Take it or levo it: an updated look at the use of levosimendan to prevent low cardiac output syndrome in pediatric patients

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Low cardiac output syndrome (LCOS) following congenital heart surgery occurs in up to 25% of pediatric patients and is associated with significant morbidity and mortality.\(^1\) Determination of an optimal therapeutic regimen to prevent this complication is an area of great interest.

Levosimendan, a novel inodilator, has been increasingly utilized and studied over the past decade. In this issue of Journal of Cardiothoracic and Vascular Anesthesia, Silvetti and colleagues present an updated systematic review and meta-analysis on the use of levosimendan in all pediatric clinical settings.\(^2\) This update is reflective of increased interest in levosimendan to prevent LCOS following congenital cardiac surgery in pediatric patients.

Levosimendan exerts its effect by binding to troponin C in the myofibril to increase its sensitivity to calcium during systole, thereby enhancing cardiac contraction and relaxation.\(^3,4\) In
this manner, levosimendan increases the efficiency of the myocyte without increasing myocardial oxygen consumption, conferring a potential advantage to its use in patients at risk for LCOS.\textsuperscript{5} Levosimendan also acts on vascular smooth muscle resulting in dilatation of systemic pulmonary and coronary blood vessels. Additionally, the active metabolites of levosimendan are more potent than the drug itself and remain active in the plasma up to 7 days following drug discontinuation.\textsuperscript{6} Levosimendan’s unique mechanism of action, along with its prolonged duration of action confer a potential physiologic advantage to its use over other traditional inodilators, such as milrinone, or inotropic agents such as epinephrine, norepinephrine or dobutamine.

Early studies in the pediatric population, while small, supported the safe use of levosimendan with potential for improved myocardial function.\textsuperscript{7, 8, 9, 10} Larger reviews, including a Cochrane review carried out in 2017 have been less encouraging than these individual small studies.\textsuperscript{11} A meta-analysis published in 2020 of 6 RCTs and 1 case control trial for a total of 436 patients found that all-cause mortality was no different in the levosimendan group compared to the control group.\textsuperscript{12} While the authors of this review did find a statistically significant reduction in the incidence of LCOS, only 3 of the 44 studies included LCOS as an outcome. Further, the largest of these studies (187 patients) did not demonstrate a difference in the incidence of LCOS, further complicating the question of levosimendan’s utility.\textsuperscript{13}
In this manuscript, the authors provide a systematic review of 44 studies published between 2004 and 2020 evaluating the use of levosimendan for cardiac dysfunction in pediatric patients (<18 years old) in all settings. The majority of these studies were conducted in Europe (30, 68.2%), and evaluated patients following cardiac surgery (31, 69.8%). Nine of these studies were randomized controlled trials (RCTs). The authors performed a meta-analysis of these nine trials comparing use of levosimendan versus control arms. Primary outcomes were Scv02 and lactate values which served as surrogate markers for LCOS. Secondary outcomes were postoperative BNP and troponin levels, all-cause mortality, ICU and hospital stay. While all nine RCTs were performed following cardiac surgery, there were significant differences between the trials. Perhaps most notably, the control arms differed among the studies with placebo utilized in two trials, milrinone in five, dobutamine in one and unspecified “standard treatment” in the final trial. The dosing regimen for levosimendan was also inconsistent across the RCTs with four studies utilizing a bolus dose followed by an infusion across a wide range of doses. One study initiated the use of levosimendan in the preoperative period. Furthermore, the assessed outcomes varied between trials with only two trials measuring Svc02 and five measuring lactate. Five of the nine studies were determined to have high risk of bias, predominantly due to lack of blinding.

The authors found a statistically significant improvement in Scv02 between groups (mean difference 4.88, p value 0.03) and a trend towards lower postoperative lactate (standard mean difference -0.37, p value 0.08.) No difference was found in the secondary outcomes, including length of ICU or hospital stay and mortality.
As noted in the manuscript, this is an update to a previously published systematic review and meta-analysis published by these authors which included studies published between 2004 and 2014.\textsuperscript{14} Compared to their original paper, this review includes twice as many studies (44 from 24) and nearly double the number of patients (1131 from 623). The initial review was limited by the heterogeneity of comparators, primary and second outcome measures and dosing regimen of study medication. This variability remained present in the updated review. The previous review found no difference in the primary outcomes of ICU stay, hospital stay, and mortality. The updated review is more granular in nature, inclusive of Scv02 and lactate levels as primary outcomes. Length of ICU and hospital stay and mortality were secondary outcomes, again found to be no different between groups. This raises the question of what is statistically significant versus what is clinically significant, a question which plagues many scientific studies. When evaluating effects of inotropes on LCOS following cardiac surgery we have a problem of what to measure. Lactate and Scv02 are surrogate markers for LCOS, as are longitudinal strain on echocardiography and troponin levels. Cardiac index may be the most direct measure of LCOS and yet its use is not consistent across studies. Numerous therapies and medicines are involved in the management of a pediatric cardiac patient in the postoperative period, so isolating the effect of one medicine by combining the statistical power of heterogeneously designed studies is problematic.

The authors provide little discussion of potential side effects associated with levosimendan. At higher doses, levosimendan causes arterial vasodilatation and lower mean arterial pressure,
potentially resulting in need for vasopressors to support blood pressure. This side effect may be particularly relevant because of its active metabolite and long duration of effect.

As with any review or metanalysis, the authors are limited by the available studies. While this meta-analysis had twice as many studies and patients as the authors’ prior review, individual studies remain small and heterogenous in methods and outcome measures. Additionally, the control groups differ between studies with some comparing levosimendan to placebo, others comparing levosimendan to dobutamine or milrinone. With small changes in effect, this fragmented assessment of levosimendan's efficacy makes it difficult for a clinician to reach for this medication over standard therapy.

Summary: Levosimendan’s mechanism of action and safety profile provide optimism for potential future use in the perioperative setting of pediatric cardiac surgery. The statistically significant effects demonstrated in this review are limited to surrogates of LCOS and depend on too few studies with heterogenous methodology. We agree with the author’s conclusion that additional research with a larger controlled and multicenter study is needed, as the utility of levosimendan in pediatrics is not yet demonstrated.

**Author Contributions:**
Genevieve E. Staudt: This author wrote both the initial and final version of the manuscript.
Bevan P. Londergan: This author provided significant edits to the manuscript
Susan S. Eagle: This author provided significant edits to the manuscript.

**Declaration of Competing Interest**
The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.
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