The effect of vasopressor dosing strategy on microcirculatory perfusion in preclinical models of sepsis: a systematic review

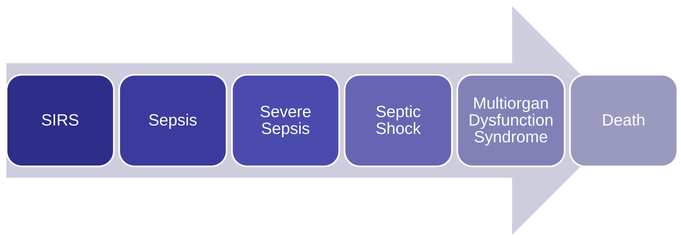
Tyler James[1], Homer Yang[2], Francois Lamontagne[3], Emilie Belley-Cote[4], Frederick D'Aragon[4], Duncan J. Stewart[5,6], Manoj M Lalu[2]

[1]University of Ottawa, Faculty of Medicine, [2]Department of Anesthesiology The Ottawa Hospital Research Institute, [3]Department of Médecine, Université de Sherbrooke, [4]Department of Clinical Epidemiology and Biostatistics, McMaster University, [5]Regenerative Medicine Program, The Ottawa Hospital Research Institute, [6]Department of Cell and Molecular Medicine

Introduction

Sepsis

- Sepsis is a systemic inflammatory response due to an infection[1]
- The inflammatory response can cause excessive vasodilation contributing to a decreased blood pressure[3]
- If blood pressure is decreased drastically it can dangerously lower organ perfusion resulting in septic shock and vital organ failure[4]
- The mortality rate of septic shock is 20-30% and it is the number one cause of death in critically ill patients[2,5]



The Role of Vasopressors in Septic Shock

- Vasopressors are drugs used clinically to counteract vasodilation and increase blood pressure[6]
- Along with antibiotic treatment and fluid resuscitation, vasopressors are nearly universally used to treat septic shock by increasing blood pressure[7]
- Surviving Sepsis Clinical Practice Guidelines suggest titrating vasopressor dose to achieve a mean arterial blood pressure ≥ 65 mm Hg, however this recommendation has weak supporting evidence[8]
- Interestingly, increasing blood pressure using vasopressors induces vasoconstriction, which may reduce microcirculatory blood flow to vital organs and cause harm
- By using invasive methods to measure microcirculatory flow, preclinical studies of sepsis offer a unique opportunity to investigate the effects of vasopressors on microcirculation
- To date, a comprehensive summary of vasopressor dosing strategies on microcirculatory flow in sepsis has not been completed

Objective

We propose a systematic review and meta-analysis to answer the following question:

In preclinical studies using animal models of sepsis, what is the effect of different vasopressor dosing strategies on microcirculatory flow?

Methods

Electronic Search: EMBASE Classic, EMBASE, Ovid Medline, In-Process & Other Non-Indexed Citations and Ovid Medline, BIOSIS, manual review of bibliographies of selected articles (inception to February 2015)

Study Design: Eligible studies include only controlled comparison (randomized, nonrandomized and quasi-randomized) animal experiments

Population: Preclinical *in vivo* models that mimic the pathophysiology of human patients with septic shock

Intervention: At least two different vasopressor dosing strategies

Primary Outcome: *Microcirculatory perfusion* measured by the following methods:

- Tonometry
- Indocyanine green clearance
- Laser Doppler flowmetry
- Spectrophotometry
- Orthogonal polarizing spectral imaging
- Sidestream darkstream imaging
- Radiolabelled microspheres

Secondary Outcome: Mortality (death or self-defined surrogates of death)

Tertiary Outcomes: Hemodynamic parameters, fluid balance, acid-base status, cardiac biomarkers, kidney function, liver enzymes

All outcomes will be grouped by time of measurement: ≤6 h, 6-12 h, >12-≤24 h, and > 24 h following initiation of vasopressor

Data Extraction: Using DistillerSR®, two independent reviewers (TJ, ML) will extract data into pre-piloted forms

Risk of Bias Assessment: Cochrane Risk of Bias Assessment Tool[9]

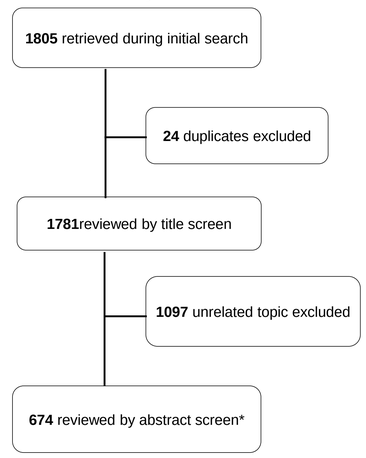
- Random sequence generation
- Baseline characteristics
- Allocation concealment
- Blinding of personnel and outcome assessment
- Incomplete outcome data
- Selective outcome reporting

Construct Validity: Potential "clinical relevance" will be evaluated by

- Presence of intercurrent illness
- Use of an infectious model of sepsis
- Initiation of therapy after establishment of disease
- Use of concurrent therapy

Results

Study Flow



*This is an ongoing study

Future Directions

- Abstract and Full Text screening will be completed
- Study Characteristic, Risk of Bias and Construct Validity data from the included studies will be extracted
- *A priori* defined outcome measures will be extracted

Acknowledgements

- We thank Risa Shorr (OHRI Librarian) for assistance in generating a systematic search strategy
- We thank the Department of Anesthesiology for funding access to DistillerSR®
- This work was supported by an Undergraduate Research Opportunity Program Award from the University of Ottawa

References

1. King, E.G., Bauza, G.J., Mella, J.R., Remick, D.G. (2013). Pathophysiologic mechanism in septic shock. *Laboratory Investigation*. 94:4-12
2. Mayr, F.B., Yende, S., Angus, D.C. (2014). Epidemiology of severe sepsis. *Virulence*. 5(1):4-11
3. Young, J.D. (2004) The heart and circulation in severe sepsis. *Br J Anaesth*. 93(1):114-20
4. De Backer, D., Orbegozo Cortes, D., Donadello, K., Vincent, J.L. (2014) Pathophysiology of microcirculatory dysfunction and the pathogenesis of septic shock. *Virulence*. 5(1):73-9
5. Peake, S.L., Delaney, A., Bailey, M., Bellomo, R., Cameron, P.a., Cooper, D.J., *et al.* (2014). Goal directed resuscitation for patients with early septic shock. *N Engl J Med.* 371(16):1496-506
6. Kanter, J., DeBlieux, P. (2014). Pressors and inotropes. *Emerg Med Clin North Am*. 32(4):823-34
7. Marik, P.E. (2014). Early management of severe sepsis: concepts and controversies. *Chest*. 145(6):1407-18
8. Dellinger, R.P., *et al.* (2008). Surviving sepsis campaign: international guidelines for management of severe sepsis and septic shock. *Crit Care Med*. 36(4):1394-1396
9. Higgins, J. et al (2011). The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. *Br Med J*, *343*:d5928.