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Evidence about inotropes: when is enough, enough?

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Restoring and maintaining cardiac output is a cornerstone of resuscitation of critically ill patients. We know that patients who are able to increase their cardiac output have better outcomes [1], but previous research has demonstrated that administering high dose catecholamines to achieve supranormal oxygen delivery can be harmful [2]. Inotropes are now advised only if there is evidence of a low cardiac output and ongoing hypoperfusion [3].

Are there alternative inotropes to catecholamines?

Levosimendan is an interesting alternative as its main mode of action is to sensitise troponin C to calcium, thus increasing contraction but without impairing relaxation. Because intracellular calcium levels are not altered, the increased myocardial contractility is achieved without significantly increasing myocardial oxygen demand and thus, in theory, it would appear to have a beneficial pharmacodynamic profile [4]. Furthermore, levosimendan causes opening of cardiomyocyte mitochondrial potassium channels and with associated antioxidant effects it

may offer a degree of cardiac protection, particularly in an ischaemic myocardium.

What is the evidence to support levosimendan use in clinical practice?

In a recent edition of *Intensive Care Medicine*, Koster and colleagues [5] undertook a systematic review with meta-analysis and trial sequential analysis (TSA) of levosimendan in critically ill adult patients with low cardiac output syndromes. This detailed and thorough analysis included a total of 49 trials (6,688 patients) and, because of the heterogeneity of the patient populations, considered two main a priori defined subgroups, those patients having cardiac surgery and those who did not. In the trials of low cardiac output without cardiac surgery (mainly heart failure and a few sepsis trials) they report an association between levosimendan and reduced mortality when considering all control groups, relative risk (RR) 0.76, TSA-adjusted 95 % confidence intervals (CI) 0.59–0.97. However, when restricting their analysis to only trials with a lower risk of bias the RR was 0.86 (TSA-adjusted 95 % CI 0.48–1.55). In the cardiac surgery trials levosimendan had an RR of 0.52 (95 % CI 0.37–0.73) for all trials compared to all control groups, but there were not sufficient numbers of trials and patients to undertake a trial sequential analysis, especially as only three trials were considered to be at lower risk of bias.

How should these results be interpreted?

The main message from this meta-analysis is that more evidence from high quality randomised controlled trials is needed to provide definitive answers. The authors suggest

at least 1,100 more patients would need to be recruited to high quality trials to provide conclusive evidence to support a 20 % relative mortality reduction with levosimendan outside of cardiac surgery. A number of such ongoing trials are identified in the review and the results of these trials are therefore eagerly awaited.

Does levosimendan currently have a role in the critically ill patient?

Although the TSA-adjusted 95 % CI clearly crosses one in the low risk of bias trials, it should be noted that the test of interaction considering the risk of bias subgroups was not significant, so there was no clear evidence of a differential result based on the assessment of bias. Furthermore the funnel plots did not demonstrate any obvious publication bias and the Manhattan error matrix plots showed that there is more evidence to suggest benefit than evidence to suggest harm when using levosimendan. Therefore, although more evidence is needed, the current evidence base for levosimendan is probably better than that available for many other treatments routinely used within the ICU.

How does this compare to current inotropes and vasopressors?

Inotropes and vasopressors are some of the most commonly used drugs in the ICU, but it is only in recent years that we have had good evidence to help guide our choices. Dopamine remained part of international guidelines until its use was demonstrated to be associated with more adverse events, particularly arrhythmias, than norepinephrine [6]. Studies have suggested that there may be no difference in outcomes depending on whether we use norepinephrine or epinephrine [7, 8] and this has led some commentators to question if catecholamines are all “equally good or bad” [9].

As well as the example of high dose dobutamine to achieve supranormal oxygen delivery leading to increased mortality [2], other studies have demonstrated that higher

catecholamine vasopressor load is associated with more adverse effects and worse outcomes [10]. The notion of decatecholaminisation (the reduction of endogenous and exogenous adrenergic stimulation) has been proposed, and recently a randomised controlled trial reported that using esmolol in persistently tachycardic septic shock patients might improve haemodynamics, organ dysfunction and potentially survival [11]. While this relatively small single-centre trial needs repeating before it becomes part of clinical care, it reinforces the idea that avoiding excess catecholamine stimulation and particularly avoiding tachycardia may be useful. It is interesting that in the vasopressin and septic shock trial (VASST) there was a significant reduction of heart rate in the vasopressin-treated patients in the less severe shock group [12], the same group who also had a reduction in mortality in the overall trial. We await the results of ongoing trials to see if this effect can be repeated when vasopressin is administered early and in higher doses to maximise norepinephrine avoidance [13].

Therefore when managing shocked patients it would seem sensible to avoid catecholamines when possible. Ensuring adequate but not excessive fluid replacement [14] is the first step; accepting the lowest blood pressure that perfuses the vital organs is the next. A target mean arterial pressure of 65 mmHg is recommended as a reasonable starting point [3], only increasing in those individuals who may have a history of hypertension or atherosclerosis, but also perhaps accepting lower targets in the young previously fit patient. If then vasopressors or inotropes are needed we should use the lowest doses of catecholamines possible and maybe consider alternatives, such as vasopressin or levosimendan, accepting that we still await further evidence from ongoing trials [13, 15].

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