CRITICAL CARE

LETTER

Can a meta-analysis that mixes apples with oranges be used to demonstrate that levosimendan reduces mortality after coronary revascularization?

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See related research by Maharaj and Metaxa, http://ccforum.com/content/15/3/R140

We read with a great deal of interest the recently published meta-analysis of Maharaj and Metaxa [1] describing the effects of levosimendan on mortality after coronary revascularization. The authors concluded that levosimendan is able to reduce mortality in patients undergoing myocardial revascularization. Their conclusion, however, is unreliable and misleading for several reasons.

The basic reason is that their meta-analysis did not include comparable studies, thus violating the basic principle of meta-analysis. We believe that the inclusion in meta-analyses of studies so radically different is a methodological bias: characteristics of patients, doses used and timing of drug administration were discordant enough to make a true meta-analysis impossible. What is missing is a critical analysis of individual studies: the authors have only tried to give a pooled estimate of effectiveness of levosimendan administration.

As Green [2] points out about meta-analyses: 'Meta-analysis should only be performed when the studies are similar with respect to population, outcome and intervention.' The article of Moharaj and Metaxa does not follow these simple principles. We believe it is not correct to include in the same analysis studies where levosimendan is used for the treatment of postoperative cardiogenic shock and studies where it is used as ischemic preconditioning before cardiopulmonary bypass [3,4]. For example, the study of Tritapepe and colleagues [5] included in this meta-analysis describes the effects of a single low dose (24 mcg/kg) of levosimendan infused before cardiopulmonary bypass in patients undergoing surgical myocardial revascularization only for the assessment of the possible preconditioning effect of the drug.

Although we believe that levosimendan is an effective drug for the treatment of cardiogenic shock, we also believe this meta-analysis does not provide enough evidence that levosimendan can decrease mortality after myocardial revascularization.

Authors' response

Ritesh Maharaj and Victoria Metaxa

We would like to thank Dr Meco and colleagues for their interest in our recently published meta-analysis [1]. The main goal of meta-analyses is to obtain a summary estimate across data sets and is substantially different to the aims of an individual trial [6,7]. Accounting for trial level differences remains a significant analytical challenge when pooling results, and we report how these differences may influence conclusions [8]. In our report we offer a qualitative assessment of the combinability or clinical heterogeneity by way of the study descriptors [1]. A small amount of between-trial heterogeneity can be accounted for by using the random effects model as opposed to the fixed effects model. In our report the effect of levosimendan versus control using the random effects model remained consistent (odds ratio 0.43 (95% confidence interval 0.21 to 0.89)).

Subgroup meta-analysis attempts to examine the effects of potential confounding, though we appreciate that such analyses should be interpreted with some

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consideration. We have conducted subgroup analyses comparing levosimendan in the elective versus emergent setting, as well as comparisons between levosimendan with other vasoactive agents and placebo. The findings of these analyses are explained in the manuscript and are aimed at improving the clinical relevance of the conclusions drawn. These methods aim to address the obvious heterogeneity that does exist and show a consistent clinical and biological signal in favor of levosimendan compared with control. A meta-analysis published ahead of print evaluating the role of levosimendan in mortality reduction and hospitalization included 45 studies that ranged from cardiology to sepsis and vascular and cardiac surgery settings [9]. Subgroup analysis of patients receiving a bolus, no bolus and dose >0.1 mcg/kg/minute all showed statistical significance in favor of levosimendan.

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