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ASTER Trial: Acetaminophen and Organ Dysfunction in Patients With Sepsis

Acetaminophen (paracetamol) has several pharmacological effects that are potentially beneficial in sepsis, including analgesia, antipyresis, and cyclooxygenase-2 inhibition. Observational studies and small clinical trials suggest acetaminophen improves survival and kidney function in sepsis patients with elevated cell-free haemoglobin. However, a large trial for treating fever in suspected infections showed no mortality benefit.

These findings highlight the need for further research, leading to the NHLBI PETAL Network's Acetaminophen and Ascorbate in Sepsis: Targeted Therapy to Enhance Recovery (ASTER) platform. This trial tested intravenous acetaminophen versus placebo in sepsis patients with respiratory or circulatory organ dysfunction.

Eligible patients were 18 years or older with sepsis, defined by clinical evidence of infection and orders for antibiotics. They had to meet either of these criteria: (1) hypotension requiring vasopressors after at least 1 L of intravenous fluid or (2) respiratory failure, indicated by mechanical ventilation, noninvasive ventilatory support, or at least 6 L/min of supplemental oxygen.

Patients in the acetaminophen arm received 1 g of acetaminophen in 100 mL diluent (or 15 mg/kg if under 50 kg) intravenously every 6 hours for five days (20 doses). Those in the placebo arm received an identical intravenous infusion of 100 mL of 5% dextrose in water on the same schedule.

The primary efficacy variable was the number of days alive and free of organ support (dialysis, assisted ventilation, and vasopressors) up to day 28. The secondary goal was to assess if preenrollment cell-free haemoglobin levels could predict acetaminophen's effectiveness in future trials. The vitamin C arm of the trial was terminated early, with results to be presented separately.

Safety outcomes included monitoring AST, ALT, and bilirubin levels on study days 0 and 2 through 5, with the Hy Law index assessing drug-induced liver dysfunction. Any fluid bolus administration, new vasopressor use, or increased vasopressor dose within 120 minutes of study drug infusion was recorded due to acetaminophen's association with acute blood pressure decreases. Other safety endpoints included adverse events, hypersensitivity, or rash. Trough acetaminophen levels after the fifth dose were also measured.

Four hundred forty-seven patients were enrolled and randomised, with 227 in the acetaminophen arm and 220 in the placebo arm. Baseline characteristics and plasma biomarker levels were comparable between the two groups. Pneumonia was the most common site of infection (approximately 44% in each group), and 9% of patients had tested positive for SARS-CoV-2 within the three weeks before enrollment. At baseline, 76% of patients were receiving vasopressors, 42% were on assisted ventilation, and 44% had received acetaminophen before enrollment. The median time from inclusion to randomisation was similar in both study arms.

The primary endpoint, days alive and free of organ support (dialysis, assisted ventilation, and vasopressors) up to day 28, did not differ significantly between the acetaminophen and placebo arms. Subgroup analyses also showed no significant differences. The 28-day all-cause mortality was 17% in the acetaminophen arm compared to 22% in the placebo arm.

Hospital mortality and all-cause mortality at 90 days did not significantly differ between the treatment arms. However, improvements in SOFA scores and SOFA coagulation component scores were significantly greater on study days 2 through 4 in the acetaminophen arm. Additionally,

improvements in SOFA respiratory scores were significantly greater on study days 1 through 4. The incidence of ARDS was significantly lower in the acetaminophen arm compared to placebo. Other secondary clinical endpoints did not show significant differences between the arms.

Safety outcomes indicated no significant differences in baseline and daily measurements of AST, ALT, and bilirubin between the two groups. Few patients in either arm developed new increases in AST or ALT exceeding ten times the upper limit of normal, and rates of new indices of liver dysfunction were similarly low. Adverse events, including allergic reactions, were comparable between the acetaminophen and placebo arms. There were no differences in the need for fluid boluses or initiation/increase of vasopressors after drug administration, and fluid balance was similar between the two arms. Trough acetaminophen levels were monitored and did not exceed potentially hepatotoxic thresholds.

In patients with sepsis and respiratory or circulatory organ dysfunction, treatment with intravenous acetaminophen for five days did not improve the primary endpoint of days alive and free of organ support (dialysis, assisted ventilation, and vasopressors) to day 28 compared with placebo. There were no significant differences in 28-day or 90-day mortality between the acetaminophen and placebo groups. Among the 15 secondary outcomes examined, patients treated with acetaminophen were less likely to develop ARDS and showed improvements in total SOFA scores on days 1 through 4. Importantly, intravenous acetaminophen administered every 6 hours for five days was safe in this critically ill population, with no notable differences in biomarkers of hepatic injury, systemic hypotension, or other adverse events compared to placebo.

In critically ill patients with sepsis and either respiratory or circulatory organ dysfunction, treatment with 1 g of intravenous acetaminophen every 6 hours for five days was found to be safe. However, this regimen did not significantly improve the primary outcome of days alive and free of organ support (including mechanical ventilation, vasopressors, and kidney replacement therapy) up to day 28.

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