Beneficial impact of levosimendan in critically ill patients with or at risk for acute renal failure: a meta-analysis of randomized clinical trials

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ABSTRACT

Introduction: The incidence of Acute Kidney Injury is nowadays high in critically ill patients. Its etiology is multifactorial and a primary role is played by low cardiac output syndrome. Everything targeted to normalize cardiac output should increase the renal perfusion and abolish the secondary vasoconstriction. Levosimendan is a calcium sensitizer drug with inotropic properties that improves cardiac output and seems to increase renal blood flow. The aim of this meta-analysis was to evaluate the role of levosimendan in critically ill patients with or at risk of Acute Kidney Injury.

Methods: We performed a meta-analysis of randomized controlled trials searching for trials that compared levosimendan with any comparator. The endpoints were the number of patients receiving Renal Replacement Therapy after randomization and the number of patients developing Acute Kidney Injury.

Results: Final analysis included 33 trials and 3,879 patients (2,024 levosimendan and 1,855 control). The overall analysis showed that the use of levosimendan was associated with a significant reduction in the risk of Renal Replacement Therapy (17 of 492 [3.5%] in the levosimendan group versus 37 of 427 [8.7%] in the control group, relative risk = 0.52 [0.32 to 0.86], p for effect = 0.01) and of Acute Kidney Injury (114 of 1,598 [7.1%] in the levosimendan group versus 143 of 1,529 [9.4%] in the control arm, relative risk = 0.79 [0.63 to 0.99], p for effect = 0.048).

Conclusions: This meta-analysis suggests that the use of levosimendan is associated with a significant reduction of Renal Replacement Therapy in critically ill patients.

Keywords: levosimendan, acute kidney injury, critical care, renal replacement therapy.

INTRODUCTION

Despite considerable progress in terms of diagnosis and treatment, the incidence of Acute Kidney Injury (AKI) remains high in critically ill patients. Interventions or medications that can alter the clinical course of AKI and change the outcome of critically ill patients are scarce (1). The etiology of acute renal failure in critically ill patients is multifactorial and a primary role is played by low cardiac output...
syndrome and sepsis. The main determinants of renal perfusion are cardiac output, blood pressure and blood volume. The kidneys normally receive 20-25% of the cardiac output, although their total weight is less than 1% of total body weight. The decrease in cardiac output due to hypovolemia or cardiac dysfunction decreases renal perfusion with direct and indirect mechanisms. Indeed, in addition to the reduction in renal blood flow, activation of sympathetic nervous system, renin-angiotensin system and vasopressin secretion occur. Each intervention targeted to normalize cardiac output and systemic perfusion should be able to increase the renal perfusion and abolish the secondary vasoconstriction.

Levosimendan is a calcium sensitizer drug with inotropic properties (2). It also has vasodilating properties interacting with ATP-sensitive K⁺ channels of vascular smooth muscles cells. Levosimendan seems to reduce the release of pro-inflammatory cytokines and to prevent the cardiomyocyte apoptosis. Therefore, it improves cardiac output and seems to increase renal blood flow by its vasodilating effects. Levosimendan has already been associated with reduction of mortality in critically ill patients in a meta-analysis of randomized clinical trials, but its effects on renal function have never been systematically assessed (3).

The aim of this meta-analysis of randomized trials was to evaluate the role of levosimendan in critically ill patients with or at risk of AKI.

METHODS

We performed a systematic review and meta-analysis of randomized trials in accordance with the PRISMA (Preferred Reporting Items for Systematic reviews and Meta-Analyses) guidelines.

We searched for all randomized controlled trials that compared levosimendan with any pharmacological comparator or placebo in any clinical setting. Potentially eligible trials were identified by searching the Cochrane central register, Embase, Scopus and Medline using a combination of subject headings and text words to identify randomized controlled trials of levosimendan. The search was updated at January 2013. The full PubMed search strategy is available in the supplemental item S1. Searches were not restricted by language or publication status. To identify ongoing or unpublished trials, we searched the Clinical Trial Registry. We also examined the reference lists of eligible trials and reviews together with the abstracts of international congresses. The following inclusion criteria were used for potentially relevant studies: random allocation to treatment and comparison of levosimendan vs. control. There were no restrictions on age, drug’s dose or time of administration. Exclusion criteria were overlapping publications, abstracts published before 2010, oral administration of levosimendan, and lack of data on renal outcome. Two authors independently screened the search output to identify records of potentially eligible trials, the full texts of which were retrieved and assessed for inclusion.

The primary endpoint was the number of patients receiving Renal Replacement Therapy (RRT) after randomization; the secondary endpoint was the number of patients developing AKI (as per author definition). We also collected data on serum peak creatinine and glomerular filtration rate. We contacted trial authors to obtain any missing outcome data. We extracted data on setting, dose of levosimendan, type of comparator, outcome data and length of follow up. We assessed the risk of bias associated with the method of sequence generation, allocation concealment, blinding, and completeness of outcome data. We rated the risk of bias as being low, unclear, or high according to established criteria (4).
**Statistical analysis.** For binary outcome we calculated the natural logarithm (ln) of risk ratios (RR) and its standard deviation. We pooled these using the inverse variance method and a fixed effect model in case of low statistical inconsistency (I-square \(\leq 25\%\)) or with random-effect model (which better accommodates clinical and statistical variations) in case of moderate or high statistical inconsistency (I-square \(>25\%\)). Weighted Mean Difference (WMD) and 95% confidence intervals were computed for continuous variables using the same methods as just described (4). To assess heterogeneity in results of individual studies, we used Cochran’s \(Q\) statistic and the I-square statistic (I-square \(>25\%\) was considered as a threshold indicating significant heterogeneity). Publication bias was assessed by visually inspecting funnel plots of the primary outcome, by analytical appraisal based on the Begg adjusted-rank correlation test and on Egger’s linear regression test (a two-sided p value of 0.10 or less was regarded as significant).

Subgroup analyses were carried out to examine whether the effect of levosimendan on RRT varied by setting or type of infusion. Sensitivity analyses were done to quantify the effect of levosimendan when restricted to trials with low risk of bias. We also investigated the influence of a single study on the overall risk estimate by sequentially removing study in order to test the robustness of the main results. Statistical significance was set at the two-tailed 0.05 level for hypothesis testing. Data analysis was performed using STATA 11.0 Software (StataCorp LP, College Station, TX, USA).

**RESULTS**

**Characteristics of the included individual studies.** Our search strategy identified 599 unique publications, the titles and abstracts of which were screened for inclusion. The full text of 97 articles was retrieved, of which 33 (5-37) met the inclusion criteria (Figure 1). Reasons for exclusion of the

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**Figure 1 - Flow diagram: selection process of included articles.**
Table 1 - Description of the 33 studies included in the meta-analysis.

| Author          | Year | Journal                  | Control   | Setting          | Setting details                                                                 |
|-----------------|------|--------------------------|-----------|------------------|---------------------------------------------------------------------------------|
| Al-Shawaf E     | 2006 | J Cardiothorac Anesth    | Milrinone | Cardiac surgery  | LCOS after CABG                                                                  |
| Alvare J        | 2005 | Rev Esp Anestesiol Reanim | Dobutamine | Cardiac surgery  | LCOS after cardiac surgery with CPB                                             |
| Alvare J        | 2006 | Rev Esp Cardiol          | Dobutamine | Cardiac surgery  | LCOS after cardiac surgery with CPB                                             |
| Barisin S       | 2004 | J Cardiovase Pharmacol   | Placebo   | Cardiac surgery  | 20 min before surgery OPCABG                                                    |
| Baysal A        | 2013 | J Cardiothorac Anesth    | Inotropes | Cardiac surgery  | Cardiac surgery                                                                  |
| Bonios MJ       | 2012 | Int J Cardiol            | Dobutamine | Cardiology       | HF (end stage)                                                                  |
| Bragadottir G   | 2013 | Crit Care Med            | Placebo   | Cardiac surgery  | Cardiac surgery                                                                  |
| De Hert Sg      | 2007 | Anesth Analg             | Milrinone | Cardiac surgery  | Cardiac surgery with CPB                                                        |
| Flevari P       | 2006 | Am J Cardiol             | Placebo   | Cardiology       | HF (decompensated advanced)                                                     |
| Fuhrmann JT     | 2008 | Crit Care Med            | Enoximone | Cardiology       | Patients with acute myocardial infarction and cardiogenic shock                 |
| Hou ZQ          | 2013 | Cardiovasc Ther          | Placebo   | Cardiology       | LVEF < 40%                                                                      |
| Ilyasoy A       | 2010 | Turk J Med Sci           | Dobutamine | Cardiology       | ADHF                                                                            |
| Jarvela K       | 2008 | J Cardiothorac Anesth    | Placebo   | Cardiac surgery  | After induction in aortic valve surgery with severe aortic valve stenosis and LV hypertrophy |
| Kurt IH         | 2010 | Heart Vessels            | Standard of treatment | Cardiology | HF (NYHA class III-IV)                                                                  |
| Lahtinen P      | 2011 | Crit Care Med            | Placebo   | Cardiac surgery  | Heart valve surgery                                                              |
| Leppikangas H   | 2008 | Acta Anaesthesiol Scand  | Placebo   | Vascular surgery | Infrarenal abdominal aortic aneurysm                                              |
| Levin R         | 2008 | Rev Esp Cardiol          | Dobutamine | Cardiac surgery  | LCOS after CABG                                                                  |
| Malfatto G      | 2012 | J Cardiovase Pharmacol   | Furosemide | Cardiology       | HF (chronic)                                                                    |
| Mehrazza A      | 2007 | JAMA                     | Dobutamine | Cardiology       | ADHF                                                                            |
| Moertl D        | 2005 | Eur J Heart Fail         | Pge1      | Cardiology       | HF (decompensated chronic)                                                      |
| Momenni M       | 2011 | J Cardiothorac Anesth    | Milrinone | Neonatal cardiac surgery | Cardiac surgery                                                                 |
| Morelli A       | 2005 | Intensive Care Med       | Dobutamine | Sepsis           | LV dysfunction post septic shock after 48 hours of conventional treatment       |
| Morelli A       | 2010 | Crit Care               | Dobutamine | Septic shock     |                                                                                   |
| Nijhawan N      | 1999 | J Cardiovase Pharmacol   | Placebo   | Cardiac surgery  | ASA III-IV undergoing elective cardiac surgery                                  |
| Packer M        | 2013 | JACC Heart Fail         | Placebo and standard HF treatment | Cardiology | Cardiology                                                                       |
| Parissis JT     | 2006 | Heart                   | Placebo   | Cardiology       | HF (NYHA III-IV and LVEF<30 %)                                                  |
| Ricci Z         | 2012 | Intensive Care Med       | Standard isotropic management | Pediatric cardiac surgery | Cardiac surgery                                                                  |
| Ristikankare A  | 2012 | J Cardiothorac Anesth    | Placebo   | Cardiac surgery  | Cardiothoracic surgery                                                           |
| Slaysky MT      | 2000 | Circulation             | Placebo   | Cardiology       | HF (NYHA class III-IV)                                                          |
| Tritapepe L     | 2009 | Br J Anaesth             | Placebo   | Cardiac surgery  | CABG                                                                            |
| Yilmaz MB       | 2007 | Cardiovasc Drugs Ther    | Dobutamine | Cardiology       | Worsening of HF                                                                 |
| Yontar OC       | 2010 | Anq Bras Cardiol        | Dobutamine | Cardiology       | HF (ischemic)                                                                   |
| Zemljic G       | 2007 | J Card Fail              | Nothing   | Cardiology       | HF (advanced, waiting for heart transplantation)                                 |

LCOS = low cardiac output syndrome; CABG = coronary artery bypass grafting; OPCABG = off-pump coronary artery bypass grafting; CPB = cardiopulmonary bypass; HF = heart failure; ADHF = acute decompensated heart failure; NYHA = New York Heart Association; ASA = American Society of Anesthesiology Physical Classification System; LV = left ventricle; LVEF = left ventricular ejection fraction.
remaining articles are detailed in Figure 1. The list of the 97 major exclusions is available in the supplemental Table S1. The 33 included trials randomized 3,879 patients (2,024 to levosimendan and 1,855 to control). Clinical heterogeneity was mostly due to setting, dose and control treatment (Tables 1 and 2). In details, 15 studies used levosimendan in a cardiological setting (decompensated heart failure, NYHA III-IV), 15 in cardiac surgery (two of these in pediatric patients), two studies were conducted in septic patients and one in vascular surgery patients. Twenty-

Table 2 - Description of levosimendan administration in the 33 studies included in the meta-analysis.

| Author          | Year | Levosimendan bolus (ug/kg) | Levosimendan continuous infusion (ug/kg/min) | Length of levosimendan infusion (hours) |
|-----------------|------|---------------------------|---------------------------------------------|----------------------------------------|
| Al-Shawaf E     | 2006 | 12                        | 0.1-0.2                                     | 24                                     |
| Alvarez J       | 2005 | 12                        | 0.2                                         | 24                                     |
| Alvarez J       | 2006 | 12                        | 0.2                                         | 24                                     |
| Barisin S       | 2004 | 12 or 24                  |                                             |                                        |
| Baysal A        | 2013 | 6                         | 0.1                                         | 24                                     |
| Bonios MJ       | 2012 |                           | 0.3                                         | 6 hours for 6 months                   |
| Bragadottir G   | 2013 | 12                        | 0.1                                         |                                        |
| De Hert SG      | 2007 | 12                        | 0.1                                         | 19+4                                   |
| Flevari P       | 2006 |                           | 0.1                                         | 24                                     |
| Fuhrmann JT     | 2008 | 12                        | 0.1 for 50 min then 0.2                     | 50 min- other 23 hours                 |
| Hou ZQ          | 2013 | 12                        | 0.05 or 0.1 or 0.2                          | 24                                     |
| Iyisoy A        | 2010 | 12                        | 0.1                                         | 24                                     |
| Jarvela K       | 2008 |                           | 0.2                                         | 24                                     |
| Kurt IH         | 2010 | 12                        | 0.1                                         | 24                                     |
| Lahtinen P      | 2011 | 24                        | 0.2                                         | 24                                     |
| Leppikangas H   | 2008 | 24                        | 0.2                                         | 24                                     |
| Levin R         | 2008 | 10                        | 0.1                                         | 24                                     |
| Malfatto G      | 2012 |                           | 0.1-0.4                                     | 24                                     |
| Mebazaa A       | 2007 | 12                        | 0.2                                         | 24                                     |
| Moertl D        | 2005 | 12                        | 0.1                                         | 24                                     |
| Momeni M        | 2011 |                           | 0.05                                        | 48                                     |
| Morelli A       | 2005 |                           | 0.2                                         | 24                                     |
| Morelli A       | 2010 |                           | 0.2                                         | 24                                     |
| Nijhawan N      | 1999 | 18 or 26                  | 0.2 or 0.3                                  | 6                                      |
| Packer M        | 2013 | 12 (6 if under treatment with other inotropic or vasodilating drugs) | 0.1 (0.2 if tolerated 0.1-0.05 if not tolerated) | 24                                     |
| Parisisis JT    | 2006 | 6                         | 0.1-0.4                                     | 24                                     |
| Ricci Z         | 2012 |                           | 0.1                                         | 72                                     |
| Ristikankare A  | 2012 | 12                        | 0.2                                         | 24                                     |
| Slawsky MT      | 2000 | 6                         | 0.1-0.4                                     | 4-6                                    |
| Tritapepe L    | 2009 | 24                        |                                             |                                        |
| Yilmaz MB       | 2007 |                           | 0.1-0.2                                     | 24                                     |
| Yontar OC       | 2010 | 0.3-0.6                   | 0.1-0.2                                     | 24                                     |
| Zemljic G       | 2007 | 12                        | 0.1                                         | 24                                     |
three authors administered a loading dose and thirty-one used a continuous infusion (twenty-one of them following bolus). Dose varied between 0.3 and 0.6 mcg/kg as intravenous bolus and between 0.05 and 0.4 mcg/kg/min as a continuous infusion. Thirteen studies (39% of all) used placebo as control while ten (30% of all) used dobutamine and 31% other comparators. Study quality appraisal indicated that studies were of variable quality (supplemental Table S2) with 13 (39%) of them having low risk of bias.

**Quantitative data synthesis.** Overall analysis on principal endpoint (Figure 2) showed that the use of levosimendan was associated with a significant reduction in the risk of RRT (17 of 492 [3.5%] in the levosimendan group versus 37 of 427 [8.7%] in the control group, RR = 0.52, 95% confidence interval (CI) 0.32 to 0.86, p for effect = 0.01, p for heterogeneity = 0.9, I-square = 0%, with 13 studies included). Visual inspection of funnel plots did not identify a skewed or asymmetrical shape (Figure 3) and quantitative evaluation did not suggest a presence of publication bias, as measured by the Begg test (p = 0.3) and Egger test (p = 0.9). All but one studies reporting RRT data administered levosimendan as bolus and the reduction in the need for RRT was confirmed in these 12 studies (17 of 480 [3.5%] in the levosimendan group versus 37 of 415 [8.9%] in the control arm.

![Figure 2 - Forest plot for the risk of Renal Replacement Therapy.](image)

**Figure 2 - Forest plot for the risk of Renal Replacement Therapy.** The use of levosimendan was associated with a significant reduction in the risk of RRT (17 of 492 [3.5%] in the levosimendan group versus 37 of 427 [8.7%] in the control group, RR = 0.52, 95% CI 0.32 to 0.86, p for effect = 0.01, p for heterogeneity = 0.9, I-square = 0%, with 13 studies included).

RR = risk ratio; CI = confidence interval.
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Funnel plot with pseudo 95% confidence limits

**Figure 3** - Funnel plot for the risk of Renal Replacement Therapy.

*RR = risk ratio; se = standard error.*

**RR = 0.52, 95% CI 0.31 to 0.86, p for effect = 0.01, p for heterogeneity = 0.9, I-square = 0%**. All but two studies reporting RRT data administered levosimendan in the perioperative period and the reduction in the need for RRT was confirmed in these 11 studies (12 of 378 [3.2%] in the levosimendan group versus 29 of 363 [8%] in the control arm, RR = 0.48, 95% CI 0.26 to 0.89, p for effect = 0.02, p for heterogeneity = 0.9, I-square = 0%).

The analysis on secondary endpoints showed that the use of levosimendan was associated with a significant reduction in AKI risk (114 of 1,598 [7.1%] in the levosimendan group versus 143 of 1,529 [9.4%] in the control arm, RR = 0.79, 95% CI 0.63 to 0.99, p for effect = 0.048, p for heterogeneity = 0.8, I-square = 0%, with 19 studies included). This result was confirmed in the perioperative setting (39 of 411 [9.5%] in the levosimendan arm versus 69 of 396 [17%] in the control arm, RR = 0.60, 95% CI 0.42 to 0.86, p for effect = 0.005, p for heterogeneity = 0.9, I-square = 0%, with 13 studies included).

Glomerular filtration rate was better after randomization in patients receiving levosimendan (WMD = 8.08, 95% CI 3.35 to 12.80, p for effect = 0.001) in the 8 studies reporting it while no difference was found in peak serum creatinine values (WMD = -0.02, 95% CI -0.11 to 0.07, p for effect = 0.7) in the 15 studies reporting it.

Sensitivity analyses considering only data from studies with low risk of bias confirmed a trend towards reduction in the risk of RRT (3 of 238 [1.3%] in the levosi-
Figure 4 - Analysis of the influence of levosimendan versus any control on the overall risk of Renal Replacement Therapy. This figure shows the influence of individual studies on the summary Risk Ratio. The middle vertical axis indicates the overall RR and the two vertical axes represent the 95% CI. RR = risk ratio; CI = confidence interval.

We performed a comprehensive and updated review of randomized controlled trials to investigate the role of levosimendan in the prevention and treatment of AKI in critically ill patients. The most important result of this study is the reduction in the need for RRT in levosimendan-treated critically ill patients. In critically ill patients sepsis, major surgery (especially cardiac surgery) and acute decompensated heart failure are the most common triggers of AKI. The mainstay of prevention and treatment of AKI is the treatment of the cause of acute renal failure and withdrawal of nephrotoxic agents. If there are pre-renal or post-renal factors to be corrected, they must be identified. The optimization of hemodynamic conditions
should be the main goal of care and intravascular volume must be monitored and maintained in the normal range. In addition to the optimization of hemodynamic status and suspension of nephrotoxic agents no other pharmacological intervention has been shown to be effective in the prevention and treatment of AKI and a recent web based survey suggested that the 15 interventions that might improve clinically relevant endpoints in critically ill patients with or at risk for AKI are supported by low levels of evidence.

Levosimendan [the (-) enantiomer of 4-(1,4,5,6-tetrahydro-4-methyl-6-oxo-3-pyridazinyl) phenylhydrazonopropanedinitrile] is a new calcium enhancer with calcium-sensitizing activity. The mechanism of action that makes the levosimendan effective in preventing and treating kidney damage may be related to its beneficial action on the normalization of hemodynamic conditions. The main mechanism of action of this drug is an increase in affinity of troponin C for calcium and therefore the stabilization of the conformation of troponin C. This mechanism of action translates into inotropic effect without determining increase intracellular cAMP or the intracellular calcium concentration at the doses used in clinical practice. This mechanism leads to acceleration of actin-myosin cross-bridge formation rate and deceleration of the dissociation rate. The binding becomes considerably weaker during diastole, when the intracellular calcium concentration is low, and this has a beneficial effect on the relaxation of myocardial muscle cells, resulting in improvement of diastolic function. The positive inotropic effect is obtained without impairing ventricular relaxation or increasing myocardial oxygen demand.

Levosimendan also has ancillary actions that may be responsible for the beneficial actions on renal function. Levosimendan indeed activates the opening of the ATP-sensitive sarcolemma K⁺ channels of smooth muscle cells and myocytes determining their hyperpolarization with consequent vasodilatation, which may contribute to augmentation of renal perfusion and depression of central venous pressure. Central venous pressure is an independent predictor of glomerular filtration rate in patients with congestive heart failure (38). An important mechanism of action of levosimendan on renal function may be linked to its ownership of venodilation, which reduces the renal congestion and increases renal perfusion pressure. Administration of levosimendan also entails a reduction of circulating proinflammatory cytokines. This effect can be considered secondary to the inotropic and vasodilator properties of the drug, but may also result from the extracardiac downregulation of the synthesis of cytokines through transcription factors (39). In addition, the administration of this drug induces significant reduction of soluble mediators of apoptosis, such as Fas and Fas ligand (40, 41). Still, levosimendan improves endothelial function through downregulation of soluble cell adhesion molecules such as ICAM-1 and VCAM1 and regulates the mediators implicated in oxidative and nitrosative stress. Recent studies show that it can preserve organ function in acute and septic shock-induced myocardial depression via cooling down the oxidative burst of circulating cells (42, 43). Studies in animal models have yielded conflicting results regarding the effect of levosimendan on renal function. In fact, while in models of septic shock seem to outweigh the beneficial effects on hemodynamics, in animal models of ischemia reperfusion seems to prevail an effect of organ protection (44-49).

Bragadottir et al. (11) carried out a randomized, placebo-controlled clinical trial over the effects of levosimendan on the renal blood flow, the GFR, the renal oxygen
consumption and the renal oxygen supply/demand, in cardiac surgical setting. The main result of this paper is that levosimendan induces renal vasodilation, preferentially of pre-glomerular resistance vessels, increasing both renal blood flow and glomerular filtration rate, without impairing renal oxygen demand/supply relationship as demonstrated by the lack of effect on renal oxygen extraction. The careful analysis of the literature has identified 33 studies that evaluated the effect of levosimendan on renal function performed on critically ill patients in four different settings: cardiology (16 studies), cardiac surgery (15 studies), vascular surgery (1 study) and sepsis (2 studies). Although in most of them the impact of levosimendan on renal function was not the pre-planned primary outcome and most of them are individually statistically underpowered, many of them suggested a trend of benefit on renal function, and the pooled data analysis of 4,082 patients included in the meta-analysis suggests a beneficial effect of levosimendan on renal function including glomerular filtration rate, AKI as per author definition and RRT with sensitivity analyses confirming the validity of our findings.

The findings of our manuscript could be compared to those of three other papers. In a previous meta-analysis Landoni et al. highlighted the beneficial effects of levosimendan in critically ill patients (3). However, the authors did not investigate the renal outcomes and the search was updated at November 2010. A more recent meta-analysis Landoni et al. suggested a beneficial effect of levosimendan in AKI as per author definition and RRT with sensitivity analyses confirming the validity of our findings.

The main limitation of the present meta-analysis is that several included RCTs were of suboptimal quality. Furthermore, traditional limitations of meta-analyses due to variations in the treatment regimens, in populations or major subgroups within trials, and in the conduct of the trials apply to this study. On top of that, great variability of clinical setting and a relative small number of studies analyzed for primary end point (RRT) should be acknowledged.

CONCLUSION

This meta-analysis shows that the use of levosimendan is associated with a significant reduction in incidence of RRT in critically ill patients. Since meta-analyses are hypothesis generating, large multicenter, randomized, placebo-control clinical trials designed to assess the role of levosimendan in the treatment of acute renal failure in critically ill patients are warranted.

REFERENCES

1. Landoni G, Bove T, Székely A, Comis M, Rodseth RN, Pascero D, et al. Reducing mortality in acute kidney injury patients: systematic review and international web-based survey. J Cardiothorac Vasc Anesth. 2013; 27: 1384-98.
2. Papp Z, Édes I, Fruhwald S, De Hert SG, Salmenperä M, Leppikangas H, et al. Levosimendan: Molecular mechanisms and clinical implications: Consensus of experts on the mechanisms of action of levosimendan. Int J Cardiol. 2012; 159: 82-7.
3. Landoni G, Biondi-Zoccai G, Greco M, Greco T, Bignami E, Morelli A, et al. Effects of levosimendan on mortality and hospitalization. A meta-analysis of randomized controlled studies. Crit Care Med. 2012; 40: 634-46.
4. Higgins JPT, Green S. Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 [updated March 2011]. The Cochrane Collaboration, 2011. Available from www.cochrane-handbook.org.
5. Al-Shawaf E, Ayed A, Vislocky I, Radimir B, Dehrib N, Tarazi R. Levosimendan or Milrinone in the Type 2 Diabetic Patient With Low Ejection Fraction Undergoing Elective Coronary Artery Surgery. J Cardiothorac Vasc Anesth. 2006; 20: 353-7.
6. Alvarez J, Taboada M, Rodríguez J, Carucevo Z, Bouzada M Campana O, et al. Hemodynamic effects of levosimendan following cardiac surgery. Rev Esp Anestesiol Reanim. 2005; 52: 389-94.
7. Alvarez J, Bouzada M, Fernández AL, Carucevo Z, Taboada M Rodríguez J, et al. Hemodynamic effects of levosimendan compared with dobutamine in patients with low cardiac output after cardiac surgery. Rev Esp Cardiol. 2006; 59: 338-45.
8. Barisin S, Husedzinovic I, Sonicz Z, Bradic N, Barisin A,
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Tonkovic D. Levosimendan in off-pump coronary artery bypass: a four-times masked controlled study. J Cardiovasc Pharmacol. 2004; 44: 703-8.

Baysal A, Yanartas M, Dogukan M, Gundogus N, Kocak T, Koksal C. Levosimendan improves renal outcome in cardiac surgery: A randomized trial. J Cardiothorac Vasc Anesth. 2014;28:586-594.

Bonios MJ, Terrovitis JV, Dragos SK, Katsaros F, Fantosio C, Nanas SN, et al. Comparison of three different regimens of intermittent inotrope infusions for end stage heart failure. Int J Cardiol. 2012; 159: 225-9.

Bragadottir G, Redfors B, Ricksten SE. Effects of levosimendan on glomerular filtration rate, renal blood flow, and renal oxygenation after cardiac surgery with cardiopulmonary bypass: a randomized placebo-controlled study. Crit Care Med. 2011; 39: 1641-5.

De Hert SG, Lorosomradee S, Cromheecke S, Van Der Linden PJ. The effects of levosimendan in cardiac surgery patients with poor left ventricular function. Anesth Analg. 2007; 104: 768-73.

Flevari P, Parissis JT, Leftieriotis D, Panou F, Kourea K, Kremastinos DT. Effect of Levosimendan on Ventricular Arrhythmias and Prognostic Autonomic Indexes in Patients With Decompensated Advanced Heart Failure Secondary to Ischemic or Dilated Cardiomyopathy. Am J Cardiol. 2006; 98: 1641-5.

Fuhrmann JT, Schmeisser A, Schulze MR, Wunderlich C, Schulze MR, et al. Levosimendan is superior to enoximone in refractory cardiogenic shock complicating acute myocardial infarction. Crit Care Med. 2009; 37: 2263-9.

Hou Q, Sun Z, Su CY, Tan H, Zhong X, Hu B, et al. Effect of Levosimendan on Estimated Glomerular Filtration Rate in Hospitalized Patients with Decompensated Heart Failure and Renal Dysfunction. Cardiovasc Ther. 2012; 31: 108-14.

Ilysoy A, Celik T, Celik M, Bugan B, Yaman H. Comparative effects of levosimendan and dobutamine infusion on p wave dispersion in patients with acute decompensated heart failure. Turk J Med Sci. 2010; 40: 761-70.

Jarvaela K, Maaranen P, Sisto T, Ruokonen E. Levosimendan in Off-Pump Coronary Artery Bypass: A Four-Times Masked Controlled Study. J Cardiothorac Vasc Anesth. 2008; 22: 693-8.

Kurt IH, Sayazer K, Batur MK. Short-term effect of levosimendan on free light chain kappa and lambda levels in patients with decompensated chronic heart failure. Heart Vessels. 2010; 25: 392-9.

Lahtinen F, Pitkänen O, Pölenen P, Turpeinen A, Kiviniemi V, Uusaro A. Levosimendan reduces heart failure after cardiac surgery: A prospective, randomized, placebo-controlled trial. Crit Care Med. 2011; 39: 2263-70.

Leppikangas H, Tenhunen JJ, Lindgren L, Salenius JP, Ruokonen E. Effects of levosimendan on indocyanine green plasma disappearance rate and the gastric mucosal-arterial pCO2 gradient in abdominal aortic aneurysm surgery. Acta Anaesthesiol Scand. 2008; 52: 785-92.

Levin RL, Degrange MA, Porcie R, Salvagio F, Blanco N, Botbol AL, et al. The calcium sensitizer levosimendan gives superior results to dobutamine in postoperative low cardiac output syndrome. Rev Esp Cardiol. 2008; 61: 471-9.

Maffatto G, Della Rosa F, Villani A, Rella V, Branzi G, Facchini M, et al. Intermittent levosimendan infusions in advanced heart failure: favourable effects on left ventricular function, neurohormonal balance, and one-year survival. J Cardiovasc Pharmacol. 2012; 60: 450-5.

Malfatto G, Della Rosa F, Villani A, Rella V, Facchini M, Cohen-Solal A, Kleber FX, Pocock SJ, et al. Levosimendan vs dobutamine for patients with acute decompensated heart failure: the SURVIVE Randomized Trial. JAMA. 2007; 297: 1883-91.

Moertl D, Berger R, Huelsmann M, Bojic A, Pacher R. Short-term effects of levosimendan and prostaglandin E1 on hemodynamic parameters and B-type natriuretic peptide levels in patients with decompensated chronic heart failure. Eur J Heart Fail. 2005; 7: 1156-63.

Moemen M, Rubay J, Matta A, Rennetov M, Veyckemans F, Poncelet AJ, et al. Levosimendan in congenital cardiac surgery: a randomized, double-blind clinical trial. J Cardiovasc Thorac Anesth. 2011; 25: 419-24.

Morelli A, De Castro S, Teboul JL, Singer M, Rocco M, Conti G, et al. Effects of levosimendan on systemic and regional hemodynamics in septic myocardial depression. Intensive Care Med. 2005; 31: 638-44.

Morelli A, Donati A, Ertmer C, Rebberg S, Lange M, Orecchioni A, et al. Levosimendan for resuscitating the microcirculation in patients with septic shock: a randomized controlled study. Crit Care. 2010; 14: R232.

Nijkhuizen N, Nicolosi AC, Montgomery MW, Aggarwal A, Pagel FS, Waritffer DC. Levosimendan enhances cardiac performance after cardiopulmonary bypass: a prospective, randomized placebo-controlled trial. J Cardiovasc Pharmacol. 1999; 34: 219-28.

Packer M, Colucci W, Fisher L, Massie BM, Teerlink JR, Young G, et al. Effect of levosimendan on the short-term clinical course of patients with acutely decompensated heart failure. JACC Heart Fail. 2013; 1: 105-11.

Parissis JT, Adamopoulos S, Farmakis D, Filippatos G, Paraskevaidis I, Panou F, et al. Effects of serial levosimendan infusions on left ventricular performance and plasma biomarkers of myocardial injury and neurohormonal and immune activation in patients with advanced heart failure. Heart. 2006; 92: 1769-72.

Ricci Z, Garisto C, Favia I, Vitale V, Di Chiara L, Cogo PE. Levosimendan infusion in newborns after corrective surgery for congenital heart disease: Randomized controlled trial. Intensive Care Med. 2012; 38: 1196-204.

Ristikankare A, Pohjolainen R, Eriksson H, Valtonen M, Leino K, Salmenpera M. Effects of levosimendan on renal function in patients undergoing coronary artery surgery. J Cardiothorac Vasc Anesth. 2012; 26: 591-5.

Slavsky MT, Colucci WS, Gottlieb SS, Greenberg BH, Haeusslein E, Hare J, et al. Acute hemodynamic and clinical effects of levosimendan in patients with severe heart failure. Study Investigators. Circulation. 2000; 102: 2222-7.

Tritapepe L, De Santis V, Vitale D, Guarracino F, Pellegrini F, Pietropaoli P, et al. Levosimendan pre-treatment improves outcomes in patients undergoing coronary artery bypass graft surgery. Br J Anaesth. 2010; 104: 198-204.

Yilmaz MB, Yalta K, Erdem A, Turgut O, et al. Levosimendan improves renal function in patients with acute decompensated heart failure: comparison with dobutamine. Cardiovasc Drugs Ther. 2007; 21:431-5.

Yontar OC, Yilmaz MB, Yalta K, Erdem A, Tandogan I. Acute effects of levosimendan and dobutamine on QRS duration in patients with heart failure. Arq Bras Cardiol. 2010; 95: 738-42.

Zemljic G, Bunc M, Yazdanbakhsh AP, Vrtovec B. Levosimendan Improves Renal Function in Patients With Advanced Chronic Heart Failure: Awaiting Cardiac Transplantation. J Card Fail. 2007; 13: 417-21.

Zanni M, Navis G, Smilde TDJ, Voors AA, van der Bij W, Tonkovic D, et al. Effects of levosimendan and acute renal failure on hemodynamic parameters and B-type natriuretic peptide levels in patients with decompensated chronic heart failure. Eur J Heart Fail. 2005; 7: 1156-63.

Zemljic G, Bunc M, Yazdanbakhsh AP, Vrtovec B. Levosimendan Improves Renal Function in Patients With Advanced Chronic Heart Failure: Awaiting Cardiac Transplantation. J Card Fail. 2007; 13: 417-21.
40. Parissis JT, Adamopoulos S, Antoniades C, Kostakis G, Rigas A, Kyrozopoulos S, et al. Effects of levosimendan on circulating pro-inflammatory cytokines and soluble apoptosis mediators in patients with decompenated advanced heart failure. Am J Cardiol. 2004; 93: 1309-12.
41. Adamopoulos S, Parissis JT, Iliodromitis EK, Paraskevaidis I, Tsiapras D, Farmakis D, et al. Effects of Levosimendan Versus Dobutamine on Inflammatory and Apoptotic Pathways in Acutely Decompensated Chronic Heart Failure. Am J Cardiol. 2006; 98: 102-6.
42. Parissis JT, Karavidas A, Bistola V, Arapi S, Paraskevaidis I, Farmakis D, et al. Effects of levosimendan on flow-mediated vasodilation and soluble adhesion molecules in patients with advanced chronic heart failure. Atherosclerosis. 2008; 197: 278-82.
43. Grossini E, Caimmi PP, Molinari C, Teodori G, Vacca G. Hemodynamic effect of intracoronary administration of levosimendan in the anesthetized pig. J Cardiovasc Pharmacol. 2005; 46:333-42.
44. Yakut N, Yasa H, Bahriye Lafci B, Ortac R, Tulukoglu E, Aksun M, et al. The influence of levosimendan and iloprost on renal ischemia-reperfusion: an experimental study. Interact Cardiovasc Thorac Surg. 2008; 7: 235-9.
45. Zagé RA, Johnson AC, Lund S, Hanson SY, Abrass CK. Levosimendan protects against experimental endotoxemic acute renal failure. Am J Physiol Renal Physiol. 2006; 290: F1453-62.
46. Rehberg S, Ertmer C, Vincent JL, Spiegel HU, Kohler G, Erren M, et al. Effects of combined arginine vasopressin and levosimendan on organ function in ovine septic shock. Crit Care Med. 2010; 38: 2016-23.
47. Paigel PS, Hettrick DA, Warltier DC. Influence of levosimendan, pimobendan, and milrinone on the regional distribution of cardiac output in anesthetized dogs. Br J Pharmacol. 1996; 119:609-15.
48. Oldner A, Konrad D, Weitzberg E, Rudehill A, Rossi P, Wanecek M. Effects of levosimendan, a novel inotropic calcium-sensitizing drug, in experimental septic shock. Crit Care Med. 2001; 29: 2185-93.
49. Grossini E, Molinari C, Pollesello P, Bellomo G, Valente G, Mary D, et al. Levosimendan protection against kidney ischemia/reperfusion injuries in anesthetized pigs. J Pharmacol Exp Ther. 2012; 342: 376-88.
50. Niu ZZ, Wu SM, Sun WY, Hou WM, Chi YF. Perioperative levosimendan therapy is associated with a lower incidence of acute kidney injury after cardiac surgery: a meta-analysis. J Cardiovasc Pharmacol. 2014; 63: 107-12.
51. Yilmaz MB, Grossini E, Silva Cardoso JC, Édes I, Fedele F, Pollesello P, et al. Renal effects of levosimendan: A consensus report. Cardiovasc Drugs Ther. 2013; 27: 581-90.