

Critical Review Form

Meta-analysis

Meta-analysis of Hemodynamic Optimization in High-risk Patients, Crit Care Med 2002; 30: 1686-1692

Objective: To review pertinent randomized clinical studies that describe hemodynamic goals in acutely critically ill patients and to evaluate outcome of resuscitation therapy in association with physiological, clinical, and therapeutic influences (p. 1686).

Methods: MEDLINE search of English-language of randomized clinical trials of supranormal cardiac index (CI), pulmonary artery occlusion pressure (PAWP), and oxygen delivery/consumption goals. Patient populations were defined by three inclusion criteria: critically ill patients with high-risk elective surgery, severe trauma, and septic shock. Therapeutic goals were $CI > 4.5 \text{ L/min m}^2$, $PAWP < 18$, and $DO_2 > 600 \text{ mL/min m}^2$ or Oxygen consumption $> 170 \text{ mL/min m}^2$. Interventions were fluids first then inotropes if hemodynamic targets were not achieved. Experimental design differences between the 21 studies included therapeutic goals (normal versus supranormal), early versus late fluid administration, and differences in disease severity as determined by the control group mortality. "Late" was defined as > 12 hours after surgery, 24 hours after injury, or after occurrence of organ failure. Optimum criteria for randomization, blinding, and drop-out analysis were also considered by the authors in assessing study quality.

Guide	Question	Comments
I	<i>Are the results valid?</i>	
1.	Did the review explicitly address a sensible question?	Yes , three questions addressed: 1) In goal-directed therapy, are there outcome differences when normal physiological parameters are used for treatment goals compared with using supra-physiological target goals. 2) What roles are played by time factors, various associated clinical conditions, control group mortality, and differences in therapy between control and protocol groups? 3) Is there a single, optimal hemodynamic goal for all critically ill patients, or does this depend upon age, severity of illness, physiologic reserve, capacities, organ failures, and other co-morbid conditions?
2.	Was the search for relevant studies details and exhaustive?	The authors did not include EMBASE, CINCAHL, Cochrane, or Web of Science in their search strategy. Nor did they ascertain ongoing or previously unreported industry sponsored trials, contact content experts for vague references not identified by computerized search strategies, or a bibliography search of their referenced papers. One could therefore legitimately question whether they truly identified all the relevant literature.

3.	Were the primary studies of high methodological quality?	Although the inclusion criteria were stringent and logical for the question posed, the authors did not use a validated quality assessment tool (such as the Jadad scale) to grade the quality of the primary studies. The study characteristics evaluated were: randomization process, blinding, and dropout analysis (p. 1687).
4.	Were the assessments of the included studies reproducible?	Uncertain, because the authors did not use a validated tool. Also, uncertain whether search strategy could be reproduced because they provided no details about the literature search (Who conducted it? Was a kappa analysis performed among two searchers? If so, how were discrepancies resolved?)
II.	<i>What are the results?</i>	
1.	What are the overall results of the study?	<p>Two groups were assessed: mortality > 20% and mortality < 15% then each of these groups were split into two groups:</p> <p>1) Mortality > 20%</p> <p>a) goals to supranormal after organ failure: 6 studies, meta-analysis reveals no benefit (mortality difference $0\% \pm 0.07$, $p < 0.05$).</p> <p>b) goals to supranormal before organ failure: 7 studies meta-analysis show benefit in favor of protocol groups (mortality difference 0.23 ± 0.07, $p < 0.05$).</p> <p>2) Mortality < 15%</p> <p>a) goals to supranormal: 3 studies (no individual meta-analysis performed).</p> <p>b) goals to normal: 5 studies (no individual meta-analysis performed).</p> <p>Among this group of lower mortality subjects, all 8 studies were lumped into a meta-analysis with no difference in mortality noted (0.01 ± 0.03, $p > 0.05$).</p>
2.	How precise are the results?	See confidence intervals on Figure 1, p. 1690. Overall, the CI's are fairly wide, but among the subgroup with mortality > 20%, early intervention improved mortality in all seven trials with only two crossing unity. The pooled results of these studies had a relatively narrow CI (0.16-0.30).
3.	Were the results similar from study to study?	All 95% Confidence Intervals overlap, so no major outliers. Studies are found on both sides of unity arguing against a publication bias.

<i>III.</i>	<i>Will the results help me in caring for my patients?</i>	
1.	How can I best interpret the results to apply them to the care of my patients?	Contrary to discouraging results in earlier systematic reviews of goal directed therapy, hemodynamic optimization may play a crucial role in the management of some critically ill patients - those treated early, whether for post-operative stress, trauma or sepsis – before the onset of organ dysfunction.
2.	Were all patient important outcomes considered?	The most important outcome was considered: mortality. Other patient important outcomes should be considered in later trials and systematic reviews including quality of life and hospital length of stay.
3.	Are the benefits worth the costs and potential risks?	No cost-benefit analysis was performed.

Limitations

- 1) Limited search strategy without details about who conducted the search or a Kappa assessment for inclusion or discrepancy resolution procedures.
- 2) Multiple definitions undefined: critically ill, high-risk elective surgery, severe trauma, and septic shock.
- 3) Uncertain about generalizability of lumping together trials of such heterogeneous patients as post-operative, trauma, and sepsis for quantitative review. For our PICO purposes, only two trials included septic patients.
- 4) No validated randomized control trial quality assessment tool was used.

Bottom Line

Achieving supranormal values of oxygen delivery does not work in patients where organ failure has developed. Early goal-directed therapy, however, before the onset of organ failure, leads to a 23% reduction in mortality among those with a high baseline mortality (>20% in control groups). The ED must play a leading role in hemodynamic optimization of high-risk patients in first expeditiously identifying these patients and then initiating EGDT in a timely fashion before the onset of the systemic inflammatory response syndrome and the onset of organ failure.