Chapter 11

The effect of pharmacological antipyresis on mortality in patients with sepsis: a sub-analysis of the PHANTASi trial

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ABSTRACT

Objective
There are no accepted international guidelines on the use of paracetamol for fever control in sepsis. Fever is important for immune function and it therefore seems counterintuitive to administer antipyretic drugs in sepsis. The aim of this study is to determine whether antipyretic medication influences mortality in patients with sepsis.

Design
We performed a sub-analysis of the Prehospital Antibiotics Against Sepsis (PHANTASi) trial.

Setting
This study was conducted in a pre-hospital setting. Interventions were given in the ambulance. Patients were included between June 2014 and June 2016.

Patients
Patients were included in the original study when they had a diagnosed or suspected infection, a temperature > 38 °C or < 36°C and at least one other criterion of the systemic inflammatory response syndrome (SIRS).

Interventions
We compared patients with sepsis who received paracetamol in the ambulance and patients who did not. The primary outcome was 28-day mortality. Outcomes were adjusted for sex, age and sepsis severity. In addition we compared the 28-day mortality for hypothermic and hyperthermic patients.

Main Results
2528 patients were included in the primary outcome analysis: 254 patients received paracetamol in the ambulance and 2274 did not. There was no significant difference in 28-day mortality between the paracetamol and non-paracetamol groups (OR: 0.63 [95% CI 0.35 to 1.13]; p=0.12). We established that paracetamol administration caused a significantly larger decrease in temperature compared to no treatment (0.26°C [95% CI [0.15-0.36]; p<0.001). Furthermore, hyperthermic patients had lower mortality rates when compared to hypothermic patients (OR: 0.20 [95% CI: 0.11-0.37]; p<0.001). When different cut-off values in temperature were examined, patients with higher body temperatures had consistently lower mortality rates than patients with lower body temperatures.

Conclusions
Our results suggest that administration of paracetamol does not influence mortality rates in patients with sepsis, regardless of the initial body temperature.

Keywords
Sepsis  Hyperthermia
Paracetamol  Hypothermia
Antipyretics  Mortality
INTRODUCTION

Sepsis is a life threatening syndrome. The incidence of severe sepsis is estimated to be over 300 cases per 100,000 population (1). In-hospital mortality rates can be as high as 25% for severe sepsis and increase to up to 50% for patients in septic shock (1). Hyperthermia is a common symptom of sepsis (2). Septic patients with hypothermia have higher mortality rates than patients with hyperthermia (3). Thus, fever appears to have a protective role in patients with sepsis (4). Some patients with sepsis receive antipyretic medication to suppress fever in the ambulances, although fever is not an indication for administration of paracetamol in the Dutch Ambulance Protocol (5). As patients with higher temperatures have lower mortality rates, it seems counterintuitive to administer antipyretic drugs.

In the last decade, a substantial amount of literature has been published on the use of antipyretics in patients with sepsis. The majority of these studies have been unable to provide an estimate of the effect, or did not find any effect, of antipyretics on mortality in sepsis (4, 6-13). One study found significant evidence favoring antipyresis as a method to improve survival in these patients (14), while others found significant evidence that antipyretic treatment raises mortality rates in septic patients (15-18). As the available literature is contradictory and inconclusive, there is no general agreement or protocol about the use of paracetamol for fever control in sepsis.

Therefore the primary aim of this study is to determine whether patients with sepsis who are given antipyretic treatment in the ambulance, in the form of paracetamol, have different mortality rates than patients with sepsis who do not receive this treatment. In addition, we will determine whether hyperthermia leads to improved outcomes as opposed to hypothermia in the general sepsis population.

MATERIALS AND METHODS

Study design
A sub-analysis of the Prehospital Antibiotics Against Sepsis (PHANTASi) trial was conducted. The PHANTASi trial was a large randomized controlled trial investigating the effects of antibiotics administration in patients with sepsis. Patients in the intervention group received ceftriaxone in the ambulance (in addition to usual care), while those in the control group received only usual care (fluid resuscitation and supplementary oxygen) and received their first dose of antibiotics at the emergency department.

Patients were included between June 2014 and June 2016 (19). Eligible patients were those who had a “diagnosed or suspected infection, a temperature > 38 °C or < 36°C and at least one other criterion of the systemic inflammatory response syndrome (SIRS): a heart rate >90 beats per minute or respiratory rate >20 per minute or both)”(19). Due to the fact that there are currently no pre-hospital leukocyte tests, this SIRS criterion was not one of the inclusion criteria.
Sepsis severity was categorized into three categories as per the 2001 SSCM/ ESCIM/ ACCP/ ATS/ SIS International Sepsis definitions Conference guidelines (20): sepsis, severe sepsis and septic shock.

Patients who were under the age of 18 were excluded. Eligible patients were transported to the emergency department of one of the 34 participating hospitals in the Netherlands.

A variety of different parameters were recorded in the study, such as temperature in the ambulance, temperature at the emergency department and paracetamol usage in the ambulance. A detailed description of the original study design as well as the case report form are published elsewhere (19, 21).

**Methodology**

In total 2,672 patients were included in the PHANTASi trial. In this sub-analysis, patients who received paracetamol in the ambulance (paracetamol group) were compared to those who did not receive paracetamol in the ambulance (non-paracetamol group). Patients in the paracetamol group received a dose of 1,000 mg paracetamol. The tympanic temperature of patients was measured in the ambulance before the administration of paracetamol and after arrival at the emergency department. There was no data on the time period between these measurements, but we assume it is at least 26 minutes, as the average time between antibiotics administration in the intervention group of the PHANTASi trial and arrival at the emergency department was 26 minutes (19-34) (19).

As patients with a temperature between 36 °C and 38°C were excluded from the original study, we defined a hypothermia group (temperature <36.0°C) and a hyperthermia group (temperature >38°C).

**Outcomes**

The primary outcome of this sub-analysis was the all-cause mortality difference at 28-days between the paracetamol group and the non-paracetamol group. Secondary outcomes were the temperature differences in the groups between the ambulance measurement and the emergency department measurement. The all-cause mortality difference at 28-days between the two groups based on the initial temperature in the ambulance was also analyzed. Various cut-off points were evaluated. Several of these outcomes were also analyzed for the temperature measured at the emergency department to establish replicability. Odds ratios were calculated as effect sizes.

A priori, the decision was made to adjust all outcomes for sepsis severity, as this was found to be a major factor influencing the mortality in the original study. Adjustments were also made for gender and age. We did not adjust for the antibiotic intervention from the original study, as this intervention did not cause statistically different mortality rates.

**Statistical analysis**

Continuous variables were compared using an independent samples T-test, after testing for normality of distribution, and reported as means and standard deviations.
Dichotomous and categorical variables were reported as proportions and compared with a chi-square test. The cases with missing values were excluded from analyses. All analyses of the primary and secondary outcomes were done using a logistic regression model, to allow adjustment for sex, age and sepsis severity. All analyses were done with IBM SPSS statistics 22. A two-sided p-value <0.05 was considered to be statistically significant.

**Ethics**

The study protocol of the PHANTASi trial was approved by the medical ethical committee of the Amsterdam University Medical Center, Location VU University Medical Center, the coordinating center and all ethical bodies of each participating hospital. Due to the complexity of the PHANTASi trial, the ethics committees granted approval to obtain deferred consent when necessary. Informed consent before study enrolment or deferred consent was obtained from all patients or their legal representatives or surrogates. All effort was made by EMS personnel to obtain informed consent before study inclusion provided the acuity of the situation allowed it.

**RESULTS**

In total, 2,528 patients were included in the primary outcome analysis. 254 patients received paracetamol in the ambulance and 2,274 did not. At baseline, there were several differences between the groups. Patients in the paracetamol group were younger (70.0 vs. 73.0 years; p=0.004) and had a different distribution of the National Early Warning Score (NEWS) in the ambulance (p=0.03). Relatively, patients in the paracetamol group more often had a NEWS between 0-3, whereas the non-paracetamol group more often had a NEWS between 4-6. A NEWS of over 6 points was seen equally in the groups. Otherwise, the groups were comparable concerning baseline condition. See table 1 for further details.

At 28 days, 205 patients had died (8.1%) in the complete study population. In the paracetamol group 13 (5.1%) patients had died and in the non-paracetamol group 192 (8.4%) patients had died (OR: 0.59 [95% CI 0.33 to 1.04]; p=0.07). After adjustment for sex, age and sepsis severity, the odds ratio and p-value did not change significantly (OR: 0.63 [95% CI 0.35 to 1.13]; p=0.12) Thus, there was no significant difference in 28-day mortality between the paracetamol and non-paracetamol groups. An analysis of 28-day mortality between the paracetamol and non-paracetamol groups for just the hyperthermic patients, yielded similar results (OR: 0.75 [95% CI 0.41 to 1.35]; p= 0.33). This outcome was also adjusted for sex, age and sepsis severity.

**Temperature differences: paracetamol vs non-paracetamol group**

There was a significant difference between the paracetamol and non-paracetamol groups, when the temperature measured in the ambulance and the temperature measured in the emergency department were compared. Paracetamol administration caused an average decrease in temperature of 0.49°C. In the non-paracetamol
group there was also a decrease in temperature, but to a lesser extent with 0.23°C (mean difference: 0.26°C (95% CI [0.15-0.36]; p<0.001 (see appendix for further details)). The Levene’s test for equality of variance was significant (p=0.01) and therefore, equal variances between the groups were not assumed in this calculation (appendix).

**Mortality: hypothermic and hyperthermic patients in the ambulance**

In the group of hypothermic patients, 18 (33.3%) had died after 28 days, while in the group of hyperthermic patients, 168 (7.2%) had died (OR: 0.16 [95% CI: 0.09-0.28]; p<0.001). After adjustment for sex, age and sepsis severity, the outcome did not change significantly (OR: 0.20 [95% CI: 0.11-0.37]; p<0.001) (table 2). The mortality rates were significantly higher in patients with hypothermia compared to hyperthermic patients. Baseline characteristics of these groups were also studied (table 3). Notable is the difference in sepsis severity between the groups (p <0.001). Relatively, patients with hypothermia more often had severe sepsis or septic shock.

Mortality differences between groups based on the first temperature measurement was also analyzed (table 2). Every cut-off point showed significantly higher mortality rates in the patients with the lower initial temperature. The largest differences in odds of mortality were seen at the lower cutoff values.

**Mortality: hypothermic and hyperthermic patients in the emergency department**

A difference in mortality rates was found between hypothermic and hyperthermic patients in the emergency department. The odds ratio of mortality for hyperthermic patients was 0.13 compared to the hypothermic patients (95% CI: 0.06-0.28; p<0.001). After adjustment for sex, age and sepsis severity, the outcome did not change significantly (OR: 0.20 [95% CI: 0.08-0.49]; p<0.001) (table 3).
Table 1. Baseline characteristics paracetamol and non-paracetamol groups: percentages within patient groups (chi-square test for categorical variables and independent t-test for age).

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Categories</th>
<th>Non-paracetamol group (n=2274)</th>
<th>Paracetamol group (n=254)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex</td>
<td>Women</td>
<td>1309 (57.6%)</td>
<td>157 (61.8%)</td>
<td>0.19</td>
</tr>
<tr>
<td></td>
<td>Men</td>
<td>965 (42.4%)</td>
<td>97 (38.2%)</td>
<td></td>
</tr>
<tr>
<td>Age (mean)</td>
<td></td>
<td>73.0 ± 13.4</td>
<td>70.0 ± 15.7</td>
<td>0.004</td>
</tr>
<tr>
<td>Sepsis severity</td>
<td>Sepsis</td>
<td>1253 (55.1%)</td>
<td>147 (57.9%)</td>
<td>0.69</td>
</tr>
<tr>
<td></td>
<td>Severe sepsis</td>
<td>958 (42.1%)</td>
<td>100 (39.4%)</td>
<td></td>
</tr>
<tr>
<td>Temperature in ambulance</td>
<td>Hypothermia</td>
<td>52 (2.4%)</td>
<td>2 (0.8%)</td>
<td>0.17</td>
</tr>
<tr>
<td></td>
<td>Hyperthermia</td>
<td>2144 (97.6%)</td>
<td>243 (99.2%)</td>
<td></td>
</tr>
<tr>
<td>Temperature in emergency department</td>
<td>Hyperthermia</td>
<td>25 (1.3%)</td>
<td>1 (0.5%)</td>
<td>0.51</td>
</tr>
<tr>
<td></td>
<td>Hypothermia</td>
<td>1790 (98.7%)</td>
<td>196 (99.5%)</td>
<td></td>
</tr>
<tr>
<td>Charlson Comorbidity Score</td>
<td>0-3</td>
<td>1915 (84.2%)</td>
<td>205 (80.7%)</td>
<td>0.15</td>
</tr>
<tr>
<td></td>
<td>&gt;3</td>
<td>359 (15.8%)</td>
<td>49 (19.3%)</td>
<td></td>
</tr>
<tr>
<td>Early Warning Score</td>
<td>0-3</td>
<td>286 (17.5%)</td>
<td>42 (23.7%)</td>
<td>0.03</td>
</tr>
<tr>
<td></td>
<td>4-6</td>
<td>482 (31.5%)</td>
<td>41 (23.2%)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>&gt;6</td>
<td>781 (51.0%)</td>
<td>94 (53.1%)</td>
<td></td>
</tr>
</tbody>
</table>

*for age: Levene’s test for equality of variances: p<0.001.
Table 2. Secondary outcomes: temperature groups for different cut-off values in temperature (n = number of patients within group, % = percentage between the groups). Logistic regression models with outcomes adjusted for sex, age and sepsis severity.

<table>
<thead>
<tr>
<th>Temperature cutoff (in °C)</th>
<th>Low temperature group (n / %)</th>
<th>High temperature group (n / %)</th>
<th>Adjusted OR</th>
<th>Adjusted 95% CI</th>
<th>Adjusted p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>35.0</td>
<td>15 (0.6%)</td>
<td>2,513 (99.4%)</td>
<td>0.22</td>
<td>0.07 to 0.69</td>
<td>0.01</td>
</tr>
<tr>
<td>35.5</td>
<td>35 (1.4%)</td>
<td>2,493 (98.6%)</td>
<td>0.19</td>
<td>0.09 to 0.41</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>36.0</td>
<td>55 (2.2%)</td>
<td>2,473 (97.8%)</td>
<td>0.20</td>
<td>0.11 to 0.36</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>36.5</td>
<td>57 (2.3%)</td>
<td>2,471 (97.7%)</td>
<td>0.20</td>
<td>0.11 to 0.37</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>37.0</td>
<td>63 (2.5%)</td>
<td>2,465 (97.5%)</td>
<td>0.22</td>
<td>0.12 to 0.40</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>37.5</td>
<td>71 (2.8%)</td>
<td>2,457 (97.2%)</td>
<td>0.22</td>
<td>0.13 to 0.39</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>38.0</td>
<td>180 (7.1%)</td>
<td>2,348 (92.9%)</td>
<td>0.35</td>
<td>0.23 to 0.53</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>38.5</td>
<td>717 (28.4%)</td>
<td>1,811 (71.6%)</td>
<td>0.64</td>
<td>0.47 to 0.87</td>
<td>0.004</td>
</tr>
<tr>
<td>39.0</td>
<td>1383 (54.7%)</td>
<td>1,145 (45.3%)</td>
<td>0.67</td>
<td>0.49 to 0.91</td>
<td>0.011</td>
</tr>
<tr>
<td>39.5</td>
<td>1887 (74.6%)</td>
<td>641 (25.4%)</td>
<td>0.57</td>
<td>0.38 to 0.85</td>
<td>0.006</td>
</tr>
<tr>
<td>40.0</td>
<td>2298 (90.9%)</td>
<td>230 (9.1%)</td>
<td>0.36</td>
<td>0.17 to 0.79</td>
<td>0.010</td>
</tr>
</tbody>
</table>

Table 3. Baseline characteristics hypothermia and hyperthermia groups: percentages within patient groups (chi-square test for categorical variables and independent t-test for age).

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Categories</th>
<th>Hypothermia (n=54)</th>
<th>Hyperthermia (n=2335)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex</td>
<td>Women</td>
<td>39 (72.2%)</td>
<td>1343 (57.5%)</td>
<td>0.04</td>
</tr>
<tr>
<td></td>
<td>Men</td>
<td>15 (27.8%)</td>
<td>992 (42.5%)</td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td></td>
<td>74.6 ± 12.7</td>
<td>72.7 ± 13.7</td>
<td>0.30</td>
</tr>
<tr>
<td>Sepsis severity</td>
<td>Sepsis</td>
<td>17 (31.5%)</td>
<td>1312 (56.2%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td></td>
<td>Severe sepsis</td>
<td>32 (59.3%)</td>
<td>960 (41.1%)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Septic shock</td>
<td>5 (9.3%)</td>
<td>63 (2.7%)</td>
<td></td>
</tr>
<tr>
<td>Charlson Comorbidity</td>
<td>0-3</td>
<td>45 (83.3%)</td>
<td>1959 (83.9%)</td>
<td>0.85</td>
</tr>
<tr>
<td>Score</td>
<td></td>
<td></td>
<td>376 (16.1%)</td>
<td></td>
</tr>
</tbody>
</table>

*for age: Levene’s test for equality of variances: p=0.46.
DISCUSSION

In this study we did not find a mortality difference between septic patients who received paracetamol and patients who did not, although we confirmed that the former had a significantly larger decrease in temperature between the measurement in the ambulance and at the emergency department. An analysis of the hyperthermic patients alone showed similar results, indicating that paracetamol does not influence mortality rates in patients with sepsis, regardless of the initial temperature in the ambulance. Thus, lowering of body temperature does not seem to cause higher mortality rates. The high mortality rates are more likely caused by failure of the immune system, resulting in lower temperatures in these patients.

To the best of our knowledge, this is the first study to investigate mortality differences between septic patients who receive paracetamol and patients who do not, combined with an analysis of the temperature difference between these groups caused by this treatment. Furthermore, our study seems to be the first to investigate this subject in a prehospital setting.

Our findings are similar to most of the articles that have been published on this subject (4, 6-13). Schortgen et al. found decreased mortality rates after the use of antipyretics early in septic shock (14). In their study, only external cooling was used for antipyresis, which led to an average temperature decrease of 1.6 °C. This differs considerably from the antipyretic effects that can be expected of paracetamol administration. Previous work has described an average temperature difference of 0.28 (p=0.009) and 0.64 (p<0.001), respectively, between those who received paracetamol and those who did not, in the time period between 30 and 60 minutes after administration (22). This is the likely timeframe in which measurements took place in our study.

Several studies found higher mortality rates in patients with sepsis who receive antipyretic medication (15-18). A study by Schulman et al. was stopped after the first interim analysis since the intervention group, which received antipyresis, had higher mortality rates (16). However, this difference in mortality was not statistically significant. Ye et al. reported about a specific subpopulation of patients in the ICU which differs considerably from our patient population (17). Lee et al. reports that paracetamol usage is associated with a higher 28-day mortality, independent of fever (15). Furthermore, the authors found no association of a body temperature with mortality in the study by Lee et al., which negates the hypothesis that mortality rates are higher because of the decrease in temperature. Zhang et al. reported that antipyretic therapy by external cooling is associated with higher mortality rates at body temperatures above 39 °C (18). This is again different to our approach with only paracetamol as antipyretic therapy.

We found that patients with sepsis who were initially hypothermic have significantly higher mortality rates than hyperthermic patients. We compared mortality rates between groups based on various cut-off values in temperature. Patients with higher temperatures had consistently lower mortality rates than patients with lower temperatures. These findings are significant for all cut-off values we examined. It is
notable that we found a significant difference at the cut-off value of 35.0 °C as the group sizes are 15 vs 2,513 patients respectively, showing that hypothermic patients with sepsis have considerably higher mortality rates than hyperthermic patients.

Our study has several strengths. Firstly, temperature measurements in the ambulance were followed up by measurements in the emergency department within a short period of time, likely between 30 and 60 minutes. Therefore we could establish that our results were reproducible when we analyzed measurements that were done soon after the initial measurements. Secondly, all patients’ charts were analyzed by a panel of experts to make sure that the included patients did have sepsis. Furthermore, compared to other studies conducted on this subject, we were able to include considerably more patients.

There are some limitations to this study. Firstly, there is no documentation of paracetamol usage prior to administration in the ambulance. Because the paracetamol and non-paracetamol groups were not randomized, it is possible that patients in the non-paracetamol group, on average, received more paracetamol prior to inclusion in the study, thereby diminishing any mortality differences. One of the hypotheses is that antipyretics could cause higher mortality rates in septic patients by reducing temperature, as fever is suggested to be important for both “immune function and for its bacteriostatic properties” (10). However, we confirmed that the paracetamol group had a significantly larger decrease in temperature after administration of this drug, and thus we did not confirm this hypothesis in our study. Furthermore, this difference in body temperature is comparable with the difference found in a study on the effects of paracetamol when compared to placebo (22). We can thus assume that a larger antipyretic and thereby more clinically relevant effect cannot be expected from paracetamol.

Another limitation is that there was no documentation on the use of paracetamol in the hospital. This problem was unavoidable due to the type of study we conducted. We did however show that a significant decrease in temperature was established by paracetamol in a critical phase of the illness. This is the main effect that we aimed to quantify.

Lastly, as with any sub-analysis, the different study arms are not randomized. Although we have adjusted the outcome for several confounders, the possibility remains that the results are influenced by confounders that were not measured in the original study. This limitation is even more relevant as there was no clear protocol for the administration of paracetamol in the ambulance. In the Dutch Ambulance Protocol, fever is not an indication for administration of paracetamol and should only be considered as analgesic (5). There is no guideline on a pain score that should always be followed by administration of paracetamol in this protocol. Therefore, there is a substantial chance of bias in this regard. However this bias was inevitable given the nature of this study.
CONCLUSION

Administration of paracetamol to lower body temperature does not seem to influence mortality rates in patients with sepsis, regardless of initial temperature in the ambulance. Our results suggest that fever might not have a protective role in sepsis, but the negative effects of hypothermia may create the false appearance of a protective effect of fever. Hypothermia is an ominous sign in patients with sepsis and should immediately make the clinician aware of the criticalness of the situation. Administration of paracetamol to lower temperature does not seem to influence the underlying pathophysiological mechanisms for the high mortality rates in hypothermic patients and can be administered to patients with sepsis on an individual basis.
REFERENCES