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

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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 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 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 cardia 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[1]. Moreover, levosimendan has vasodilatory effects through control of adenosine triphosphate (ATP)-dependent potassium channels on vascular smooth muscle cells [2]. In addition to these effects, levosimendan expressed anti-apoptotic, anti-oxidative and anti-inflammatory actions [3].

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 [4]. The drug was approved for clinical use for the first time in Sweden in the year 2000 [2].

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 [5].

However, the current level of clinical evidence is insufficient to determine the clinical value of levosimendan in patients subjected to cardiac surgery [6-10] and some authors restricted the beneficial survival effects of levosimendan to patients with significant preoperative ventricular systolic dysfunction[11,12].

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 (I^2) 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 heterogenicity (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 heterogenicity (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 Heterogenicity 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 Heterogenicity 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 Heterogenicity 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 Heterogenicity 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).

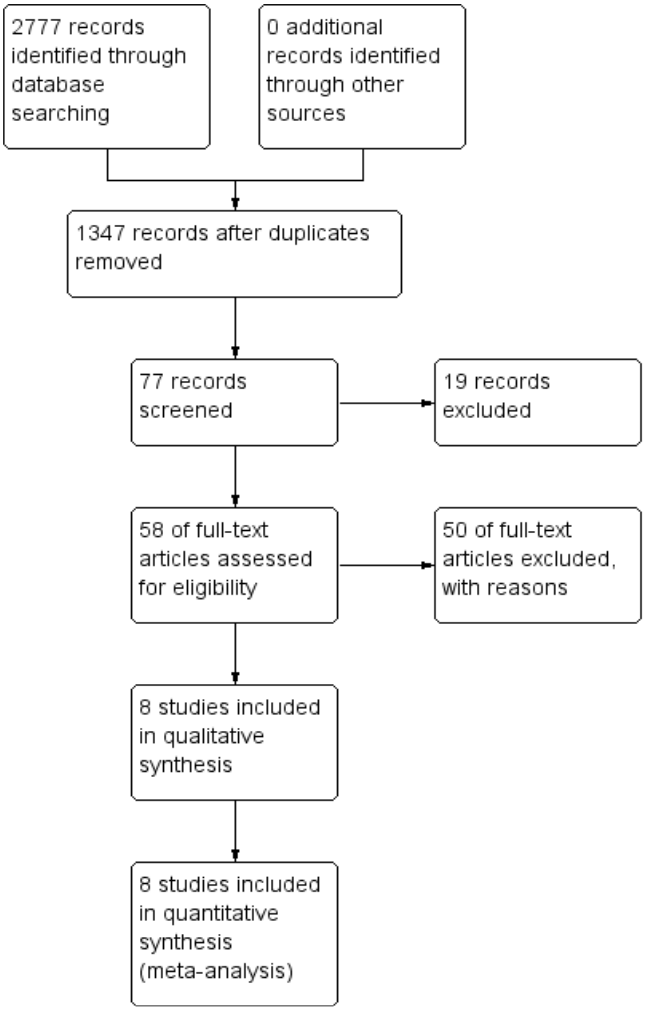


Fig.1 PRISMA graph.

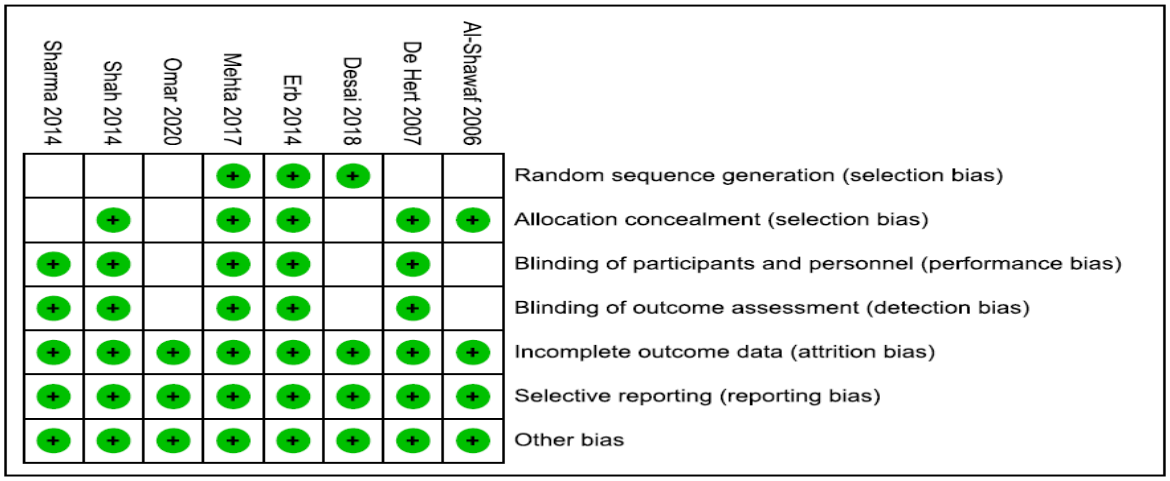
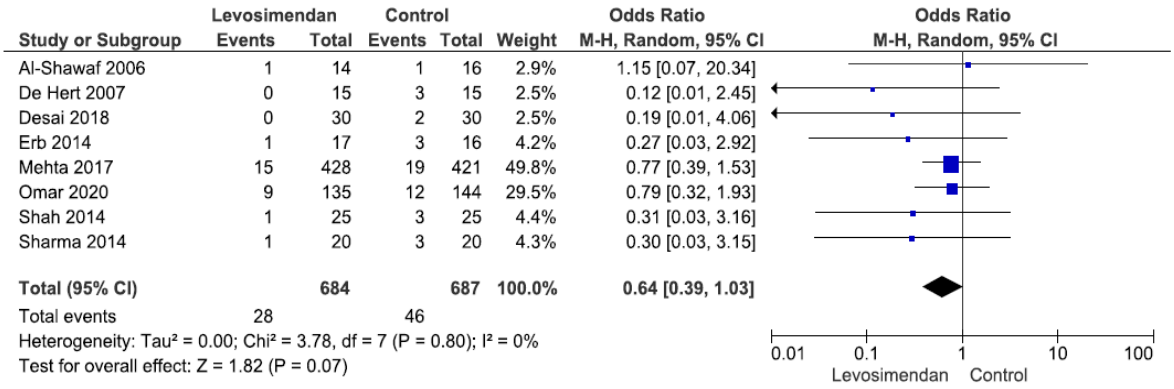


Fig.2 Risk of bias of the included studies.



3 Forest plot for perioperative mortality.

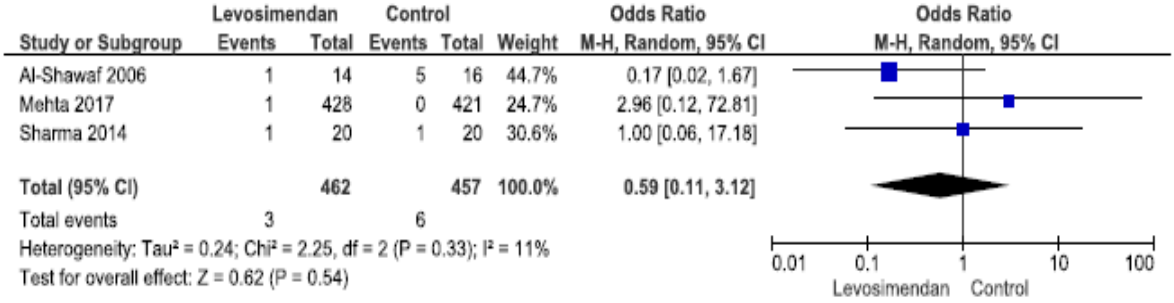


Fig.4 Forest plot for postoperative myocardial infarction.

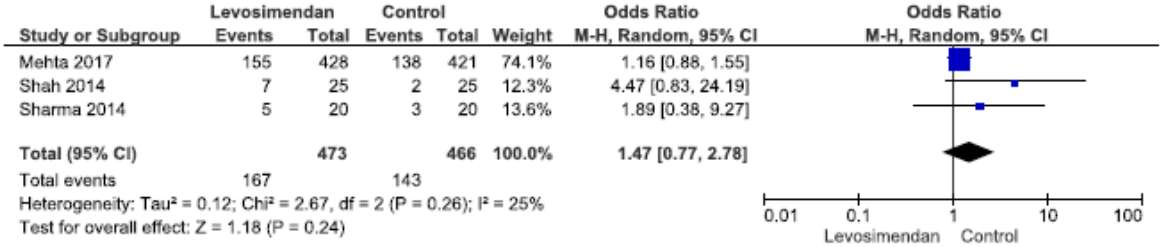


Fig.5 Forest plot for hypotension.

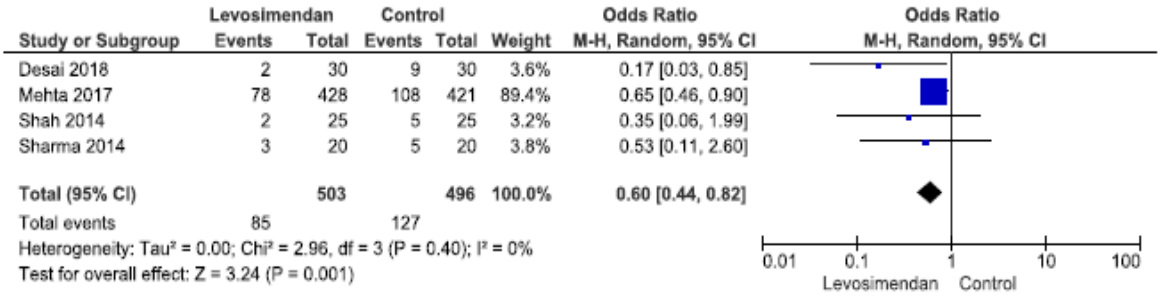


Fig.6 Forest plot for low cardiac output syndrome.

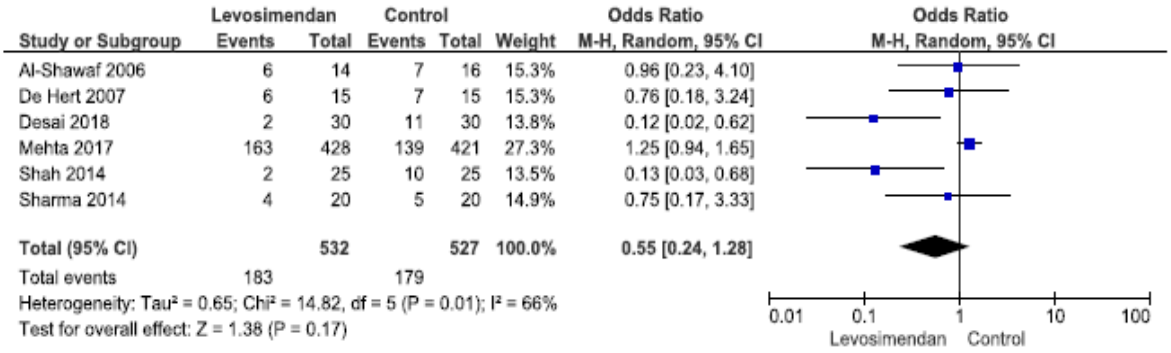


Fig.7 Forest plot for atrial fibrillation.

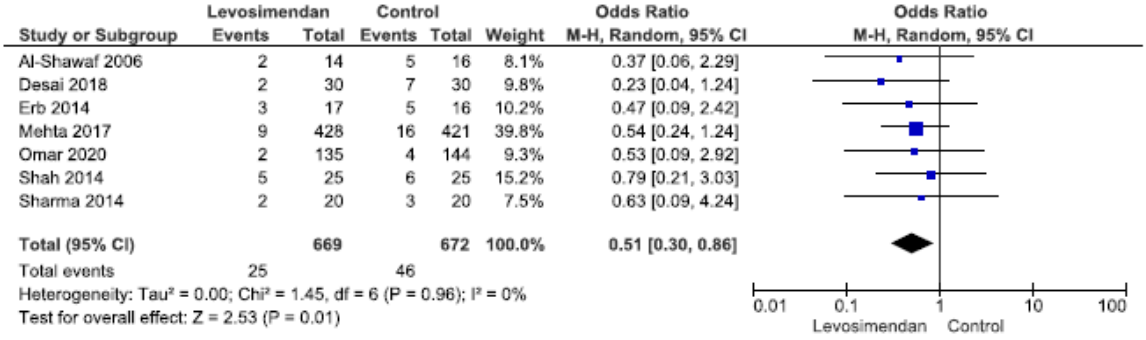


Fig.8 Forest plot for renal injury and/or renal replacement therapy.

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 post-operative 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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Author contributions

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

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REFERENCES:

1. Shi WY, Li S, Collins N, et al. Peri-operative Levosimendan in Patients Undergoing Cardiac Surgery: An Overview of the Evidence. *Heart Lung Circ.* 2015;24(7):667-672.
2. Papp Z, Agostoni P, Alvarez J, et al. Levosimendan Efficacy and Safety: 20 Years of SIMDAX in Clinical Use. *J Cardiovasc Pharmacol.* 2020;76(1):4-22.
3. Farmakis D, Alvarez J, Gal TB, et al. Levosimendan beyond inotropy and acute heart failure: Evidence of pleiotropic effects on the heart and other organs: An expert panel position paper. *Int J Cardiol.* 2016;222:303-312.
4. Pollesello P, Parissis J, Kivikko M, Harjola VP. Levosimendan meta-analyses: Is there a pattern in the effect on mortality? *Int J Cardiol.* 2016; 209:77-83.
5. Pisano A, Monti G, Landoni G. Levosimendan: new indications and evidence for reduction in perioperative mortality? *Curr Opin Anaesthesiol.* 2016; 29(4):454-461.
6. Conte SM, Florisson DS, De Bono JA, Davies RA, Newcomb AE. Levosimendan Following Cardiac Surgery. *Heart Lung Circ.* 2019;28(3): e19-e20.
7. Hummel J, Rucker G, Stiller B. Prophylactic levosimendan for the prevention of low cardiac output syndrome and mortality in paediatric patients undergoing surgery for congenital heart disease. *Cochrane Database Syst Rev.* 2017;3:CD011312.

8. Putzu A, Clivio S, Belletti A, Cassina T. Perioperative levosimendan in cardiac surgery: A systematic review with meta-analysis and trial sequential analysis. *Int J Cardiol.* 2018;251:22-31.
9. Santillo E, Migale M, Massini C, Incalzi RA. Levosimendan for Perioperative Cardioprotection: Myth or Reality? *Curr Cardiol Rev.* 2018;14(3):142-152.
10. Zhou X, Hu C, Xu Z, et al. Effect of levosimendan on clinical outcomes in adult patients undergoing cardiac surgery: a meta-analysis of randomized controlled trials. *Interact Cardiovasc Thorac Surg.* 2018;26(6):1016-1026.
11. Chen QH, Zheng RQ, Lin H, Shao J, Yu JQ, Wang HL. Effect of levosimendan on prognosis in adult patients undergoing cardiac surgery: a meta-analysis of randomized controlled trials. *Crit Care.* 2017;21(1):253.
12. Sanfilippo F, Knight JB, Scolletta S, et al. Levosimendan for patients with severely reduced left ventricular systolic function and/or low cardiac output syndrome undergoing cardiac surgery: a systematic review and meta-analysis. *Crit Care.* 2017;21(1):252.
13. Weber C, Esser M, Eghbalzadeh K, et al. Levosimendan Reduces Mortality and Low Cardiac Output Syndrome in Cardiac Surgery. *Thorac Cardiovasc Surg.* 2020;68(5):401-409.
14. Xie Y, Xing Z, Wei J, et al. Levosimendan Postconditioning Attenuates Cardiomyocyte Apoptosis after Myocardial Infarction. *J Healthc Eng.* 2022;2022:2988756.
15. Apostolo A, Vignati C, Della Rocca M, et al. Why Levosimendan Improves the Clinical Condition of Patients With Advanced Heart Failure: A Holistic Approach. *J Card Fail.* 2021.
16. Burkhoff D, Borlaug BA, Shah SJ, et al. Levosimendan Improves Hemodynamics and Exercise Tolerance in PH-HFpEF: Results of the Randomized Placebo-Controlled HELP Trial. *JACC Heart Fail.* 2021;9(5):360-370.
17. Baeeri M, Rahimifard M, Armandeh M, et al. The Effect of Levosimendan on Phosphine-Induced Nephrotoxicity: Biochemical and Histopathological Assessment. *Drug Res (Stuttg).* 2022;72(2):109-118.
18. Zhao L, Tian L, Wang S, Yang W, Lu X, Zhu C. Levosimendan in rats decreases acute kidney injury after cardiopulmonary resuscitation by improving mitochondrial dysfunction. *Transl Androl Urol.* 2021;10(7):3010-3020.

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

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مقدمه: **:**المرضـــى الذين يخضـــعون لجراحة القلب المفتوح مع المجازة القلبية الرئوية **(CPB)** يعانون من نقص تروية القلب المحيط بالجراحة العالمي يليه ضخه .هذا يؤدي إلى درجات مختلفة من الخلل الوظيفي في عضلة القلب بسبب تكوين الجذور الحرة ، وضـعف الأوعية الدموية التاجية والكالسـيوم الزائد .إذا كانت الحالة شـديدة بما فيه الكفاية يمكن أن تسـبب متلازمة النتاج القلبي المنخفض بعد الجراحة **(LCOS)** ، وهي مضـــاعفات تهدد الحياة مع انتشـــار حوالي 10 ٪ ومعدل وفيات بنسبة 17 ٪.

الهدف من الدراســـه: الهدف من هذا التحليل المنهجي هو تقديم تحديث للأدله الســـريريه الحاليه فيما يتعلق بالقيمه السريريه للاستخدام قبل وبعد الجراحه لليفوسميندان مع المرضي البالغين الذين يعانون من ضعف شديد في البطين الايسر و يخضعون لجراحة القلب.

اسـتراتيجية البحث لتحديد الدراسـات : سـيتم اجراء هذا التحليل المنهجي وفقا لبيان **PRISMA** . سـتتضـمن قواعد البيـانـات التي تم البحـث عنهـا قواعـد بيـانـات **PUBMED** و **WEB OF SCIENCE** و **SCOPUS** و **COHRANCE** للمراجعات المنهجيه ... تم اسـتخراج كلمات البحث الأسـاسـيه من المقالات المسـترجعه في البدايه وتضمنت " ليفوسميندان " و " جراحة القلب " باستخدام عامل البحث المنطقي **AND** .

النتائج : أظهرت النتائج أن اسـتخدام الليفوسـيميندان كان مرتبطًا بانخفاض خطر الإصـابة بمتلازمة الانتاج القلبي المنخفض وإصـابة الكلى و / أو العلاج بالبدائل الكلوية. ارتبط اسـتخدام **Levosimendan** أيضًـا بعلامة انخفاض خطر الوفيات المحيطة بالجراحة. لم يلاحظ أي فروق ذات دلالة إحصـائية حول استخدام **levosimendan** فيما يتعلق باحتشاء عضلة القلب بعد الجراحة ، وانخفاض ضغط الدم أو الرجفان الأذيني .كما تم التأكيد سابقًا ، أجريت الدراسات المشمولة في هذا التحليل المنهجي فقط على المرضى الذين يعانون من ضعف شديد في البطين الأيسر**(LVEF≤ 35.0** ٪ **.(**في الواقع ، اشـتمل دراسـتان منهجيتان على دراسـات بدرجة مماثلة من الخلل البطيني. سـانفيليبو وآخرون. (2107) عمل على 5 دراسات بما في ذلك 1224 مريضًا ، ولخصص المؤلفون إلى أن إعطاء ليفوسيميندان كان مرتبطًا بانخفاض كبير في معدل الوفيات. كما لاحظوا أن استخدام الليفوسيميندان كان مرتبطًا بانخفاض معدل العلاج بالبدائل الكلوية ومتلازمة النتاج القلبي المنخفض. في عمل آخر ، ويبر وآخرون. وجد التحليل التلوي (2020) أن الليفوســيمندان كان مرتبطًا بانخفاض معدل الوفيات وانخفاض معدلات **LCOS** وإصابة الكلى الحادة.

الخلاصـة والتوصـية : يخلص التحليل التلوي الحالي إلى أن استخدام **levosimendan** مرتبطة بتحسين البقاء على قيد الحياة في المستشفى وانخفاض معدلات متلازمة الانتاج القلبي المنخفض وإصابة الكلى و / أو العلاج البديل الكلوي في المرضـــى الذين يعانون من ضـــعف شـــديد في البطين الأيســـر يخضـــعون لجراحة القلب. لذلك، ينصـــح بشـــدة باســـتخدام **levosimendan**في هؤلاء المرضى.