**The use of vasoactive drugs in the management of septic shock: a systematic review and meta-analysis**

J Briggs¹, D Horner², M Nirmalan¹ ²

University of Manchester¹
Oxford Road
Manchester
M13 9PL

Central Manchester NHS Foundation Trust²
Oxford Road
Manchester
M13 9WL

Introduction:

Despite modern medical advances, septic shock continues to be a common and global clinical problem, with an estimated mortality of >25% in most critical care units.¹ There is clear consensus and clinical evidence that response time and early intervention remain critical determinants of mortality.² Yet there is limited agreement regarding the specifics of initial therapy. In particular, selection of vasoactive agent to manage persistent hypotension and tissue hypo-perfusion in septic shock remains eagerly debated.

The Surviving Sepsis Campaign (SSC) guidelines address this issue, but acknowledge their recommendation of noradrenaline/dopamine as first line agents to be based on weak evidence supported mostly by pre-clinical animal and phase 1 human studies. They also comment on the lack of evidence to suggest a worse clinical outcome with other drugs, such as adrenaline, highlighted in recent prospective trials.³ Other authors challenge the SCC guidance by specifically highlighting the multiple risks of conventional vasopressor use in isolation.⁴

To fuel the discussion further, a developing focus in the current literature is emerging in support of agents with potential vasodilatory properties, used in conjunction with standard vasopressors to initially manage septic shock.⁵ This concept aims to reduce the susceptible tissue ischaemia and cardiovascular dysfunction often seen with escalating doses of vasopressor agents. Fenoldopam and dobutamine are two such examples. Studies comparing levosimendan to noradrenaline in animal models of sepsis have also shown an interesting and significant increase in microvascular perfusion with levosimendan, despite cardiac output improvement in both groups.⁶ Further controlled trials in human subjects are eagerly awaited.

Objectives:

Current reviews of this subject matter are either outdated,⁷ or omit to collate results together in search of underlying trends.⁸ Therefore, we undertook a systematic review of the literature and meta-analysis regarding the use of vasoactive agents in the management of septic shock. Using short term mortality as a definitive end point, we set out to address two specific null hypotheses:

1. Noradrenaline is not superior to any other vasopressor agent when used as first line agent for treatment of septic shock.
2. Combining a vasopressor with a vasodilating agent is not superior to conventional solo vasopressor use, in the treatment of septic shock.

Methods:

We performed a systematic review of prospective randomised controlled trials using a three tiered search strategy, to include trial type, intervention and medical condition. In acknowledgement of the previously published Cochrane review on the topic in 2004, we limited our search dates to 2003- July 2010. We included all 19 papers identified and cited by the preceding Cochrane review by default.

From over 6000 hits originally, 25 articles were retained for inclusion using pre-specified criteria. Added to the 19 articles included in the Cochrane review predating 2004, this left 44 articles in total to be screened for inclusion in the meta-analysis. A Bibliographic review of all 44 articles provided no details of further relevant randomised controlled trials. The 44 articles were reviewed in full independently by two authors (JB & DH) and included in the final analysis if deemed appropriate by both. A third author (MN) resolved any dispute. 22 articles were eventually accepted for the meta-analysis.

Results:

Of the 22 studies included in the analysis, only 8 were considered of high methodological quality using predefined criteria.
A total of 13 studies with 3,031 patients addressed the first null hypothesis. A relative risk of 1.02 was generated for noradrenaline vs. other vasoconstrictor agents in relation to short term mortality, with 95% confidence intervals (CI) spanning 1 (0.95-1.10, p=0.53). A further analysis using only studies considered at 'low risk of bias' (n=2,777) generated similar data, with a relative risk of 1.02 (95% CI 0.92-1.13, p=0.32). These figures would strongly support acceptance of the null hypothesis, that no difference in mortality outcome is seen with the use of noradrenaline compared to other vasopressors in the treatment of septic shock.

The second null hypothesis was evaluated using a total of 8 studies involving a total of 825 patients. Using short term mortality as an endpoint, a relative risk of 0.92 was deduced for vasodilator+vasoconstrictor use, when compared to vasoconstrictor alone in septic shock (95% CI 0.76-1.11, p=0.40). Although the CI are wide here, a second meta-analysis of only papers deemed at 'low risk of bias' demonstrates a clinically relevant trend. This subgroup analysis reduces the analysis to 3 studies only involving 670 patients, concluding a relative risk of 0.85 for the VD+VC group (95% CI 0.70-1.02, p=0.08). These figures demonstrate a possible trend towards rejection of the null hypothesis and come with low heterogeneity (Chi^2 = 0.15, I^2 = 0%).

The above data can be extrapolated to give an absolute risk reduction of 6.6% in short term mortality, when using a vasodilator+vasoconstrictor approach to treat septic shock. Number Needed to Treat (NNT) is 15.2.

**Conclusion:**

The results of this systematic review and meta-analysis support acceptance of the first null hypothesis, that noradrenaline as a solo agent does not reduce mortality in septic shock when compared to any other vasopressor agent.

With regard to the secondary outcome, this meta-analysis would suggest that using a vasodilator combined with a vasoconstrictor agent to treat septic shock may have a beneficial effect in reducing short term patient mortality, compared to conventional solo vasopressor use. This current evidence combined with contemporary pathophysiological arguments that support a combined vasopressor/dilator approach call for a more robust RCT to investigate the hypothesis further. Based on the findings from our present meta-analysis, a power calculation would suggest it necessary to recruit a total of 1344 patients to a future study, in order to demonstrate a 6.6% reduction in mortality with 80% power and an alpha value of 5%.

**References:**