Zaaqoq and Yende *Critical Care* 2013, **17**:306
http://ccforum.com/content/17/2/306

CRITICAL CARE

JOURNAL CLUB CRITIQUE

A touch of cooling may help

Akram M Zaaqoq[1] and Sachin Yende*[1,2]

University of Pittsburgh Department of Critical Care Medicine: Evidence-Based Medicine Journal Club, edited by Sachin Yende

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 (ΔSOFA) 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 ≥38.3°C [5,6]. Approximately 90% of patients with severe sepsis are febrile [7]. During sepsis, fever occurs in response to endogenous (IL-1β, TNFα, IFNγ, 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
[1]Department 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-κB, 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

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

Published: 6 March 2013

References

1. Niederman MS, Fein AM: **Sepsis syndrome, the adult respiratory distress syndrome, and nosocomial pneumonia. A common clinical sequence.** *Clin Chest Med* 1990, **11:**633-656. PMID: 2268994
2. Vincent JL, Sakr Y, Sprung CL, Ranieri VM, Reinhart K, Gerlach H, Moreno R, Carlet J, Le Gall JR, Payen D; Sepsis Occurrence in Acutely Ill Patients Investigators: **Sepsis in European intensive care units: results of the SOAP study.** *Crit Care Med* 2006, **34:**344-353. PMID: 16424713
3. Annane D, Aegerter P, Jars-Guincestre MC, Guidet B; CUB-Réa Network: **Current epidemiology of septic shock: the CUB-Rea Network.** *Am J Respir Crit Care Med* 2003, **168:**165-172. PMID: 12851245
4. Namas R, Zamora R, Namas R, An G, Doyle J, Dick TE, Jacono FJ, Androulakis IP, Nieman GF, Chang S, Billiar TR, Kellum JA, Angus DC, Vodovotz Y: **Sepsis: something old, something new, and a systems view.** *J Crit Care* 2012, **27:**314.e1-e11. PMID: 21798705
5. Dellinger RP, Levy MM, Carlet JM, Bion J, Parker MM, Jaeschke R, Reinhart K, Angus DC, Brun-Buisson C, Beale R, Calandra T, Dhainaut JF, Gerlach H, Harvey M, Marini JJ, Marshall J, Ranieri M, Ramsay G, Sevransky J, Thompson BT, Townsend S, Vender JS, Zimmerman JL, Vincent JL; International Surviving Sepsis Campaign Guidelines Committee; American Association of Critical-Care Nurses; American College of Chest Physicians; American College of Emergency Physicians; Canadian Critical Care Society; European Society of Clinical Microbiology and Infectious Diseases; *et al.*: **Surviving Sepsis Campaign: international guidelines for management of severe sepsis and septic shock: 2008.** *Crit Care Med* 2008, **36:**296-327. PMID: 18158437
6. O'Grady NP, Barie PS, Bartlett JG, Bleck T, Carroll K, Kalil AC, Linden P, Maki DG, Nierman D, Pasculle W, Masur H; American College of Critical Care Medicine; Infectious Diseases Society of America: **Guidelines for evaluation of new fever in critically ill adult patients: 2008 update from the American College of Critical Care Medicine and the Infectious Diseases Society of America.** *Crit Care Med* 2008, **36:**1330-1349. PMID: 18379262
7. Remick DG, Xioa H: **Hypothermia and sepsis.** *Front Biosci* 2006, **11:**1006-1013. PMID: 16146792
8. Soszynski D: **[The pathogenesis and the adaptive value of fever].** *Postepy*

Hig Med Dosw 2003, **57:**531-554. PMID: 14737969
9. Eyers S, Weatherall M, Shirtcliffe P, Perrin K, Beasley R: **The effect on mortality of antipyretics in the treatment of influenza infection: systematic review and meta-analysis.** *J R Soc Med* 2010, **103:**403-411. PMID: 20929891
10. Jiang Q, Cross AS, Singh IS, Chen TT, Viscardi RM, Hasday JD: **Febrile core temperature is essential for optimal host defense in bacterial peritonitis.** *Infect Immun* 2000, **68:**1265-1270. PMID: 10678936
11. Hasday JD, Garrison A: **Antipyretic therapy in patients with sepsis.** *Clin Infect Dis* 2000, **31(Suppl 5):**S234-S241. PMID: 11113029
12. Poblete B, Romand JA, Pichard C, Konig P, Suter PM: **Metabolic effects of i.v. propacetamol, metamizol or external cooling in critically ill febrile sedated patients.** *Br J Anaesth* 1997, **78:**123-127. PMID: 9068325
13. Launey Y, Nesseler N, Malledant Y, Seguin P: **Clinical review: Fever in septic ICU patients – friend or foe?** *Crit Care* 2011, **15:**222. PMID: 21672276
14. Arons MM, Wheeler AP, Bernard GR, Christman BW, Russell JA, Schein R, Summer WR, Steinberg KP, Fulkerson W, Wright P, Dupont WD, Swindell BB: **Effects of ibuprofen on the physiology and survival of hypothermic sepsis. Ibuprofen in Sepsis Study Group.** *Crit Care Med* 1999, **27:**699-707. PMID: 10321658

doi:10.1186/cc12515
Cite this article as: Zaaqoq AM, Yende S: **A touch of cooling may help.** *Critical Care* 2013, **17:**306.