UAMS Journal Club Summary
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Early versus Late Initiation of Vasopressors in Septic Shock

Clinical Bottom Line

We found conflicting evidence related to early vs late initiation of vasopressors. The systematic review and meta-analysis provides low-moderate quality evidence of decreased mortality when vasopressors are initiated early in septic shock, but the data presented has a number of limitations most significant of which is that the trials included all had different definitions of "early" vs "late" initiation of vasopressor. The observational trial found a significant increase in mortality in early vasopressor use, however the data is inherently limited by its nature as an observational trial and based on the population characteristics of the participants included, results may not be generalizable. All in all, more randomized controlled trials are needed before a definitive decision can be said on whether vasopressor should be started early in septic shock. For now clinicians should decide on timing of vasopressors based on individual patient characteristics and severity of illness.

PICO

P – patients with septic shock as defined by Sepsis 3.0 criteria
I – early vs late initiation of vasopressors during sepsis resuscitation
C – not necessarily a control group as both groups had interventions but they were separated by early vs late
O – Mortality benefit (primary), length of ICU stay, volume of fluid received, time to goal MAP

Background

Extensive evidence supports the use of early fluid administration as part of the treatment for septic shock. When fluids alone are not sufficient, clinicians turn to vasopressors for further hemodynamic support. The optimal timing of vasopressor administration is uncertain. Hemodynamic goals may be achieved faster with early vasopressors, but this might increase the risk of worsening tissue perfusion and disruption of fluid administration. These studies aim to evaluate mortality benefit, as well as other secondary outcomes, in relation to the timing of vasopressor initiation during septic shock.

Study 1:

Li, Y, Li J, and Zhang, D. Timing of norepinephrine initiation in patients with septic shock: a systematic review and meta-analysis. Critical Care. 2020. 24:288.

PubMed Link: https://ccforum.biomedcentral.com/articles/10.1186/s13054-020-03204-x

Validity Rating: Low-Moderate quality evidence (not very many studies included), however individual studies included were rated as high quality based on the Newcastle-Ottawa Scale

The Basics:
This systematic review and meta-analysis included both cohort and randomized controlled trials that looked at early vs late vasopressor initiation in septic shock. The primary outcome was mortality benefit with several secondary outcomes also reviewed. A total of five studies were included.

Inclusion Criteria:
RCTs and cohort studies from inception to March 1, 2020. Patients had to be >18 years old with septic shock. Studies had to include a primary outcome of short term mortality and had to be comparing early vs late initiation of vasopressor with clinically relevant secondary outcomes

Exclusion Criteria:
Studies without clear comparisons of the above outcomes were excluded. Review articles and pediatric studies were also excluded.

Primary Outcomes:
Short term mortality (hospital mortality, 28-day and 30-day mortality)

Secondary Outcomes:
ICU length of stay
Time to achieve goal MAP (>65mmHg)
Volume of intravascular fluids received within 6 hours

Results:
Overall there was a significant increase in short-term mortality when vasopressors were started later as opposed to earlier. There was on significant difference in ICU length of stay. There was a significant decreased in time to achieve target MAP as well as volume of fluids within 6 hours in the early vasopressor group compared to the late vasopressor group.

Limitations/Bias:
Although the date seems to strongly support early initiation of vasopressors, there are several limitations to this study. First, there are only five studies included so the sample size for the data obtained is not very large. Additionally when comparing the individual studies used, there was a wide variation in what each study defined as “early” vs “late” initiation of vasopressors which makes it difficult to draw conclusions. Lastly, the individual studies included had very heterogeneous populations with different comorbidities. The overall conclusions should therefore be interpreted with caution.

<u>Study 2:</u>

Yeo, Hye Ju, et al. “Vasopressor Initiation within 1 Hour of Fluid Loading Is Associated with Increased Mortality in Septic Shock Patients.” *Critical Care Medicine*, Publish Ahead of Print, 2021, https://doi.org/10.1097/ccm.0000000000005363.

Pub Med link: https://pubmed.ncbi.nlm.nih.gov/34612848/

The Basics:

This was a prospective observational study that looked at mortality in sepsis in groups that received vasopressors within the first hour of fluids compared with those who received vasopressors after an hour. Propensity matching was used to match patients in each group.

Inclusion Criteria: Patients 19 and older with a diagnosis of sepsis by Sepsis-3 criteria.

Exclusion Criteria: Patients younger than 19; vasopressors before sepsis was diagnosed; fluids before sepsis was diagnosed; patients to which no fluid were given or no vasopressors given.

Primary Outcome: 28 -day mortality

Secondary Outcomes:
Organ dysfunction on day 3
Mechanical Ventilation
LOS (ICU and Hospital)
Medical Events (ARDS, Arrythmias, cardiac arrest)

Results:

Patients who received vasopressors within one hour of getting fluids had a higher 28-day mortality and organ dysfunction. Univariate Cox analysis early vasopressor use had a Hazard Ratio (HR 1.59 95% CI, 1.10-2.28). Relative risk of 28-day mortality was 1.4, indicating a greater risk of mortality in the early vasopressor use. In the early vasopressor use group, 28-day mortality had an absolute risk reduction (ARR) was 14.1 and number needed to harm (NNH) of seven (7). Confidence intervals were narrow. More evidence is needed to determine the optimal time for vasopressor initiation.

Limitations/Biases:

This study was a prospective trial which is a lower level of evidence than a randomized control trial. There are several areas of bias present in this study, the most significant of which is the selection bias in which sicker patients received earlier vasopressors. Although propensity matching was used this bias persisted. The early group had higher initial SOFA scores. The population in South Korea is also more homogenous and have lower rates of underlying conditions than the general US population therefore it is not directly applicable to our patient population.