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Levosimendan and Body Protection Updates

Gallego Molina, Loras Borraz P, Guerrero-Orriach Jose L*, Ramirez-Fernandez A, Ramirez Aliaga M, Rodriguez-Capitán MJ , Bermudez L, Biteri A, Raigon A, Baena M, Rubio, Navarro M and Cruz Manas J

Department of Anaesthesia, Hospital Virgen de la Victoria, Málaga, Spain

***Corresponding author:** Jose Luis Guerrero Orriach, Department of Anaesthesia, Hospital Virgen de la Victoria, Málaga, Spain, Tel: 0034951032051; E-mail: guerreroorriach@terra.com

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Introduction

Levosimendan, a pyridazinone-dinitrile derivative, is a widely known drug and has an known role in the context of severe low output syndrome (LCOS) as well as at right ventricular failure. It has demonstrated its advantages over drugs that often have been used in such cases as dobutamine or los phosphodiesterase III inhibitors. In addition to its properties as inotropic drug, derived from its use, energy and neurohormonal changes were detected which confer it body protective properties [1]. Our goal has been to review the role of this new drug as an inodilator and body protector.

Mechanism of action

Levosimendan, as an {[4-(1,4,5,6-tetrahydro-4-methyl-6-oxo-3-pyridazinyl) phenyl] hydrazono} propanedinitrile enantiomer, owes its protective effect to its action at different levels in the cardiovascular system, not only on the ATP-sensitive K channels. It has short-term effects, which correlate with plasma drug levels, although there has been a long-term significant decrease in mortality which evidences that its cardiovascular effects do not correspond only with the average life term of the drug, which is only 1 hour, being responsible for its beneficial prolonged effects (2-5 instead) metabolites as OR-1896 and the (-) acetamidem ofN- [4- (1,4,5,6-tetrahydro-4-methyl-6-oxo-3-pyridazinyl) phenyl] enantiomer, whose half-life is 75-80 hours [2-5]. The effects of this drug depend on the type and diameter of the vessel, being them more striking at coronary microcirculation level than at skeletal muscle level arteries [6].

The mechanism of action of Levosimendan is complex and includes the following targets:

It acts as myocardial cell calcium sensitizer due to the binding of its stereoselective manner to troponin C in its N-terminal (NTNC) [7-9]. The N-terminal domain of the TnC is responsible for regulating calcium-dependent contraction. Troponin interacts with troponin I (TnI), the inhibitory subunit, and this interaction is modulated by calcium binding so that the binding of calcium to the TnC separates the TnI and promotes contraction [10]. Levosimendan stabilizes the calcium binding to troponin C, allowing a longer interaction between TNC and TnI, and improving the responsiveness of myofilaments to calcium without increasing its cytoplasmic levels, thus resulting a more efficient contraction [11]. This effect is dose-dependent and produces an improved contractility, stroke volume and cardiac output without inducing an increased risk of arrhythmias or increased levels of ATP or oxygen consumption [12]. It also reduces myocardial stunning and does not prolong myocardial relaxation [13,14], even when Levosimendan has shown a positive lusotropic effect by reducing the isovolumetric relaxation and improving LV filling, which makes it convenient in cases of both systolic and diastolic dysfunction because of its lusotrope and inodilator effects.

In addition to this the decreased preload and afterload which follow the administration of Levosimendan is due to the activation and opening of potassium channels at smooth muscles of arterial and peripheral venous vessels level, and also of the coronary and cerebral ones after a period of anoxia [15], improving the oxygen delivery to myocytes. Experimental studies revealed the attenuation effect of Levosimendan in the presence of K ATP dependent channel blockers on low resistance vessels, which highlights one of its main targets [16,17] even when it also produces its effect at the voltage-dependent K and calciumdependents channels at large conductance vessels level [18]. Their vasodilatory mechanism is based on a flow of K + with a consequent hyperpolarization of the cell by reducing cell excitability and lowering intracellular calcium by decreasing the probability of L-type calcium channel opening and Na/Ca 2+ stimulation [10,19]. It is speculated that OR-1896, which is one of the metabolites of Levosimendan, acts at the level of KATP dependent channels and level K-dependent channel calcium (BKCa) [20]. It has been observed in porcine endothelial cells that Levosimendan results in nitric oxide production through the activation of endothelial nitric oxide synthase (eNOS) through the opening of K ATP mitochondrial dependent channels, with its consequent vasodilator effects [21].

Another known mechanism of Levosimendan and its OR-1896 metabolite is a selective inhibition of phosphodiesterase (PDE) III. According to previous studies PDE III and PDE IV provide the only route to degrade cAMP in cells and hence regulate intracellular cAMP gradients, and seems to be responsible for the modulation of the amplitude and duration of response of the cAMP Beta agonists [22,23]. It has been discussed whether Levosimendan acts through the cAMP signaling pathways. It has been shown that the affinity of the cAMP PDE III is superior to other isoforms and is responsible for the maintenance of basal levels of cAMP [24]. The PDE III inhibition however produces a smaller cAMP increase which is transient, unlike other isoforms, and this suggests that its inhibition probably induces an activation of PDE IV mediated by PKA and therefore cAMP decreased levels [25-27]. Several studies have shown that to produce a significant increase in intracellular cAMP and also inotropic effects it is required an inhibition of both PDE III and PDE IV isoforms, and that the sole inhibition of PDE III does not lead to significant increases in cAMP [28]. Levosimendan however does not act at other isoenzymes level but only on PDE III at therapeutic concentrations, and therefore this inhibition is insufficient to explain the positive inotropic effect. The inotropic effects of Levosimendan are reached at lower concentrations than the ones required for inhibition of PDE IV, suggesting that inhibition of this enzyme and therefore CAMP elevation are not prerequisites for positive inotropic effect [29].

Compared to milrinone, Levosimendan performs this effect without altering the energy balance of the cardiac cell [30].

The action of Levosimendan on mitochondrial ATP dependent K channels play an important role because of its cardioprotective effect and myocardial ischemic preconditioning. This is reflected as a reduction in infarct size, a decreased myocardial stunning and arrhythmia incidences and an increased volume of the mitochondrial matrix [31]. This cardioprotective effect was demonstrated by Du Toi et al. in hearts of Guinea pig, noting that myocardial recovery after episodes of ischemia reperfusion was better with Levosimendan than with dobutamine due to K ATP mitochondrial dependent channels, since this effect disappeared with K channel blockers [32].

Body Protection

In the management of acute heart failure the goal of treatment is not focused only towards the correction of hemodynamic disorders and symptomatic improvement, being also directed towards the body protection, counteracting cardiac remodeling and extracardiac disorders resulting from this scheme [33]. Myocardial dysfunction occurs in this situation involving an acute myocardial damage, with consequent remodeling and both systemic and pulmonary circulatory dysfunction. In this context Levosimendan has proved to have protective effects on different organs.

The cardioprotective effect of Levosimendan is multifactorial and primarily due to a decrease in preload and afterload, improving cardiac work. It has been found that Levosimendan produces an improvement in both systolic and diastolic function, unlike other calcium-sensitizing drugs that can worsen myocardial relaxation and elevate diastolic pressure during heart failure [34]. The effects are even more pronounced at high frequencies and under predominantly diastolic dysfunction [35], and occur without a substantial increase in oxygen consumption [36]. Furthermore, this drug increases coronary blood flow and perfusion of cardiac cells [37].

In addition to that, Levosimendan has anti-ischemic effects, reducing the infarcted area, and it has been shown in literature as a cardioprotective drug during situations of myocardial ischemia-reperfusion [38]. It has also been shown that a decrease of the extubation time and minor myocardial damage, inotropic requirement and ICU stay occurs after performing pre- or postoperatively administered coronary artery bypass [39]. Schwarte et al. observed in canine models that cardiac output in situations of hypoxemia in patients pre-treated with Levosimendan was significantly higher than without the drug, and that this happened without an increase in oxygen consumption or any worsening of anaerobiosis markers (pH, base excess and lactate), or gastric mucosa microvasculature oxygenation [40]. Levosimendan has furthermore proved to be effective during weaning patient in extracorporeal circulation due to improved endothelial function, hemodynamics and its inotropic and lusotropo effect [41,42] and has been associated with increased and premature correction of altered hemodynamic parameters, a lower requirement for inotropic or vasopressor support, shorter need for balloon counterpulsation use and less time spent in intensive care in patients with postoperative LCOS after coronary surgery with CPB [43]. Administered preoperatively in patients with severe left ventricular dysfunction, it was detected a lower mortality during postoperative LCOS situations even in patients with severe left ventricular dysfunction [44].

In animal studies it was observed that the effect of Levosimendan mimics ischemic preconditioning and improves cell function and cell viability through the opening of ATP dependent K channels [45,46]. Zangrillo et al. showed in a meta-analysis a decrease in the numbers of troponin C at discharge from hospital, demonstrating its cardioprotective effect and preserving cardiac function and overall tissue perfusion [47].

Levosimendan also plays an important role in situations of myocardial failure in septic patients. Sepsis has a number of systemic disorders, among which is found a decrease in myocardial contractility and complianza. Sepsis situation furthermore promotes a lower response to B-adrenergic [48-54] and calcium desensitization [52,55-59] due to a dysfunction of this type of receptors, which means a drawback. Morelli et al. suggest in their study that Levosimendan produces beneficial effects at the level of systemic and regional circulation in patients with septic shock with myocardial dysfunction against increasing doses of dobutamine [60]. In septic patients presenting adult respiratory distress syndrome (ARDS) is observed an increase in pulmonary vascular resistance and right ventricular overload. Levosimendan in these patients reduces systolic right ventricular overload, which appears evidenced by a decrease in pulmonary artery pressure medium, pulmonary vascular resistance index and gradient PAD-PAOP (diastolic pressure of the artery pressure pulmonar- pulmonary artery occlusion) in association with an increase in ejection fraction and right ventricular cardiac index [61].

Levosimendan has demonstrated anti-inflammatory and anti-apoptotic effects. Meng Jian-biao et al. have shown that Levosimendan decreases biomarkers plasma levels of myocardial damage in patients in septic shock [62,63]. Anti arrhythmogenic properties are also assigned as a result of its anti-inflammatory effect, with a lower incidence and higher resolution of episodes of atrial fibrillation in patients after cardiac surgery [64]. It reduces levels of proinflammatory cytokines such as IL-6 and TNF-α which are responsible for heart failure, apoptosis of cardiomyocytes and LV remodeling [65] intervening in the vicious circle of hemodynamic dysfunction and neuroendocrita at heart failure.

Levosimendan has also shown to have body protective effects against damages in hypoxia. The presence of renal dysfunction is a common finding in postoperative patients undergoing cardiac surgery and is associated with prolonged hospitalization and increased mortality [66,67]. The presence of right ventricular dysfunction and pulmonary hypertension with elevated creatinine levels and decreased urine output is an independent predictor of mortality, worsening prognosis [68,69]. In these patients the administration of Levosimendan has shown a decrease in the diameter of the tricuspid annulus and pulmonary pressures and consequently a decrease in renal venous pressure that could improve kidney function as central venous pressure is an independent predictor factor of glomerular filtration rate in patients with heart failure [70,71]. To the above said is also added a vasodilator effect mediated by ATP-dependent K channels which also improves renal perfusion. Antioxidants and antiapoptotic effects of this drug may also have a role in renal ischemia reperfusion injury in renal function improvement [72]. It has been observed that decreasing action of angiotensin-2 in kidney results in an increase in glomerular area surface which would improve renal perfusion [73].

Neurologic complications after cardiac surgery are a major cause of morbidity and mortality rates, presenting cognitive impairment to 83% of patients.

At neuronal level, Levosimendan has demonstrated neuroprotective effects in the spinal column, with better neurological outcome, administered during or after the period of ischemia, which has its involvement in patients who are undergoing aortic clamp [74]. Enolase values, as a marker of neurologic damage, usually rises in the immediate postoperative period in patients undergoing aortic clamping. Levosimendan has proved to present a neuroprotective effect, since this marker levels were unchanged in patients undergoing interventions under risk of neurological dysfunction, preserving neuronal tissue [70]. The neuroprotective effect may be mediated through the mitochondrial K ATP channels due to its protective effect of ischemia-reperfusion. Finally, at splanchnic level Levosimendan has proved to improve oxygenation of the gastrointestinal mucosa decreasing the ischemia by increased blood flow at liver and intestine [75].

Pharmacokinetics

The pharmacokinetic characteristics of Levosimendan allow a fast distribution (distribution volume 0.2 L/kg) and reach a steady state after 4 hours of continuous infusion (linear pharmacokinetics at doses of 0.05-0.2 mcg/kg/min). It binds to plasma proteins almost entirely (97-98%), mainly to albumin.

It has a clearance of about 3 mL/min/kg, with an average life term of about one hour. It is completely metabolized and excreted in urine and feces; the main route is by conjugation with glutathione to form inactive metabolites.

The minor route, approximately a 5% of the drug in the intestine, is reduced to an intermediate, active metabolite called OR-1855, which is subsequently acetylated to the active metabolite OR-1896. The formation of these metabolites is slow, reaching peak plasma concentrations within 24-48 hours after administration of Levosimendan continuous infusion for 24 hours. The average life term of both OR-1896 and OR-1855 is about 80 hours. As already mentioned, the cardiovascular effects of the drug are maintained for 7-9 days after administration [76].

OR 1896 can be found in plasma at cardiac surgery patients, but its formation is slower compared with heart failure patients [77].

Peak levels were observed 5-6 days after Simdax. The data refer patients with an ejection fraction <30% candidates for elective cardiac surgery have a longer effect on stroke volume index [78].

Population analysis have shown that neither age nor race nor sex influence the pharmacokinetics of Levosimendan.

Levosimendan is an intravenous drug. It should be started with a dose of 6-12 mcg/kg/min for 10 minutes and continue with continuous infusions of 0.05-0.2 mcg/kg/min for 24 hours, adjusting the infusion rate to the answer, as hypotension or tachycardia may occur due to the caused vasodilation. The guidelines of the European Society of Cardiology do not recommend the use of Levosimendan bolus if the systolic pressure is below 100 mmHg and recommend the use of norepinephrine to treat the resulting hypotension once the intravascular volume has been optimized [79]. Dosage should however be tailored according to the clinical situation.

There were not observed any signs of tolerance or rebound effect developement after discontinuation of the drug.

Pharmacokinetics of Levosimendan are similar in healthy subjects and in patients with renal mild to moderate insufficiency, although it seems to prolong the life term of its metabolite OR-1896. Regarding hepatic impairment, the elimination of Levosimendan is slightly reduced in patients with mild hepatic impairment due to cirrhosis. It has not been assessed the effects in moderate to severe impairment nor its effects on OR-1896.

Treatment with Levosimendan

Heart failure

The first published clinical studies (LIDO and RUSSLAN) were designed to demonstrate the superiority of Levosimendan compared to dobutamine in the treatment of acute heart failure (AHF). Based on these data, they make Levosimendan the inotropic drug of choice in patients with AHF and signs of peripheral hypoperfusion.

- LIDO, 203 patients randomized double-blind study, whose inclusion criteria were: severe heart failure associated with low cardiac output (EF <0.35, cardiac index <2.5 L/min/m^2, pulmonary capillary wedge pressure (PCWP)>15 mmHg and in need of inotropic support [80].

Percentage of patients with increased cardiac >30% decrease in spending and simultaneously PCWP ≥ 25% after 24 hours was 28% with Levosimendan *vs* 15% with dobutamine p<0.03.

It was done a mortality monitoring as a secondary criterion for evaluation for 31 days, in which the group assigned to Levosimendan died an 8% compared to 17% of patients who died with DBT.

- RUSSLAN, double-blind randomized placebo-controlled trial with 504 patients with acute myocardial infarction complicated with left ventricular failure, in need of inotropic support. Mortality was prospectively followed for 14 days after starting treatment. Mortality was 12% in patients treated with Levosimendan and 20% in those treated with placebo [81].

New trials came later:

- CASINO, a study evaluating the effectiveness of Levosimendan vs dobutamine vs placebo in patients with acute decompensated HF with LVEF <35%. It was stopped prematurely, evaluating mortality at 6 months (18% Levosimendan vs. 28.3% placebo vs 42% DBT) [82].

- REVIVE-1, a placebo-controlled pilot study in 100 patients (Revive 1) with acute decompensated HF double-blind study was conducted, which showed improved symptoms and decreased pro-BNP in the Levosimendan group, in addition to reducing mortality in a subgroup analyzed after 30 days in Levosimendan treated patients [83].

- REVIVE 2, 600 patients randomized double-blind placebo-inclusion criteria for acute decompensated HF, LVEF <35% in the 12 months before and NYHA IV. All treatments except basal IV milrinone were allowed. The results confirmed those of revives 1 in a larger sample [84].

- BNP values have proven to be strong predictors of later outcomes in patients ICAD admitted. There is also a clear relationship between mortality and BNP levels in patients with HF. It has also studied the association between Levosimendan and decreased levels of BNP, being related to clinical improvement after six months [85].

- SURVIVE, a study involving 1327 patients with acute HF decompensation requiring additional treatments after an inadequate response to IV diuretics or vasodilators. Randomized double blind to

receive Levosimendan vs dobutamine for at least 24 h. Used as main variable the all-cause mortality at 180 days, but no statistically significant differences were observed. However an analyzed subgroup showed a significant reduction in mortality in patients with a history of HF in the Levosimendan group, with a net profit of 19 deaths less in a month [86].

- Meta-analysis of Landoni et al. It includes 45 clinical trials with iv Levosimendan in a total of 5480 patients (of which 2915 got Levosimendan). They should be randomized controlled trials of which were excluded those without mortality data. 23 studies used Levosimendan in a cardiologic setting, while 17 they were used in cardiac surgery [87].

From 23 performed studies of the environment cardiology it has been determined that Levosimendan significantly reduced mortality in this population compared with the control group (20% *vs* 25.6%, respectively).

The survival benefit contrasts with previous results with conventional inotropic, which has shown a slightly detrimental effect. Levosimendan is the first inotropic agent that appears to improve survival in patients with acute heart failure. In the Alarm- HF trial was compared the effect of intravenous main drugs administered during the first 48 h in patients with severe heart failure in hospital mortality. The pairing according to propensity score showed that Levosimendan resulted in a significant reduction in the risk of hospital mortality [88].

In the European Cardiology Society (ESC) Guide for the treatment of acute and chronic heart failure, Levosimendan appears with a IIb grade of recommendation and B level of evidence. Due to its mechanism of action Levosimendan infusion in patients with acute decompensation increases cardiac output and stroke volume and reduces pulmonary wedge pressure and pulmonary vascular and systemic resistance. It can also be effective in chronic decompensated HF, since its inotropic effect is independent of the beta-adrenergic stimulation is an alternative for patients treated with beta blockers. The treatment is associated with a slight increase of heart rate and blood pressure reduction, especially when a loading dose is administered (not recommended loading dose if Pas <100 mmHg) [89,90].

In a recent meta-analysis of 5349 patients Levosimendan is compared with dobutamine with placebo in the treatment of decompensated heart failure. The results showed a statistically significant reduction in mortality in the Levosimendan group, but was associated with more adverse effects (hypotension, premature or migraine).

Levosimendan at Cardiac Surgery

The optimal perioperative use of inotropic and vasopressor in cardiac surgery remains controversial, but more international studies are still needed. Because of its cardioprotective effects Levosimendan is a promising drug and so far available studies suggest its superiority over traditional inotropic agents (dobutamine, PDE), as it protects the myocardium and improves tissue perfusion, while minimizing tissue damage during cardiac surgery and reperfusion periods.

In a meta-analysis of Landoni et al. 440 patients undergoing cardiac surgery, Levosimendan showed a statistically significant lower mortality than control patients. It was also shown a lower frequency of acute myocardial infarction, atrial fibrillation and acute renal failure in patients treated with Levosimendan [91].

Maharaj and Metaxa [92] performed later a similar meta-analysis with 729 patients from 17 studies. Levosimendan was associated with a reduction in mortality after coronary revascularization, and also had a favorable effect on the IC, the length of ICU stay, reductions in the rate of atrial fibrillation and levels of troponin I [92].

Left Ventricular Dysfunction

Left ventricular dysfunction has been recognized as the major risk factor for making a low cardiac output syndrome [93,94]. The use of inotropic agents in the perioperative and postoperative has also been linked to increased mortality and increased postoperative morbidity [95].

In the meta-analysis of Harrison et al. selecting 14 randomized trials, they conclude that cardiac surgery patients with a reduced ejection fraction who previously received Levosimendan had a lower mortality and lower incidence of renal dysfunction, atrial fibrillation and myocardial damage than patients not treated with Levosimendan [96].

Data suggest that the onset of Levosimendan should rather be done early (pre-operative) than tardive (postoperative), although both options have proven to have positive effects. Levin et al. [43] and Leppikangas et al. [44] both administered Levosimendan 24 hours before surgery.

Postoperative

Levin et al. [45] conducted a randomized open study on heart surgery patients who developed low cardiac output (LCOS) syndrome in the postoperative. It started using Levosimendan or dobutamine. LCOS is considered within 6 h after surgery with the following criteria: PCP>16 mmHg, IC <2.2 l/min/m^2 and mixed venous Sat <60%. 1004 surgeries were evaluated. The results were statistically significant in favor of Levosimendan in a smaller number of perioperative myocardial infarctions, chronic renal failure, ventricular arrhythmias, prolonged assisted ventilation and sepsis in this group. Also mortality and length of ICU stay were significantly lower in patients treated with Levosimendan. The drug also showed a superior effect on cardiac index and mixed venous sat, less need for additional inotropic drug, a vasopressor need or need of BCIA [43].

Lilleberg in his double-blind, randomized study with placebe, examined the effects of the administration of Levosimendan early after bypass surgery (8 mcg dose/kg or 24 mcg/kg) at hemodynamic parameters, coronary flow and myocardial. It was found that the heart rate increased significantly after the higher dose, cardiac output was significantly increased after both doses, and pulmonary and systemic resistance decreased significantly while increasing coronary flow [97,98].

Lahtinen et al. [99] demonstrated that treatment with Levosimendan decreases the incidence of heart failure after valve surgery or vascular surgery combination and coronary revascularization. Levosimendan was administered by bolus 24 mcg/kg and then 24 hours continuous infusion, or placebo after induction of anesthesia. Levosimendan reduced the incidence of heart failure, but was associated with more hypotension and use of vasopressors postoperatively.

Jorgensen et al. studied the possible effect of Levosimendanen lusitropic patients with left ventricular hypertrophy after aortic valve replacement surgery for stenosis [99].

Gandhan compared the use of Levosimendan (0.1 mcg/kg/min) with dobutamine (5 mcg/kg/min) in patients undergoing mitral valve replacement surgery for severe mitral stenosis. They observed a statistically significant increase in cardiac index after 12 h. Increased vasodilation and lower inotropic effect with Levosimendan, which required greater use of vasopressors and inotropes [100].

Preoperative

Tritapepe et al. [39] conducted a randomized, double-blind, placebo-controlled study in 106 patients undergoing coronary artery bypass graft (CABG) elective multivessel. Levosimendan was administered as a single bolus (24 mcg/kg for 10 minutes) or placebo before starting the DCP. They got significative higher postoperative values of TAM, IC and rate of cardiac output and lower SVR in the Levosimendan group. Furthermore troponin increases were significantly lower. The need for inotropic agents, assisted ventilation time and length of stay den ICU were higher in the placebo group [39].

Levin et al. [44] studied 253 patients of coronary artery bypass and ejection fraction <25% randomized into 2 groups, one group was given Levosimendan and the other placebo, preoperatively. They concluded that preoperative use of Levosimendan reduced postoperative mortality, the development of low output syndrome, the need for inotropic and vasoactive support and the use of IABC. No significant differences appeared in preoperative infusion regarding adverse effects [44].

Dogan et al. [101] in its pilot study studied the occurrence of atrial fibrillation after coronary artery bypass surgery. Levosimendan vs. placebo administration begins 6 hours before surgery (24 mcg/kg), is maintained until the bypass starts and restarts at the overheating of the patient. It was observed that the occurrence of atrial fibrillation was lower in the Levosimendan group with left ventricular dysfunction [101].

Leppikangas studied the preoperative use of Levosimendan at combined aortic valve surgery and coronary bypass. It demonstrated an increase in cardiac index and stroke volume [102].

At a meta-analysis of Zangrillo et al. [47] 139 heart surgery patients of 5 studies, Levosimendan was associated with lower increases in the level of troponin after surgery compared with milrinone and placebo, indicating a cardioprotective effect [47].

Severi conducted a study comparing administration of Levosimendan vs. IABC preoperatively in patients with heart failure and elective coronary artery bypass surgery with or without mitral valve replacement. A shorter stay in ICU was demonstrated in patients in whom the drug was used [103].

Right Ventricular Dysfunction

Very few studies have been done about the right dysfunction. Ersoy et al. [104] studied 60 patients with severe pulmonary hypertension (PAP > or = 60 mmHg) and ejection fraction <50% who underwent valve surgery. Levosimendan was administered after the anesthetic induction bolus and subsequent infusion up to a cumulative dose of 12.5 mg. They concluded that patients to whom the drug had been administered showed a significant decrease in pulmonary artery pressure [104].

Guerrero et al. [105] described a series of cases in which Levosimendan was preoperatively administered to patients with right ventricular dilatation and/or systolic dysfunction (TAPSE), finding improvement in the parameters of postoperative right ventricular function, this way opening the door to preoperative optimization of these patients [105].

At a meeting of experts at European level it was discussed the intra, peri or post-operative use of Levosimendan. As intraoperative the drug is used for its inotropic and vasodilatory effects without increasing oxygen consumption. Preoperatively cardioprotective effects for the time of surgery are however sought.

They recommend the preoperative use of Levosimendan in patients with compromised myocardial function, including the right ventricle (100% would use dysfunction preoperatively on the right), being the day before surgery the best time to administer it.

The data that we have on the drug are promising, but there are few robust trials showing an evidence on the use of Levosimendan. Although several meta-analyzes [47,96,106] show the positive effects of Levosimendan and the expansion of data is beginning to be promoted. In the Bayesian meta-analysis of on the effects of inodilators agents on mortality review phase, it is shown that Levosimendan has a 90% chance of being the best concerning survival in cardiac surgery in relation to PDE inhibitors, dobutamine and placebo [107,108].

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