominal	56
Respiratory	38
Other	12
Source of admission	
Emergency department	25
Ward	45
Other hospital	13
Operating theatre	23
Median ICU length of stay, days (IQR)	3.0 (1.5–6.5)
Median hospital length of stay, days (IQR)	18.8 (9.6–30.3)

APACHE = Acute Physiology and Chronic Health Evaluation.
ICU = intensive care unit. IQR = interquartile range.

Table 2. Characteristics of paracetamol administration for all patients

Characteristics	
Mean total paracetamol dose, g (SD)	6.4 (7.0)
Median total paracetamol dose, g (interquartile range)	4.0 (0.0–10.0)
Received paracetamol for peak temperature, % (SD)	44 (0.5)
Received paracetamol for every temperature measurement, % (SD)	10 (0.3)

Figure 1. Maximum and median temperature variation over time

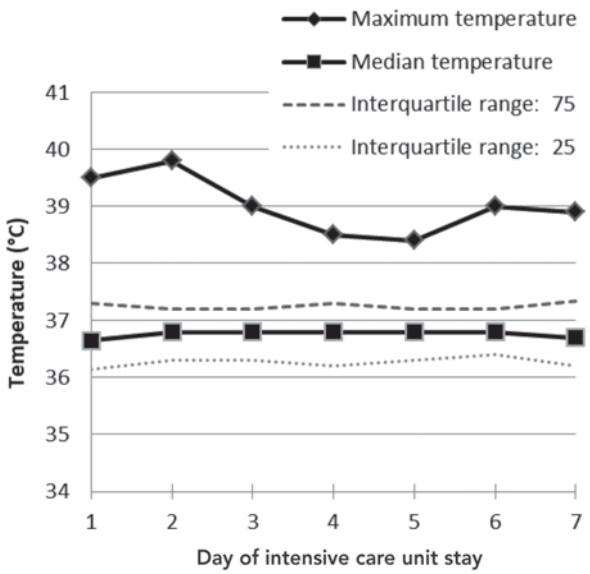
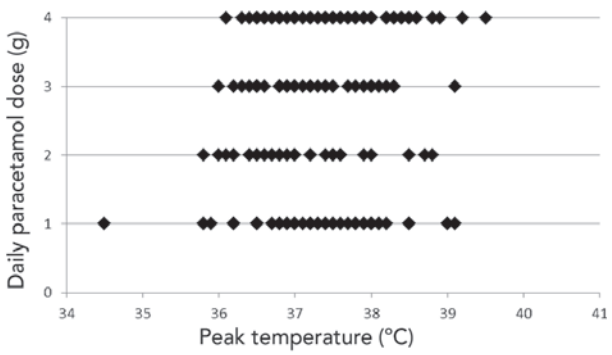


Figure 2. Daily paracetamol dose given according to peak temperature



[95% CI, 1.06–1.25]; $P < 0.001$). Moreover, after adjusting for operative status, diagnosis and severity, patients who had a temperature > 38.0° C at any point during their ICU stay were 6.8 times more likely to receive paracetamol than those that did not have a fever (OR, 6.8 [95% CI, 1.9–24.7]; $P = 0.004$).

Discussion

We conducted a retrospective observational inception cohort study of the epidemiology and associations of paracetamol administration in patients admitted to a teaching hospital with a diagnosis of severe sepsis. First, we found that most patients received paracetamol in ICU, and 80% of patients who had a fever received paracetamol at least once, but not necessarily at the time of their highest temperature. Second, patients with fever received a larger overall dose of paracetamol than those without fever. Third, although patients with fever were more likely to die in ICU, those who died in ICU did not receive more paracetamol. Finally, and more importantly, even though the presence of fever significantly increased the likelihood of paracetamol administration, the use of paracetamol was highly variable, not predictably given for the highest temperature and was not altered by the presence of recent surgery.

Table 3. Comparison of patients with fever and without fever

	With fever	Without fever	*P*
No. of patients	36	70	
Median APACHE III score (IQR)	63 (52–81)	56 (47–67)	0.01
Median APACHE III risk of death (IQR)	26 (16–43)	18 (9–24)	0.01
Mean age, years (SE)	62.7 (14.7)	64.3 (17.3)	0.37
ICU deaths, % (SE)	15% (0.06%)	0	0.001
Hospital deaths, % (SE)	20% (0.07%)	12% (0.04%)	0.25
Mean temperature, °C (SE)	37.1 (0.4)	36.5 (0.5)	0.001
Mean variation of temperature, °C (SE)	0.7 (0.2)	0.4 (0.2)	< 0.001
Median time to reach peak temperature, days (IQR)	2 (1–3)	2 (1–3)	0.85
Mean peak temperature after first peak temperature, °C (SE)	37.9 (0.5)	36.8 (0.5)	< 0.001
Mean peak temperature, °C (SE)	38.5 (0.5)	37.1 (0.6)	< 0.001
Patients who received paracetamol for peak temperature, % (SE)	56% (0.08%)	37% (0.08%)	0.07
Mean total paracetamol dose, g (SE)	10.5 (7.9)	4.2 (5.5)	< 0.001
Patients who received paracetamol at least once during first 7 days in ICU, % (SE)	80% (0.06%)	60% (0.06%)	0.004

APACHE = Acute Physiology and Chronic Health Evaluation. ICU = intensive care unit. IQR = interquartile range.

Table 4. Comparison between ICU survivors and non-survivors

	ICU survivor	ICU non-survivor	*P*
No. of patients	100	6	
Median APACHE III score (IQR)	58 (48–70)	107 (101–113)	0.002
Median APACHE III risk of death (IQR)	19 (9–30)	69 (60–89)	0.003
Mean age, years (SE)	64.0 (16.3)	61.3 (16.9)	0.71
Mean temperature, °C (SE)	36.7 (0.5)	37.3 (0.4)	0.006
Patients with temperature > 38.0° C %, (SE)	30% (0.05%)	100% (1%)	0.001
Mean standard deviation of temperature (SE)	0.50 (0.20)	0.96 (0.31)	0.001
Mean peak temperature, °C (SE)	37.6 (0.8)	38.8 (0.8)	0.005
Median time to reach peak temperature, days (IQR)	3 (1–6)	5 (4–8)	0.07
Mean peak temperature after first peak temperature, °C (SE)	37.1 (0.7)	38.2 (0.7)	0.009
Median paracetamol dose, mg (IQR)	500 (0–840)	300 (0–536)	0.34
Received paracetamol for peak temperature, SE (%)	45% (0.05%)	20% (0.20%)	0.28
Received paracetamol at least once during first 7 days in ICU, % (SE)	70% (0.05%)	60% (0.24%)	0.65

APACHE = Acute Physiological Assessment and Chronic Health Evaluation. ICU = intensive care unit. IQR = interquartile range.

To the best of our knowledge, this is one of few studies to describe the use of antipyretic therapy to treat fever in ICU patients admitted with severe sepsis. Our findings present novel information on frequency of administration, dose, relation to fever and association with outcome.

Ours was a single-centre retrospective study with a relatively small number of patients with all the inherent limitations of such studies. However, to our knowledge, it also presents the largest detailed description of the use of paracetamol in ICU patients with sepsis to date. We assumed that most of the paracetamol administered to these patients was for temperature control. This assumption seemed justified, because only a quarter of postoperative patients received paracetamol regularly. We assumed such regular administration would be for pain. The remaining three-quarters of episodes of paracetamol therapy may have been given for pain or fever. However, as only about a fifth of patients were postoperative, it seems very likely that, in the overall cohort, the vast majority of paracetamol was prescribed for temperature control. Yet,

Table 5. Comparison between postoperative and non-postoperative patients

	Postoperative patients	Non-postoperative patients	*P*
No. of patients	22	84	
Median APACHE III score (IQR)	58 (50–62)	59 (48–76)	0.4
Median APACHE III risk of death (IQR)	0.2 (0.09–0.25)	0.19 (0.1–0.3)	0.6
Mean age, years (SE)	69.5 (3.3)	62.3 (1.8)	0.06
ICU deaths, % (SE)	4% (0.04)	6% (0.02)	0.8
Hospital deaths, % (SE)	13% (0.07)	17% (0.04)	0.7
Patients with temperature > 38.0° C, % (SE)	23% (0.09)	37% (0.06)	0.2
Mean temperature, ° C (SE)	36.6 (0.13)	36.7 (0.06)	0.1
Mean peak temperature, ° C (SE)	37.3 (0.06)	37.7 (0.09)	0.01
Mean variation of temperature (SE)	0.54 (0.08)	0.52 (0.02)	0.65
Mean peak temperature after first peak temperature, ° C (SE)	37.0 (0.19)	37.2 (0.08)	0.25
Mean time to reach peak temperature, days	1.5 (0.14)	2.5 (0.19)	0.006
Received paracetamol for peak temperature, % (SE)	59% (0.12%)	39% (0.06%)	0.10
Received paracetamol at least once during first 7 days in ICU, % (SE)	68% (0.10%)	70% (0.05%)	0.90
Mean paracetamol dose, mg (SE)	565 (0.09)	418 (0.04)	0.15

APACHE = Acute Physiology and Chronic Health Evaluation. ICU = intensive care unit. IQR = interquartile range.

because of the nature of our study, we cannot report with certainty when paracetamol was given for the treatment of fever, when it was given for the treatment of pain and when it was given as fever or pain prophylaxis.

Laupland and colleagues found that fever was less likely if a patient had a higher APACHE score and that the presence of fever was not associated with ICU death, but provided no data on paracetamol use.[9] Other studies found that patients with fever had higher APACHE scores.[12,13] This is in keeping with our findings. Such studies, however, failed to provide any information on antipyretic therapy. Consistent with our study, Circiumaru and colleagues found that most cases of fever in the ICU occurred within 2 days of admission.[12] They also found that fever alone was not associated with higher mortality, but that prolonged fever was. Again, no data were provided on the dose or frequency of paracetamol therapy.

We found that ICU mortality was higher among patients with a fever than those with no fever. Previously, an investigation into postoperative patients found febrile patients were more likely to die if they had a fever, but not if fever was caused by infection.[12] Additionally, peak temperature was associated with higher mortality. Hypothermia in sepsis has also been associated with increased risk of death.[13,14] We are unable to comment on any association between hypothermia and an increased risk of mortality, as none of the patients in our cohort had documented hypothermia.

There have been only few studies evaluating the efficacy of treating fever in ICU. These studies have shown either lack of efficacy[7,8] or some efficacy[6] from fever management. However, they did not identify septic patients separately. More recently, Young and colleagues reported that, in a cohort of 51 patients with febrile sepsis, paracetamol use did not correlate with the presence of fever, and that 70% of such patients received paracetamol.[15] Our study expands on these data by showing that, although the likelihood of receiving paracetamol increases if fever is present, there is high variability and unpredictability of paracetamol prescription in septic patients overall and in septic patients with fever.

Our finding that almost all septic patients received some paracetamol while in ICU establishes the clinical relevance of this issue and highlights how common paracetamol administration is in the setting of ICU. The observations that about a 10th of septic critically ill patients and one-quarter of postoperative patients received paracetamol for every temperature measurement suggest that paracetamol was not given prophylactically in this ICU. The fact that only about half of febrile septic critically ill patients received paracetamol for their peak temperature further suggests that there was no reliable pattern of paracetamol administration in response to fever. However, the mean total paracetamol dose per patient implies repeated administration and systemic exposure to paracetamol. Of relevance, however, is the fact that the patients who received paracetamol regularly did not show any signs, symptoms or laboratory changes indicative of hepatotoxicity. This suggests paracetamol-induced hepatotoxicity may be a rare occurrence in critical care when used at the recommended dosage.

We contend that our findings, although exploratory and observational, justify the design and conduct of future prospective observational studies of paracetamol use in ICU patients to more clearly understand when, why and how this agent is administered in septic and/or febrile patients.

Conclusions

In our retrospective observational study, we found that paracetamol administration was common in critically ill septic patients and independently related to the presence of fever. However, it also appeared highly variable. In particular, although paracetamol was given frequently, it was only given to about half the patients studied when they reached their highest temperature. Even in patients where pain management was an unlikely driver of paracetamol prescription, its use appeared variable and not consistently related to body temperature. More investigations are needed to understand when, why and how paracetamol is administered to critically ill septic patients.

Competing interests

None declared.

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