PERIOPERATIVE USE OF LEVOSIMENDAN IN PATIENTS WITH SEVERE LEFT VENTRICULAR DYSFUNCTION UNDERGOING CARDIAC SURGERY: A SYSTEMATIC REVIEW AND META-ANALYSIS

Ahmed Maher Mansour 1, Osama Abbas Abd Elhamed 2, Ahmed Ahmed Fouad 2, and Ramy Mohamed Reda 2

ABSTRACT:

Background: Levosimendan is a calcium-sensitizing ionodilator. However, the current level of clinical evidence is insufficient to determine the clinical value of levosimendan in patients with severe left ventricular dysfunction subjected to cardiac surgery. The aim of this meta-analysis is to provide an update of the current clinical evidence regarding the clinical value of perioperative levosimendan use in adult patients with severe cardiac dysfunction subjected to cardiac surgery.

Methods: This meta-analysis was performed according to PRISMA statement. Databases searched included PubMed, Web of Science, Scopus and Cochrane databases for systematic reviews. Search keywords were extracted from initially retrieved articles and comprised “levosimendan” and “cardiac surgery” using the Boolean search operator AND. The reported outcomes included early mortality, development of atrial fibrillation, acute kidney injury and/or renal replacement therapy, postoperative myocardial infarction, hypotension and low cardiac output syndrome.

Aim of the work: The aim of this meta-analysis is to provide an update of the current clinical evidence regarding the clinical value of perioperative levosimendan use in adult patients with severe cardiac dysfunction subjected to cardiac surgery.

Results: The present meta-analysis showed significant association between levosimendan use and significant reduction of perioperative low cardiac output syndrome [OR (95% CI): 0.60 (0.44-0.82), p=0.001], renal injury and/or renal replacement therapy [OR (95% CI): 0.51 (0.30-0.86), p=0.01]. Also, levosimendan use was associated with a marginal trend towards lower mortality [OR (95% CI): 0.64 (0.39-1.03), p=0.07].

Conclusions: Levosimendan use is associated with reduction of perioperative low cardiac output syndrome and renal injury and/or renal replacement therapy.

Keywords: Levosimendan, Cardiac surgery, low cardiac output syndrome.

INTRODUCTION:

Levosimendan is a calcium-sensitizing ionodilator. It enhances myocardial contractility through increasing cardiac myofilament responsiveness to calcium. This occurs via binding of levosimendan to cardiac troponin-C and minimizing its calcium-binding co-efficient. It’s notable that the
levosimendan-enhanced myocardial contractility occurs without corresponding increase in oxygen demand. Moreover, levosimendan has vasodilatory effects through control of adenosine triphosphate (ATP)-dependent potassium channels on vascular smooth muscle cells. In addition to these effects, levosimendan expressed anti-apoptotic, antioxidative and anti-inflammatory actions.

These pharmacological effects made levosimendan a successful therapeutic option for a wide range of cardiac conditions including advanced heart failure, decompensated chronic heart failure, septic shock, cardiogenic shock and cardiac and non-cardiac surgery. The drug was approved for clinical use for the first time in Sweden in the year 2000.

In patients undergoing cardiac surgery in particular, levosimendan proved to have a positive impact on patients' mortality. In addition, the drug could effectively reduce postoperative cardiac injury, acute kidney injury and intensive care unit duration of stay in those patients.

However, the current level of clinical evidence is insufficient to determine the clinical value of levosimendan in patients subjected to cardiac surgery and some authors restricted the beneficial survival effects of levosimendan to patients with significant preoperative ventricular systolic dysfunction.

AIM OF THE WORK:
The aim of this meta-analysis to provide an update of the current clinical evidence regarding the clinical value of perioperative levosimendan use in adult patients with severe cardiac dysfunction subjected to cardiac surgery.

MATERIAL AND METHODS:
Search methodology:
This meta-analysis was performed according to PRISMA statement. Databases searched included Pubmed, Web of Science, Scopus and Cochrane databases for systematic reviews. Search keywords were extracted from initially retrieved articles and comprised “levosimendan” and “cardiac surgery” using the Boolean search operator AND.

Inclusion criteria
All randomized clinical English articles on adults subjected to cardiac surgery and used levosimendan perioperatively were included.

Exclusion criteria
Articles with unclear or inappropriate randomization technique or those with insufficient reporting of outcome parameters were excluded.

Study outcomes
The reported outcomes included early mortality, development of atrial fibrillation, acute kidney injury and/or renal replacement therapy, postoperative myocardial infarction, hypotension and low cardiac output syndrome.

Data processing
In the present work, Cochran Q chi square test and I-square (I²) index were used to assess heterogeneity of the estimates among the included studies. Categorical and continuous outcomes were presented as log odds ratio with 95% confidence limits (95% CI) and raw mean difference (RMD) with 95% CI respectively. p value less than 0.05 was considered statistically significant.

RESULTS:
The PRISMA graph shows steps and results of electronic searches relevant to the current meta-analysis (Fig.1). Risk of bias of the included studies is shown in Fig.2

1. Peri-operative mortality
Eight studies were included in perioperative mortality analysis including
1371 patients (levosimendan: 684 and control: 687 patients). Among the included patients, there were 28 (4.1 %) and 46 (6.7 %) mortalities in the in the levosimendan and control arms respectively. The included studies expressed no significant heterogeneity (I^2=0.0 %; p=0.8). There was a marginal trend towards lower mortality in the levosimendan arm which lacked statistical significance [OR (95% CI) = 0.64 (0.39-1.03), p = 0.07] (Fig.3).

2. Postoperative myocardial infarction

Three studies were included in postoperative myocardial infarction analysis including 919 patients (levosimendan: 462 and control: 457 patients). Among the included patients, there were 3 (0.6 %) and 6 (1.3 %) myocardial infarction events in the in the levosimendan and control arms respectively. The included studies expressed no significant heterogeneity (I^2=11.0 %; p=0.33). No statistically significant differences between the studied arms regarding postoperative myocardial infarction [OR (95% CI): 0.59 (0.11-3.12), p=0.54] (Fig.4).

3. Hypotension

Three studies were included in this analysis including 939 patients (levosimendan: 473 and control: 466 patients). Hypotension was reported in 167 (35.3 %) and 143 (30.7 %) patients in the in the levosimendan and control arms respectively. Across studies Heterogeneity was insignificant (I^2=25.0 %, p=0.26). No statistically significant differences between the studied arms regarding postoperative hypotension [OR (95% CI) = 1.47 (0.77-2.78); p=0.24] (Fig.5).

4. Low cardiac output syndrome

Four studies were included in this analysis including 999 patients. They entailed 503 and 496 patients with 85 (16.9 %) and 127 (25.6 %) events in the in the levosimendan and control groups respectively. Across studies Heterogeneity was insignificant (I^2=0.0 %, p=0.40). Patients in the levosimendan arm experienced significantly lower frequency of low cardiac output syndrome [OR (95% CI): 0.60 (0.44-0.82), p=0.001] (Fig.6).

5. Atrial fibrillation

Six studies were included in this analysis including 1059 patients. They entailed 532 and 527 patients with 183 (34.4 %) and 179 (34.0 %) events in the in the levosimendan and control groups respectively. Across studies Heterogeneity was moderate (I^2=66.0 %, p=0.01). No statistically significant differences between the studied arms regarding postoperative atrial fibrillation [OR (95% CI): 0.55 (0.24-1.28), p=0.17] (Fig.7).

6. Renal injury and/or renal replacement therapy

Seven studies were included in this analysis including 1341 patients. They entailed 669 and 672 patients with 25 (3.7 %) and 46 (6.8 %) events in the in the levosimendan and control groups respectively. Across studies Heterogeneity was insignificant (I^2=0.0 %, p=0.96). Patients in the levosimendan arm experienced significantly lower frequency of renal injury and/or renal replacement therapy [OR (95% CI): 0.51 (0.30-0.86), p=0.01] (Fig.8).
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Fig. 1 PRISMA graph.

Fig. 2 Risk of bias of the included studies.
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3 Forest plot for perioperative mortality.

Fig.4 Forest plot for postoperative myocardial infarction.

Fig.5 Forest plot for hypotension.

Fig.6 Forest plot for low cardiac output syndrome.
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<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Levosimendan</th>
<th>Control</th>
<th>Odds Ratio M-H, Random, 95% CI</th>
<th>Odds Ratio M-H, Random, 95% CI</th>
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<td>Al-Shawaf 2006</td>
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<tr>
<td>De Hert 2007</td>
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<tr>
<td>Desai 2018</td>
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<tr>
<td>Mahla 2017</td>
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<td>1.25 (0.94, 1.65)</td>
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<tr>
<td>Shah 2014</td>
<td>2</td>
<td>25</td>
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<tr>
<td>Sharma 2014</td>
<td>4</td>
<td>20</td>
<td>0.75 (0.17, 3.33)</td>
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<tr>
<td>Total (95% CI)</td>
<td>532</td>
<td>527</td>
<td>100.0%</td>
<td>0.55 (0.24, 1.26)</td>
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<tr>
<td>Total events</td>
<td>193</td>
<td>179</td>
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</tr>
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</table>

Heterogeneity: Tau^2 = 0.65; Chi^2 = 14.82, df = 5 (P = 0.01); I^2 = 66%

DISCUSSION:

The present meta-analysis of RCTs assessed the clinical value of perioperative levosimendan use in adult patients with severe cardiac dysfunction subjected to cardiac surgery. Results showed levosimendan use was associated with lower risk of low cardiac output syndrome and renal injury and/or renal replacement therapy. Levosimendan use was also associated with marker lower risk of perioperative mortality. However, this effect marginally fell short of statistical significance. No significant differences were noted between levosimendan use and control regarding postoperative myocardial infarction, hypotension or atrial fibrillation.

As previously stressed, studies included in this meta-analysis were conducted only on patients with severe left ventricular dysfunction (LVEF ≤ 35.0 %). In fact, only 2 published meta-analyses included studies with similar degree of ventricular dysfunction. Sanfilippo et al., 12 work on 5 studies including 1224 patients, the authors concluded that levosimendan administration was associated with significant reduction in mortality rate. They also noted that levosimendan use was associated with lower rate of renal replacement therapy and low cardiac output syndrome. In another work, Weber et al., 13 meta-analysis found that levosimendan was associated with lower mortality and lower rates of LCOS and acute kidney injury. Thus, our work represents an update of previous works discussing this issue.

The positive effects of levosimendan are attributed to multiple mechanisms. Levosimendan has been shown to attenuate myocardial apoptosis following myocardial infarction in animal models 14. In addition, levosimendan can increase peak oxygen uptake, decreases lung edema, increases ventilation efficiency owing to a decrease of reflex hyperventilation, and increases cardiac
output and muscular oxygen delivery and extraction \(^{15}\). Moreover, levosimendan and its long-lived active metabolite OR-1896 mobilize a set of vasodilatory mechanisms, that is, the opening of the ATP-sensitive K+ channels and other K+ channels on top of a highly selective inhibition of the phosphodiesterase III enzyme \(^{16}\).

Also, levosimendan proved to have significant reno-protective effects through improvement of oxidative stress, imbalance in the redox status, necrosis, and pathological injuries in kidney \(^{17}\). Another reno-protective mechanism entails improving mitochondrial dysfunction and suppressing the mitochondrial apoptosis pathway \(^{18}\).

In conclusion, the present meta-analysis found that levosimendan administration is related to better in-hospital survival and lower rates of low cardiac output syndrome and renal injury and/or renal replacement therapy in patients with severe left ventricular dysfunction submitted to cardiac surgery. However, well-designed randomized controlled studies conducted on this particular group of patients are scare. For buildup of rigorous clinical evidence, it recommended to perform more studies with more prolonged follow up and larger sample size.

**Ethical approval**

NA

**Data Availability Statement:**

Data of this research will be available upon reasonable request.

**Conflict of interest:**

Authors state no conflict of interest.

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The research is self-funded from the authors

**Author contributions**

All authors equally shared in formulating the idea, conception, and data collection statistics, writing and drafting the manuscript.

**Acknowledgments**

None.

**REFERENCES:**


دراسة منهجية لاستخدام عقار الليفوسميندان مع المرضى الذين يعانون من ضعف شديد في البطين الأيسر ويخضعون لجراحة القلب

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مقدمه: المرضى الذين يعانون لجراحة القلب المفتوح مع المجاجزة القلبية الرئوية (CPB) يعانون من ترودية القلب المحيط بالجراحة العالية، وفي ضخمه. هذا يؤدي إلى درجات مختلفة من خلل البطين في عضلة القلب بسبب تكوين الجذور الحرة، ومضاعفات الأوعية الدموية الحادة والكالسيوم الزائد إذا كانت الحاله شديدة، فهفي الالكالية يمكن أن تسبب متلازمة النتال القلبي المنخفض بعد الجراحة (LCOS)، وهي مضاعفات تهدد الحياة مع انتشار حوالي 10 % ومقابل وفيات بنسبة 17 %.

الهدف من الدراسة: الهدف من هذا التحليل المنهجي هو تقديم تحليل للأندية السريرية الحالية فيما يتعلق بالقيمة السريرية لاستخدام الليفوسميندان مع المرضى البالغين الذين يعانون من ضعف شديد في البطين الأيسر ويخضعون لجراحة القلب.

استراتيجية البحث لتحديد الدراسات: سيتم إجراء هذا التحليل المنهجي وفقا لبيانات SCOPUS والبحث المتضمن قواعد PRISMA و PUBMED و WEB OF SCIENCE و SCOPUS و COHRANCE للمراجعات المنقية. وتضمنت "ليفوسميندان" و "جراحة القلب" ك.castihات بحثية على البيانات المرتبطة بين الكلمتين "ليفوسميندان" و "جراحة القلب".

النتائج: أظهرت النتائج أن استخدام الليفوسميندان كان مرتبطة بانخفاض خطر الإصابة بمتلازمة الانتان القلبي المنخفض، إضافة إلى ارتفاع منخفض البطين الكلبي في الدورة الدموية، أرتبط استخدام levosimendan في المرضى الذين يعانون من ضعف شديد في البطين الأيسر بانخفاض خطر الموت. تم استخدام Levosimendan في دراسات متعددة على المرضى الذين يعانون من ضعف شديد في البطين الأيسر، ولاحظ تحسن في الحالة السريرية بعد استخدام الليفوسميندان.

الخلاصة والتوصية: ينصح بالتحكم النقائي على تحسين الحياة من خلال استخدام الليفوسميندان كعلاج للانتان القلبي المنخفض، وإضافة إلى أن تختلف من 치اقة الممرضين في استخدام الليفوسميندان. lemosimendan