

JOURNAL CLUB CRITIQUE

A touch of cooling may help

Akram M Zaaqoq¹ and Sachin Yende^{*1,2}

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Expanded abstract

Citation

Schortgen F, Clabault K, Katsahian S, Devaquet J, Mercat A, Deye N, Dellamonica J, Bouadma L, Cook F, Beji O, Brun-Buisson C, Lemaire F, Brochard L: **Multicenter randomized controlled clinical trial of fever control by external cooling to diminish vasopressor requirements in septic shock. Assistance Publique-Hôpitaux de Paris, France. *Am J Respir Crit Care Med* 2012, **185**:1088-1095.**

Background

Fever control may improve vascular tone and decrease oxygen consumption; however, fever may help combat infection.

Methods

Objective: To determine whether fever control by external cooling diminishes vasopressor requirements in septic shock.

Design: A multicenter randomized controlled trial.

Setting: Seven ICUs in France.

Subjects: Febrile patients with septic shock requiring vasopressors, mechanical ventilation, and sedation.

Intervention: Patients were randomly allocated to external cooling to achieve normothermia (36.5 to 37.8°C) for 48 hours.

Outcomes: The primary outcome was the number of patients with a 50% decrease in baseline vasopressor dose after 48 hours. Secondary outcomes were the numbers of patients with a 50% baseline vasopressor dose decrease after 2, 12, 24, and 36 hours, the percentage of patients requiring a vasopressor dose increase within 48 hours of baseline, the percentage of patients with shock reversal in the ICU, the change in Sequential Organ Failure Assessment score (Δ SOFA) versus baseline, and all-cause mortality on day 14 and at ICU and hospital discharge.

Results

There were 200 patients randomized, 101 to the cooling group and 99 to the no-cooling group. The percentage of patients with a 50% vasopressor dose decrease versus baseline was not significantly different at 48 hours of treatment (72% vs. 61%; absolute difference, 11%; 95% confidence interval (CI), -23 to 2; $P = 0.4$), although it was at 12 hours (54% vs. 20%; absolute difference, 34%; 95% CI, -46 to -21; $P < 0.001$). External cooling significantly reduced the number of patients needing a vasopressor dose increase (34% vs. 52%; absolute difference, -18%; 95% CI, -4 to -31%; $P = 0.011$) and significantly increased the shock reversal during the study period (86% vs. 73%; absolute difference, 13%; 95% CI, 2 to 25%; $P = 0.021$). Day 14 mortality was significantly lower in the cooling group (19% vs. 34%; absolute difference, -16%; 95% CI, -28 to -4; $P = 0.013$), but mortality was not different at ICU and hospital discharge.

Conclusions

Fever control using external cooling was safe, and decreased vasopressor requirements and early mortality in septic shock.

Commentary

Septic shock, defined as sepsis and hypotension refractory to fluid resuscitation, is the leading cause of death in noncoronary ICUs, and is associated with mortality of 40 to 60% [1-3]. Initiated by an infection, severe sepsis and septic shock may be due to a dysregulated inflammatory response [4].

Fever is defined as core temperature $\geq 38.3^\circ\text{C}$ [5,6]. Approximately 90% of patients with severe sepsis are febrile [7]. During sepsis, fever occurs in response to endogenous (IL-1 β , TNF α , IFN γ , prostaglandin E $_2$) and/or exogenous pyrogenic substances that reset the thermoregulatory center. Fever is an important adaptive response to infection [8]. Although it has beneficial and detrimental effects, the net role of fever in the pathophysiology of septic shock is unclear.

Beneficial effects include decreased bacterial and viral growth due to denaturation of essential enzymes, such as viral polymerase and/or promoter complexes [9,10]. Fever also alters the immune response. Heat shock

*Correspondence: yendes@upmc.edu

¹Department of Critical Care Medicine, 642A Scaife Hall, 3550 Terrace Street, University of Pittsburgh, Pittsburgh, PA 15261, USA

Full list of author information is available at the end of the article

proteins induced by fever have direct cytoprotective effects and downregulate NF- κ B, subsequently modifying the expression of inflammatory mediators and limiting the collateral damage of inflammation. Fever also enhances cytotoxic activity of effector cells, such as neutrophils and macrophages, leading to more rapid pathogen clearance [11]. Detrimental effects of fever include increased oxygen consumption. In patients with septic shock there is limited ability to meet the increased metabolic demands because of disturbances in cardiac and pulmonary function [12]. In febrile critically ill patients, the reduction of fever from 39 to 37°C led to a decrease in oxygen consumption and unloaded the cardiopulmonary system, which favored resuscitation of patients with limited oxygen delivery [13].

Pharmacologic approaches have been tested to control fever in patients with infection. For instance, ibuprofen has been studied in a randomized controlled trial in humans and no improvement of survival was found, even though the drug did have a salutary effect on core temperature and metabolic rate [14]. External cooling is another option to control fever without exposing the patient to the potential adverse effects of antipyretic drugs, such as increased risk of bleeding and hepatic and renal toxicity [12].

The current study is a multicenter randomized controlled trial, set to determine the effect of external cooling on vascular tone. The primary endpoint was 50% reduction in baseline vasopressor dose at 48 hours, while the secondary endpoints were 50% reduction in baseline vasopressor at various time points over 48 hours, vasopressor dose increase, shock reversal, change in Sequential Organ Failure Assessment score, and mortality on day 14 and at ICU and hospital discharge.

The hemodynamic improvement was evident through shock reversal, smaller change in Sequential Organ Failure Assessment score, and fewer cases of renal replacement therapy initiation in the cooling arm. Additionally, external cooling reduced day 14 mortality but did not change ICU or hospital mortality. The beneficial effect of cooling was more pronounced in the subgroup receiving the highest vasopressor dose.

The study has multiple strengths. Patients were enrolled on average within 1 hour from ICU admission and cooling was initiated promptly. Vasopressor management was protocolized. The study reported a good safety profile for external cooling, considering the patients were sedated and on mechanical ventilation and considering neuromuscular blockade was used in a large proportion of the study population. The study has some limitations. First, there was no mechanistic explanation (for example, reduced oxygen consumption, improved vascular tone, or differences in inflammatory response) for the beneficial effect of fever control. Second, the effect of fever

reduction on hemodynamic stability was temporary, since there was no difference in the number of patients with 50% reduction in vasopressor use at 48 hours. Also, no difference in mortality at ICU or hospital discharge was observed. Although most patients were on adequate antimicrobial coverage by the time of cooling, there was a trend toward an increased incidence of nosocomial infections on day 14 in the cooling group.

Recommendation

The results of this study suggest no harm in external cooling to control fever in patients with septic shock. A large multicenter randomized control trial is required to determine the efficacy and to shed insights on the underlying mechanistic effect of this intervention before it can be used routinely for septic shock patients.

Abbreviations

CI, confidence interval; IFN, interferon; IL, interleukin; NF, nuclear factor; TNF, tumor necrosis factor.

Competing interests

The authors declare that they have no competing interests.

Author details

¹Department of Critical Care Medicine, 642A Scaife Hall, 3550 Terrace Street, University of Pittsburgh, Pittsburgh, PA 15261, USA. ²The Clinical Research, Investigation, and Systems Modeling of Acute Illness (CRISMA) Center, 612 Scaife Hall, 3550 Terrace Street, University of Pittsburgh, Pittsburgh, PA 15261, USA.

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