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Original Article

Heart calcium sensitizer on morbidity and mortality of high-risk surgical patients with MODS: systematic review and meta-analysis

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Abstract: A total of 440 patients from 10 studies were included in a systematic review to evaluate the association between improved survivals from multiple organ dysfunction syndromes in patients undergoing surgical operation. Health Inter Network Initiatives (HINARI), MEDLINE and EMBASE were searched. Exclusion criteria were duplicate publications, non-human experimental studies, and no mortality data. The primary endpoint was postoperative mortality. Levosimendan was found to be associated with a reduction in postoperative mortality (11/235 [4.7%] in the levosimendan group *v* 26/205 [12.7%] in the control, odds ratio of 0.35 [0.18-0.71], *P* for effect as 0.003, *P* for heterogeneity 0.22, and I^2 as 27.4% (440 patients included), cardiac troponin release, and atrial fibrillation. No difference was found in terms of myocardial infarction, acute renal failure, time on mechanical ventilation, intensive care unit, and hospital stay. Calcium-sensitizer for congestive heart failure; Levosimendan has cardioprotective effects that could result in a reduced operative mortality.

Keywords: Meta-analysis, mortality, surgical, operative, organ, dysfunction

Introduction

Multiple organ dysfunction syndrome (MODS) is considered the most devastating sequelae of severe inflammation [1]. This has usually been associated with the Systemic inflammatory response syndrome (SIRS) that is frequently initiated by perioperative stress or traumatic insult. Multiple organ dysfunctions arises as a result of patients surviving an original insult only to be plagued by lethal progression of severe multiple organ dysfunction. This can manifest as sequential system failure, multisystem organ failure, or multiple organ failure [2].

The incidence of MODs in critically ill medical-surgical patients is up to 10% and it is reported that over 90% of patients dying in surgical ICUs have MODS [3]. Multiple organ dysfunction syndrome is implied to be a result of a diffuse inflammatory state initiated by several arms of the body's defense mechanism. The underlying pathophysiologic mechanisms appear to be nonspecific expression during various critical illnesses with complex interactions involving; hypoperfusion of vital organs, an inadequate oxygen supply and demand balance to meet subcellular requirements; adrenergic nervous system activation; excessive or uncontrolled activation of inflammatory mediators and acute phase reactants; cellular reactions with activation of leukocytes, macrophages, lymphocytes, platelets; metabolic derangements and catabolism related to stress [2].

Given the prognosis of established MODS, it is necessary to develop strategies targeted at preventing MODS in high risk patients. During critical care the biphasic character realized for disease, initial insult could be of such magnitude that provokes MODS, or the subsequent acquisition of complications in an otherwise stable ICU patient as a second avenue to MODS. This could be prevented by vigilance and surveillance [4].

In a case management approach with specific reference to levosimendan as anesthetic cardioprotection, literature databases were searched for relevant articles published. Two reviewers independently performed study inclusion and data extraction. Primary outcome measure was taken as in-hospital mortality. Subgroup analyses were performed examining the effect of population- and hospital-based studies, hospital volume and type of surgeon. This metaanalysis suggests that mortality of patients as a result of operative procedure has not changed over the decade.

Materials and methods

Information search

Health Inter Network Initiatives (HINARI)-Health Related Articles, MEDLINE (http://www.PubMed.org) and EMBASE (http://www.EMBASE.com) were searched using appropriately broad Medical Subject Heading and terms for operative and anesthelogical support and critical illness. The MEDLINE terms used to identify the operative and anesthelogical support literature included: intra-operative and immediate postoperative morbidity, mortality associated with anesthesia. These were mapped to the EMTREE terms: intra-operative therapy, length of hospital stay, incidence of post-operative wound infection, post-operative hypothermia. These searches were crossed with the following terms to identify the critical care literature: critical, intensive, intensive care, intensive care unit/s, intensive therapy, critically ill, critical illness, and critical care.

Academic and industry experts were contacted and reference lists of identified systematic reviews and evidence-based guidelines were hand searched. The search was not restricted by language. The search close out date was 2nd October 2011.

Study selection

References obtained from database and literature searches were first independently examined at the title level then abstract by 4 investigators with divergences resolved by consensus and, then, if potentially pertinent, retrieved as complete articles. The following inclusion criteria were used for potentially relevant studies: random allocation to treatment, comparison of severe infections versus sepsis, studies performed on surgical misadventure and information on the primary outcome (mortality).

The exclusion criteria were duplicate publications (in this case, only the article reporting the longest follow-up was abstracted), nonhuman experimental studies, and lack of data on mortality. Two investigators independently assessed compliance to selection criteria and selected studies for the final analysis, with divergences finally resolved by consensus.

Internal validity and risk of bias assessment

The internal validity and risk of bias of included trials were appraised according to the Cochrane Collaboration methods by two independent reviewers with divergences resolved by consensus. All included trials were appraised on the reporting of three key methodological criteria: maintenance of allocation concealment; the use of any form of blinding; and the completeness of patient follow-up [5].

Outcomes

The primary outcomes of interest included mortality, quality of life and physical function [6]. In addition, all cases related to multiple organ dysfunction syndrome (MODS) were eligible for evaluation as secondary outcomes.

Statistical analysis

Analysis was conducted using a fixed effects model [7] with the odds ratio (OR) metric [8]. Due to data sparseness yielding multiple zero-cells, the Peto method was used to calculate the OR metric [9]. The presence of an inconsistent treatment effect between studies (heterogeneity) was assessed using a formal χ^2 test of study × treatment effect interaction [5] and was quantified using the I^2 metric [10]. In the presence of important heterogeneity (heterogeneity $P < 0.10$ or I^2 metric > 50%) [11], stratified analyses were planned to investigate potential sources of heterogeneity [12].

Analysis was conducted using RevMan Version 4.2 for Windows (The Cochrane Collaboration1, Oxford, England, 2003). A two-tailed $P > 0.05$ was accepted to indicate statistical significance while a two-tailed $0.10 > P > 0.05$ but was accepted to indicate a trend towards significance.

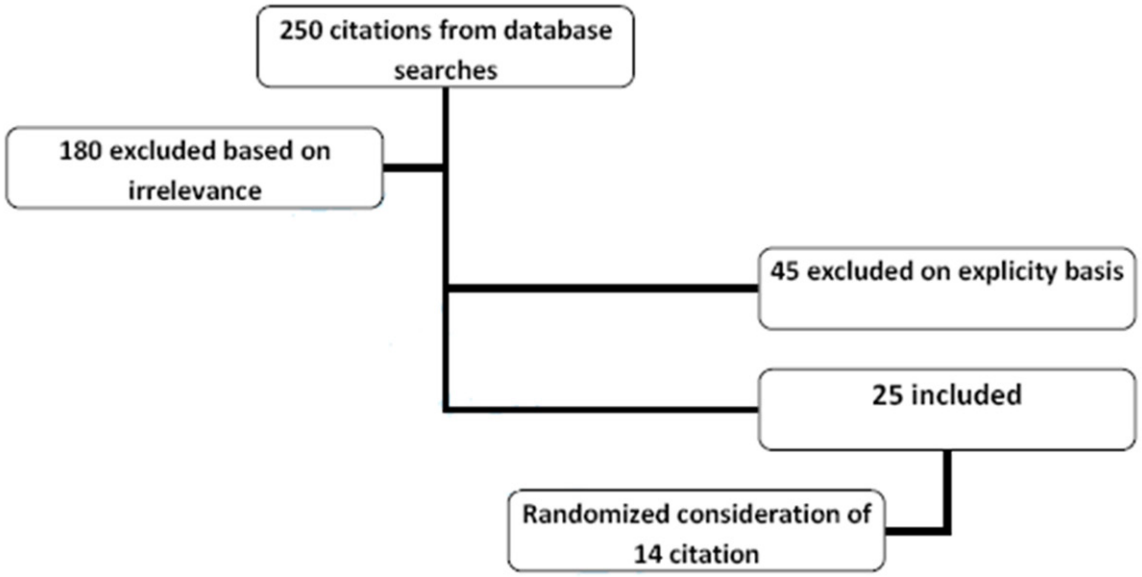

Figure 1. Flow diagram of study selection process.

Table 1. The number of patients and the administrations

Author	Levosimendan group	Control group	Administration	Bolus dose	Infusion dose	Infusion time
Al-Shawarf	18	16	LCOS	12 μg/kg	0.1 μg/kg/min	24 hrs
Alvarez 2005	15	15	LCOS	12 μg/kg	0.2 μg/kg/min	24 hrs
Alvarez 2006	25	25	LCOS	12 μg/kg	0.2 μg/kg/min	24 hrs
Barisin	21	10	Before surgery	24 μg/kg	-	-
De Hert	15	15	After CPB	-	0.1 μg/kg/min	19 hrs
De HErt	40	20	After anesthesia	-	0.1 μg/kg/min	22 hrs
Husedzinovic	12	12	Before surgery	12 μg/kg	-	-
Jarvela	12	12	After induction	-	0.2 μg/kg/min	24 hrs
Levil	69	68	LCOS	10 μg/kg	0.1 μg/kg/min	24 hrs
Tritapepe	12	12	Before CPB	24 μg/kg	-	-

CPB, cardiopulmonary bypass; LCOS, low-cardiac-output syndrome.

To assess the robustness of the underlying assumptions, a sensitivity analysis was conducted including all studies that were identified to be on-topic but were judged to be methodologically 'unsound'.

Results

Database searches, snowballing, and contacts with experts enabled access to the desired total of 250 articles. 180 were exclude as being non-pertinent titles or abstracts therefore out of 250 articles 15 studies were retrieved in complete form and assessed according to the selection criteria (**Figure 1**). Another 45 studies were further excluded because there was no outcome data and further details could not be obtained by the authors [13] or because they were not randomized. The authors identified 14 eligible randomized clinical trials of which 10 were included in the final analysis. The characteristics of studies included in this meta-analysis as shown in **Table 3**.

The cases

The trials randomized 235 patients to levosimendan and 205 to the control (**Table 1**). Eight of these studies [14-20] used levosimendan in cardiac surgery with cardiopulmonary bypass, whereas two [21, 22] used levosimendan during off-pump coronary artery bypass graft surgery. In the other seven it was administered as a bolus, [15, 18-23] and [15] used as a continuous infusion [14-18, 20, 23]. Four of which after a bolus [15, 18, 20, 23].

The dose administered was 10-24 μg/kg (intravenous bolus) or 0.1-0.2 μg/kg/min (continu-

Table 2. Bias assessment

Author	Adequate sequence generation	Concealliment allocation used	Blinding	Similar concurrent therapy	Uniform outcome	Risk of Bias
Al-Shawarf	Unclear	Yes	No	Yes	No	Moderate
Alvarez 2005	Unclear	Unclear	No	Yes	No	High
Alvarez 2006	Unclear	Unclear	No	Yes	No	High
Barisin	Yes	Yes	Yes	Yes	No	Low
De Hert	Yes	Yes	Yes	Yes	Yes	Moderate
De HErt	Yes	Yes	Yes	Yes	Yes	Low
Husedzinovic	No	Yes	Yes	Yes	No	High
Jarvela	Yes	Yes	Yes	Yes	No	Low
Levil	Yes	Unclear	No	Yes	Yes	Moderate
Tritapepe	Yes	Unclear	Yes	Yes	No	Moderate

Table 3. Characteristics of studies included in this meta-analysis

First author	Year	Country	Ethnicity
De Hert [14]	2008	UK	European
Jarvela [15]	2008	Finland	European
Levin [16]	2008	Spanish	European
Missant [17]	2007	Belgium	European
Alvarez [18]	2006	Spanish	European
du Toit [19]	2001	South Africa	South African
Hung [20]	1975	China	Asian
De Hert [21]	2007	Belgium	European
Tritapepe [22]	2006	Italy	European
Shah [23]	2014	India	Indian

ous infusion). The control was a placebo in the four studies, [14, 19, 21, 22]; dobutamine in three cases, [14, 15, 23] and milrinone in the other three [11, 17, 20] multicentric was just a single case [24].

Multiple organ dysfunction syndrome (MODS)

One of the included cases reported the incidence and severity (number of failed organs per patient) of MODS [25]. There was no significant difference in the incidence of MODS however severity of MODS demonstrated a trend towards fewer failed organ systems in patients receiving levosimendan.

A study quality appraisal showed that most studies appeared not of optimal quality, given the lack of common details on the method used for randomized sequence generation and allocation (**Table 2**). Just a few trials were of high quality, others lacked details to appraise the performance, or detection biases.

Statistical analysis

The use of levosimendan was noted to be associated with a significant reduction in operative mortality reaching 15/250 [4.7%] in the levosimendan group as compared to 26/205 [12.7%] in the control OR = 0.35 [0.18-0.71], P for effect was 0.003, and p for heterogeneity 0.22, and I^2 of 27.4% with 440 patients included) (**Figure 2**). In the levosimendan group, there was also a significant reduction in the rate of atrial fibrillation (40/175 [22.9%] in the levosimendan group against 59/156 [31.4%] in the control group, OR = 0.48 [0.29-0.78], P for effect as 0.003, while p for heterogeneity as 0.80, I^2 of 0% with 331 patients included) (**Figure 3**). Similarly in the rate of myocardial infarction (2/183 [1.1%] in the levosimendan group and 9/153 [5.9%] in the control group, OR = 0.26 [0.07-0.97], P for effect as 0.04, P for heterogeneity 0.20, and I^2 = 38.5% with 336 patients included) (**Figure 4**) and in the rate of acute renal failure: 8 of 119 [6.7%] patients in the levosimendan group and in 26 of 109 [23.9%] patients in the control arm (OR = 0.26 [0.12-0.60], P for effect of 0.002, P for heterogeneity as 0.23, and I^2 32.1% with 228 patients included) (**Figure 5**).

Subgroup analyses confirmed the reduction in the rate of mortality within the following groups: patients undergoing cardiac surgery with cardiopulmonary bypass (11/202 [5.4%] in the levosimendan group against 26/183 [14.2%] in the control group, OR = 0.38 [0.19-0.76], P for effect was 0.007, P for heterogeneity 0.37, and I^2 as 7.1% with 385 patients included), and patients receiving both an intravenous bolus and a continuous infusion of levosimendan

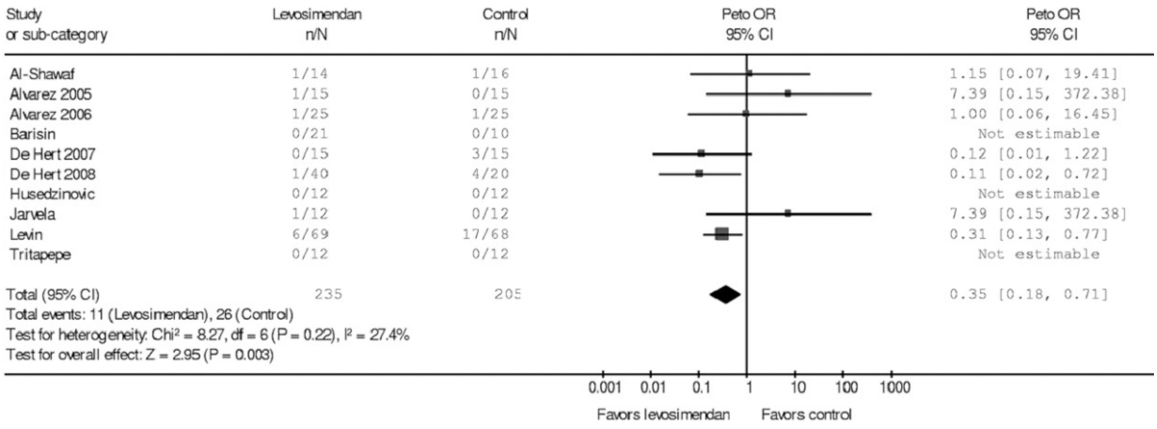

Figure 2. Forest plot for the risk of in-hospital mortality comparing levosimendan versus control. CI, confidence intervals; df, degrees of freedom; OR, odds ratio pooled estimates of postoperative mortality.

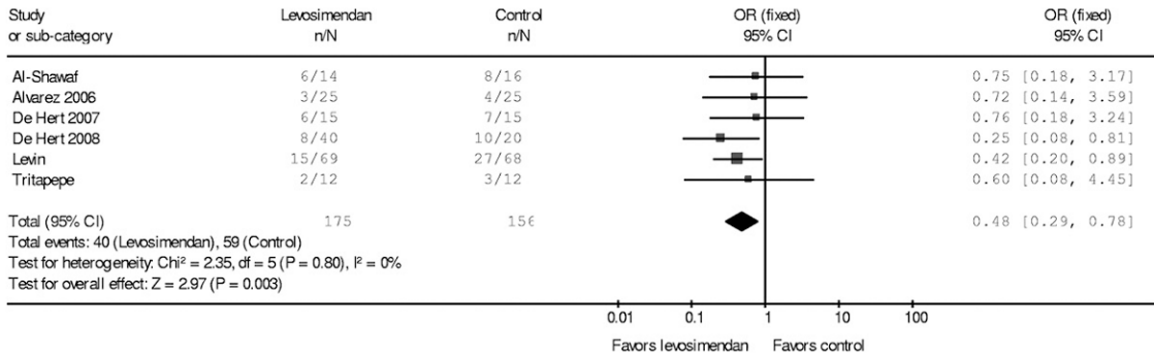

Figure 3. Forest plot for the risk of postoperative atrial fibrillation comparing levosimendan versus control. CI, confidence intervals; df, degrees of freedom; OR, odds ratio pooled estimates of postoperative mortality.

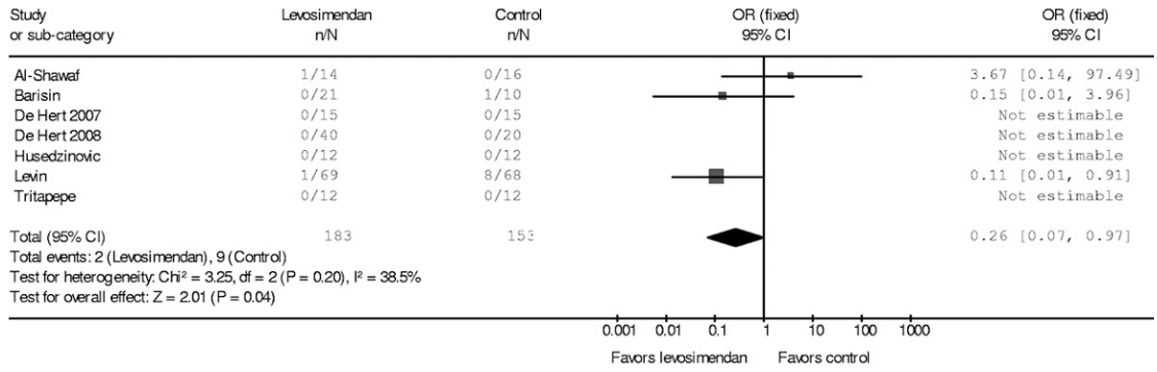

Figure 4. Forest plot for the risk of postoperative myocardial infarction comparing levosimendan versus control. CI, confidence intervals; df, degrees of freedom; OR, odds ratio pooled estimates of postoperative mortality.

(9/123 [7.3%] in the levosimendan group v 19/124 [15.3%] in the control group, OR = 0.44 [0.19-1.00], P for effect = 0.05, P for heterogeneity 0.41, with I^2 of 0% with 247 patients included).

From the quantitative data therefore levosimendan was shown to be effective in reducing mortality as compared to dobutamine (8/109 [7.3%] in the levosimendan group while 18/108 [16.7%] in patients receiving dobutamine, OR =

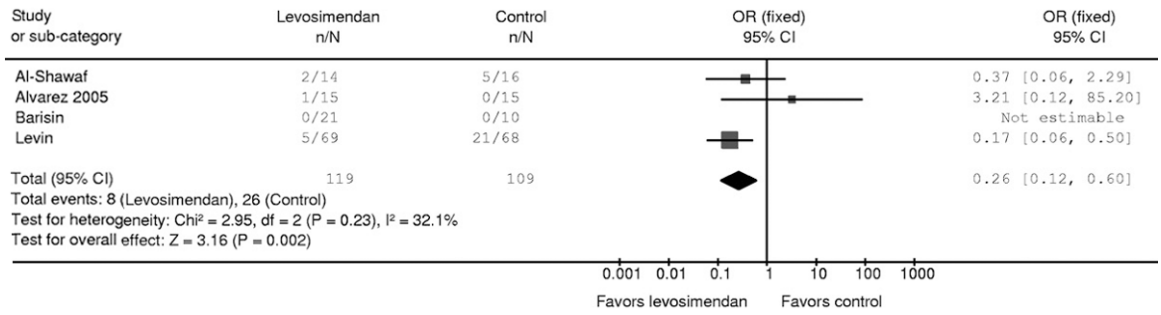

Figure 5. Forest plot for the risk of postoperative acute renal failure comparing levosimendan versus control. CI, confidence intervals; df, degrees of freedom; OR, odds ratio pooled estimates of postoperative mortality.

0.40 [0.17-0.96], p for effect as 0.04, P for heterogeneity 0.30, and I^2 of 16.2% with 217 patients included) or milrinone (2/69 [%] in the levosimendan group vrs 8/51 [%] in patients receiving milrinone, OR = 0.20 [0.05-0.86], P for effect of 0.03, P for heterogeneity as 0.39 and I^2 of 0% with 120 patients included). However there was no significant reduction in mortality when levosimendan was administered in patients undergoing off-pump coronary artery bypass graft surgery when patients received either a single bolus or a continuous infusion and when levosimendan was compared with placebo. This could be attributed to the small number of studies included in the subanalysis.

Discussions

In the meta-analysis it was mainly observed that operative use of levosimendan is associated with a reduction in multiple organ dysfunction syndrome and hence postoperative mortality after cardiac surgery. The most interesting subset, studied by the authors, was the use of levosimendan in patients with operative low-cardiac- output syndrome. Levin's group, [9] described in particular, the use of levosimendan in up to 69 patients compared with 68 controls (dobutamine). The authors observed a reduction in postoperative mortality, a lower incidence of major operative complications, and a reduction in the length of hospital stay for patients receiving levosimendan. The high mortality rate observed in the studies in this meta-analysis is justified by the high-risk profile which shown in **Table 1**.

In a previous meta-analysis [26] that involved up to 139 patients of which 74 received levosimendan while 65 receiving the control, no statistically significant difference in mortality was reported, but there was significant reductions in cardiac troponin peak release and in the time patients were hospitalized. The authors therefore suggested that further randomized controlled experience was necessary to confirm the clinical advantages of levosimendan.

In the group of organ dysfunction rescue drugs, levosimendan is usually applied the management of acutely decompensated congestive heart failure as a calcium sensitizer that increases cardiac contractility without rising intracellular calcium. It exerts the positive inotropic effects by binding to cardiac troponin C in a calcium dependent manner, sensitizing myofilaments to calcium.

Levosimendan was reported to increase cardiac output while lowering cardiac filling pressures and was associated with the reduction of cardiac symptoms, risk of death, and hospitalization. Missant's group [17] showed in an experimental model of acute post ischemic right ventricular dysfunction, that levosimendan exerted a positive inotropic effect increasing right ventricular contractility and reduced right ventricular after load. This resulted in an improvement of hemodynamics and optimized right ventriculovascular coupling. In other cases such as patients with acute decompensation of chronic heart failure, conflicting results with regard to outcome benefit have been reported [17, 27]. Unlike other positive inotropic agents, the primary actions of levosimendan are independent of interactions with ß-adrenergic receptors. Follath [27] evidenced a higher number of patients with hemodynamic improvement illustrated as an increase of 30%

and above in cardiac output but a decrease of 25% or more pulmonary capillary wedge pressure. This was in 24 hours in the group of patients with severe, low-output heart failure receiving levosimendan when compared with those receiving dobutamine with a reduction of 180-day mortality: 26% in the levosimendan group versus 38% in the dobutamine group (P = 0.029).

In another case study [28] 1,327 patients with acute decompensated heart failure were randomized with 664 patients receiving levosimendan while 663 patients dobutamine. The primary endpoint of the study was all-cause mortality during the 180 days after randomization. There were 173 deaths (26%) in the levosimendan group and 185 deaths (28%) in the dobutamine group (hazard ratio = 0.91; 95% CI, 0.74-1.13; P = 0.40). No significant statistical differences between patients receiving levosimendan and those receiving dobutamine was noted, also for all-cause mortality at 31 days, number of days alive and out of the hospital, patient global assessment, patient assessment of dyspnea at 24 hours, and cardiovascular mortality at 180 days. Based on this therefore it could be concluded that levosimendan did not significantly reduce mortality or affect any relevant clinical outcomes.

Levosimendan was also compared with placebo in the REVIVE-II study [29] that comprised 600 patients admitted to the hospital with a diagnosis of heart failure and left ventricular ejection fraction of less than 35% if they remained breathless at rest after use of diuretics and vasodilators. Plasma concentrations of brain natriuretic peptide decreased by about 250 pg/mL, and the duration of hospitalization was shortened by about 2 days (P = 0.0001) in patients receiving levosimendan, but this was not accompanied by a reduction in mortality. By 90 days, 35 deaths were recorded in the placebo group and 45 in the levosimendan group. There were more reports of hypotension (50% v 36%) and atrial fibrillation (8% v 2%) in the levosimendan group compared with the placebo group.

Interesting in the results of this meta-analysis is the view that negative effects on outcome are documented when other inotropic drugs were studied. Common inotropic agents were in fact associated with an increased risk of cardiovascular events and mortality. For instant the use of intravenous inotropic agents compared with placebo are or an active agent in patients with heart failure systematically reviewed previously [30]; whereby in 21 trials that included 632 patients receiving intravenous inotropic drugs were identified. Drugs of the various classes were but this did not reach significance and data was insufficient to determine whether symptoms improved.

Conclusion

There was little evidence that intravenous inotropic agents acting through the adrenergic pathway could improve symptoms or patient outcomes and that they might not be safe. As Fellahi [30], in their propensity-adjusted analysis to assess the consequences of catecholamines on clinical outcome (major cardiac morbidity, defined as ventricular arrhythmias, use of an intra-aortic balloon pump, and postoperative myocardial infarction, and all-cause intrahospital mortality). Up to 84 of the 657 included patients receiving catecholamines (dobutamine). A higher incidence of both major cardiac morbidity (30% vs 9%, OR = 4.2 [2.5-7.3], P ≥ 0.001) and all-cause intrahospital mortality (7/84 [8%] vs 4/573 [1%], OR = 12.9 [3.7-45.2], P ≥ 0.001) was observed in the catecholamine group compared with the control group. Just as the propensity score matched subgroup analysis did not identify a significant association between catecholamines and in-hospital mortality (adjusted OR = 2.0 [0.1-32.0], P ≥ 0.63), the authors concluded that catecholamines should only be administered but when the benefit is judged to outweigh the risks.

Disclosure of conflict of interest

None.

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