CJEM Journal Club

Quantitative resuscitation in sepsis

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Clinical question
Does a quantitative resuscitation strategy improve mortality from severe sepsis?
Article chosen
Jones AE, Brown MD, Trzeciak S, et al. The effect of a quantitative resuscitation strategy on mortality in patients with sepsis: a meta-analysis. *Crit Care Med* 2008;36:2932–3.
Study objective
The authors sought to determine whether quantitative resuscitation (structured cardiovascular intervention with intravascular volume expansion and vasoactive agent support to achieve explicit predefined physiologic end points) improves mortality in severe sepsis and whether the timing of this resuscitation impacts mortality.

BACKGROUND

Severe sepsis and septic shock are significant sources of morbidity and mortality in the emergency department (ED), with in-hospital mortality rates from sepsis remaining virtually unchanged between 1970 and 2000.[1–3] In 2001, Rivers and colleagues[4] demonstrated a 16% absolute reduction in mortality in patients with severe sepsis treated with a protocol-driven resuscitation strategy aimed at hemodynamic optimization in the ED. Their strategy, termed "early goal-directed therapy" (EGDT), used an algorithmic approach to achieve specific resuscitation end points.

In 2008, the Surviving Sepsis Campaign, a conglomeration of physicians from multiple specialties endorsed by 11 societies, updated their guidelines to recommend that such a quantitative resuscitation strategy be implemented at the time of recognition of severe sepsis.[5] This particular recommendation has met with significant controversy because it is heavily weighted on one single-centre trial.[6–8]

Quantitative resuscitation, as seen in the study by Rivers and coauthors,[4] involves structured cardiovascular intervention with intravascular volume expansion and vasoactive agent support to achieve explicit predefined physiologic end points using measurements and samples from invasive central venous and arterial monitors. A significant barrier to the widespread implementation of EGDT has been the use of such invasive monitoring.[9,10]

Also known as "goal-oriented resuscitation," quantitative resuscitation is not new, as clinical trials using some form of it have been performed for 20 years.[11] Jones and colleagues sought to determine whether the mortality benefit seen in these trials was derived from quantitative resuscitation in general, rather than the choice of specific end points.

STUDY DESIGN AND POPULATION STUDIED

The study was a systematic review and meta-analysis. The investigators looked at all randomized controlled trials of adult patients with a presumed or confirmed diagnosis of sepsis receiving a structured cardiovascular intervention aimed at achieving predefined hemodynamic end points (Box 1).

Box 1. Inclusion criteria of the subject study

- Randomized controlled trials
- Patients aged > 17 yr
- Presumptive or confirmed diagnosis of sepsis
- Experimental study using
  - intervention consisting of a structured cardiovascular resuscitation protocol administered to achieve predefined hemodynamic end points
  - a control group that received standard of care therapy

OUTCOMES MEASURED

The primary outcome measured was mortality at the end of a predetermined time frame reported by the individual authors, calculated as an odds ratio (OR) with 95% confidence intervals (CIs). In-hospital mortality was used preferentially.

The authors also examined a priori planned subgroups of *early* quantitative resuscitation; that is, therapy implemented at the time of recognition of sepsis or within 24 hours. This is in contrast to late quantitative resuscitation, which refers to therapy initiated after 24 hours, or unknown or unreported timing.

A sensitivity analysis was conducted to determine whether including only high-quality randomized controlled trials would yield different results. Studies reporting adequate concealment of allocation (grade A) were considered "high quality," and studies reporting unclear or inadequate concealment of allocation were considered grades B and C, respectively.

Post hoc analysis was done to determine whether any individual study was exerting undue influence over the results.

RESULTS

An extensive literature search yielded 903 relevant articles. Two independent reviewers screened the titles for eligibility. Their blinded interobserver agreement was 98.7% ($\kappa = 0.70$). Twenty-nine titles met the inclusion criteria. Following review of each manuscript by 3 independent reviewers, 9 studies remained, providing a total sample size of 1001.

The summary OR of 0.64 (95% CI 0.43 to 0.96) demonstrated a potentially significant reduction in mortality; however, the 9 studies demonstrated statistical heterogeneity ($p = 0.07$, $I^2 = 45\%$) and clinical heterogeneity (specifically in the timing of their intervention).

Funnel plot and Egger regression analysis did not suggest the presence of publication bias (intercept = 0.61, 95% CI –2.4 to 3.6, $p = 0.65$)

In the a priori defined subgroups of early versus late intervention, patients randomly assigned to receive early quantitative resuscitation compared with standard resuscitation had a significantly lower mortality rate of 39% (OR 0.50, 95% CI 0.37 to 0.69) compared with the control group mortality rate of 57%. The 6 early quantitative resuscitation studies included in this subgroup showed minimal heterogeneity ($p = 0.40$, $I^2 = 2.4\%$). It did not appear that the lower quality studies (grades B and C) were biasing the effect size as the sensitivity analysis yielded consistent findings.

Patients randomly assigned to the late quantitative resuscitation strategy did not have a significantly different mortality rate compared with standard resuscitation (OR 1.16, 95% CI 0.60 to 2.22).

The authors concluded that quantitative resuscitation provided a survival benefit if instituted early, a benefit that was lost if instituted late.

COMMENTARY

The meta-analysis by Jones and colleagues fulfilled all the methodological criteria for a high-quality systematic review and meta-analysis as defined by the Quality of Reporting of Meta-analyses (QUORUM) conference.[12] Specifically, the researchers conducted a thorough search of the literature. Selection of studies was systematic and reproducible with substantial interobserver agreement among reviewers. A potential flaw of the analysis is that it cannot completely exclude publication bias, specifically the exclusion of small negative trials.

With regard to other methodological quality, allocation of concealment was appropriately graded and no problems with incomplete outcome data or selective reporting biases were identified. Blinding assessors and

Table 1. Summary of findings of included trials

Study	Baseline mortality, %	Mortality timing	Time to intervention	End point
Rivers et al.[4]	44	Hospital	1.3–1.5 h	$ScvO_2$
Lin et al.[13]	71.2	ICU	< 4 h	CVP, MAP, UO
Alia et al.[14]	66	ICU	< 24 h after ICU admission	DO_2I
Yu et al.[15]	52	ICU	≤ 24 h of diagnosis or insertion of PAC	DO_2I
Yu et al.[16]	27	30-day	≤ 24 h of diagnosis or insertion of PAC	DO_2I
Tuchschmidt et al.[17]	72	14-day	< 4 h	CI

CI = cardiac index; CVP = central venous pressure; DO_2I = oxygen delivery index (calculation using cardiac index, hemoglobin, mixed venous and arterial oxygen saturation); ICU = intensive care unit; MAP = mean arterial pressure; PAC = pulmonary artery catheter; $ScvO_2$ = central venous oxygen saturation; UO = urine output.

patients of outcomes was not performed in any of the studies; however, the chance that this would significantly influence their primary outcome, mortality, is minimal.

Based on the combined baseline mortalities of the studies in the early subgroup, the number needed to treat is 6. This value is questionable given that the baseline mortality rates of the included studies were somewhat variable, as demonstrated in Table 1.[13–17]

The implications of this study are in keeping with the Canadian Association of Emergency Physicians Sepsis Guidelines[18] recommendation for a quantitative resuscitation strategy. The implications are also consistent with the Surviving Sepsis Campaign 2008 Guidelines,[5] which specifically recommend early goal-directed therapy upon recognition of severe sepsis or septic shock, with the option to substitute mixed venous oxygen saturation in place of central venous oxygen saturation as the end point.

Rivers and coworkers' landmark study of early goal-directed therapy in the ED showed a significant difference in the mortality of patients with severe sepsis. The cost of this mortality benefit was a labour-intensive protocol involving arterial and central venous catheterization and continuous central venous oxygen saturation monitoring for at least 6 hours by ED staff. There may be significant barriers to such a protocol in many EDs that are overstretched and cannot prioritize the specialized tools, staff and training needed for EGDT.

Despite significant variability in the goals and end points targeted by the studies in this meta-analysis, the mortality benefit remained. This suggests that it is not the specific end point that makes the difference but rather the fact that intervention occurs early and that it is focused on achieving a specific quantifiable goal. The implication is that other more realistically achievable quantitative end points may be used to provide a similar mortality benefit.

In applying these results to the ED one must be cautious in interpreting the term "early," which in this meta-analysis was defined as within 24 hours. Further studies are required to determine whether a shorter time frame, such as the 6 hours used in Rivers and colleagues' study of EGDT, will offer additional mortality benefit.

Although it would not obviate the need for central access, preliminary results from the Lactate Assessment in the Treatment of Early Sepsis trial indicate that using central venous lactate may be equivalent to central venous oxygen saturation as an end point.[19] Even more promising is the Protocolized Care for Early Septic Shock trial in which researchers are investigating the use of standard blood pressure and pulse oximetry as end points of resuscitation.[20]

CONCLUSION

There is clear evidence supporting the value of quantitative resuscitation within 24 hours, including approaches other than EGDT, in the treatment of patients with severe sepsis and septic shock presenting to the ED. The exact goals and end points that must be achieved within the time frame of a patient's stay in the ED require further delineation.

Competing interests: None declared.

Keywords: sepsis, quantitative resuscitation, early goal-directed therapy

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