



LEVOSIMENDAN- THE NEXT FAVOURITE DRUG IN THE MANAGEMENT OF HEMODINAMIC CARDIORENAL SYNDROME

MARIA MEȚIU¹, VANESA-LARISA BLOAJE-FLORICĂ², GABRIELA EMINOVICI³

^{1,2,3}“Lucian Blaga” University of Sibiu, ³Emergency Clinical County Hospital of Sibiu

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Abstract: Cardiorenal syndrome (CRS) is a serious condition in which cardiac dysfunction leads to renal impairment and viceversa, with a high risk of mortality. This paper is a review of the most recent studies that investigated the role of Levosimendan on kidney function in case of patients with CRS. Compared with standard therapy (diuretics, other inotropes), Levosimendan has renoprotective effects associated with a lower mortality rate, it leads to an important improvement in NYHA class, a decrease in markers of congestion (BNP) and shortage of hospitalization stay. A study from 2018, in which Levosimendan was compared with Dobutamine, indicated that although both agents increase renal perfusion, only Levosimendan can improve GFR. In conclusion, Levosimendan – through its protective profile for both heart and kidneys, provides higher survival expectancy and seems to be the ideal alternative to the standard therapy in the management of hemodynamic CRS at present.

INTRODUCTION

Cardiorenal Syndrome (CRS) is a serious condition in which cardiac dysfunction leads to renal impairment or viceversa, with a high risk of mortality. According to the latest pathophysiologic classification elaborated by Hatamizadeh et al, Hemodynamic CRS refers to acute or chronic Heart Failure (HF) that leads to acute or chronic Renal Failure.(1,2)

In case of Hemodynamic CRS hypoperfusion and venous congestion are the main factors which lead to kidney injury, resulting in a decrease in glomerular filtration rate (GFR) and fluid retention that worsens the heart workload.(3)

The incidence of renal damage in the context of HF is really high considering that 26 million patients suffer from HF worldwide (4), and more than a third of the patients with congestive HF develop renal failure.(5) This can be correlated with a huge number of hospitalizations per year, high costs and poor prognostic.(6)

Nowadays, it is supposed that renal dysfunction offers a better predictability of mortality than NYHA class or left ventricular ejection fraction, thus the aim in CRS is to maintain renal parameters functional by improving cardiac performance and renal perfusion.(4)

Regarding the treatment of HF, an important step was made by the introduction of Levosimendan on the market - a calcium sensitizer and an opener of ATP-dependent potassium channels with both inotropic and vasodilating properties.(7)

The inotropic effects of Levosimendan are due to its action on cardiomyocyte troponin C fibers. Levosimendan increases the sensitivity to ionic calcium which in turn strengthens myocardial contraction without increasing oxygen demand.

Moreover, due to its action on adenosine ATP-dependent potassium channels located in vascular smooth

muscle cells and mitochondria, Levosimendan is able to exert vasodilatory action on all peripheral vascular territories.(8)

As a consequence, Levosimendan has protective role on both heart and kidneys in heart failure.(9)

AIM

The aim of this paper is to review data from the literature concerning the role of Levosimendan on kidney function in case of patients with CRS and Levosimendan's renoprotective effects associated with a lower mortality rate in comparison to standard therapy.

MATERIALS AND METHODS

We have analysed 4 clinical studies, 9 reviews and The Task Force for the diagnosis and treatment of acute and chronic HF of the European Society of Cardiology (ESC), published in the specialty literature over the last 20 years.

We used the search engines Pubmed, Medscape, and Science Direct, and as keywords “Levosimendan”, “renal function”, “treatment guide”, “Cardiorenal syndrome” and “CSR”.

RESULTS AND DISCUSSIONS

Due to its inodilator profile, Levosimendan possesses both cardioprotective and renoprotective roles. Whilst cardiac protection is now undisputable less is known about its influence on kidney perfusion and function.(9)

In a single-centre, double-blind, randomized trial, Fedele et al demonstrated that Levosimendan has a prompt renoprotective effect in Acutedecomensated HF, primarily due to the increase in renal perfusion through a preferential vasodilating reaction on arteries and veins. Contrary to what was previously suggested, Levosimendan induces vasodilatation before the increase in cardiac output mediated by its inotropic

¹Corresponding author: Eminovici Gabriela, B-dul. Corneliu Coposu, Nr 2-4, Sibiu, România, E-mail: geminovici@ymail.com, Phone: +40269 215050

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effect. As a consequence, Levosimendan leads to a hemodynamic status improvement.(10)

A series of comparative studies have shown that Levosimendan is superior to standard therapy (diuretics, inotropic agents) in the context of HF associated with renal dysfunction.(4,13)

In 2018, a randomized double-blind controlled study conducted by American Heart Association was the first to compare Levosimendan with Dobutamine in terms of Renal Blood Flow (RBF), Glomerular Filtration Rate (GFR) and renal oxygenation in patients with chronic CRS. Although both drugs achieved an augmentation in RBF, only Levosimendan increased GFR by 22 % while Dobutamine had no effect. In this context, GFR increases but the oxygen consumption does not change.(9) Similar observations were made in the Levosimendan Infusion versus Dobutamine (LIDO) trial, in which Levosimendan was compared with Dobutamine in severe low-output HF.(11)

While Dobutamine is not indicated in patients who have been under treatment with beta-blockers, Levosimendan is efficient in this situation.(12)

Another study conducted by Stergiou et al reported that Levosimendan obtained satisfying results in terms of hospitalization stay, NYHA class, BNP as well as cystatin C levels while administration of standard therapy led to modest results.(13)

Moreover, several meta-analyses evaluating approximately 5000 patients of 50 randomized controlled trials support Levosimendan's role in reducing mortality.(14) In the Alarm-HF Registry it is demonstrated that Levosimendan is responsible for a lower mortality rate compared with traditional inotropic agents.(12)

According to 2016 European Society of Cardiology guidelines (class II b level of evidence C) the administration of Levosimendan is indicated in case of patients with symptomatic hypotension and hypoperfusion caused by beta-blockers. Levosimendan administered intravenously inhibits the effects of beta-blockers due to the fact that both drugs act independently.(15)

Although formal guidelines for CRS are still missing, a treatment algorithm for patients suffering from acute CRS has been proposed by Rafouli-Stergiou et al.

They suggest that Levosimendan can be used in both "warm and wet" states and "cold and wet" states, but under certain conditions depending on systolic blood pressure(SBP).

In the first category-"warm and wet"- Levosimendan should be the first line of treatment if SBP >100 mmHg, and as an adjuvant to standard therapy if SBP=90-100 mm Hg.

On the other hand, for "cold and wet" states, Levosimendan should be administered only if SBP=85-100 mmHg.(13)

CONCLUSIONS

In conclusion, Levosimendan – through its protective profile for both heart and kidneys - provides higher survival expectancy and should be used more frequently as an alternative to the standard therapy in the treatment and management of hemodynamic CRS.

Although Levosimendan proves to be efficient in the treatment of HF, the medication has its own limits.

The administration of Levosimendan is recommended only in certain cases and also, the costs are still expensive.

Further research is needed in order to certify Levosimendan's superiority over Dobutamine in renal function.

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