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Short Review

Levosimendan in sepsis

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More Information

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Levosimendan is a calcium sensitizer and its inotropic effect is mainly attributed to the troponin C of the myocardial fine filaments with calcium. Levosimendan also inhibits phosphodiesterase III. In contrast to inotropic effects, this does not increase calcium entry into the cell, which explains that levosimendan does not worsen myocardial diastolic dysfunction and may even improve diastolic function. Levosimendan does not increase the use of myocardial oxygen and increases coronary vasodilation and myocardial oxygen delivery. Levosimendan opens potassium channels and causes hyperpolarization in smooth muscle cell membrane, thus causing vasodilatation [1]. Levosimendan has also been reported to have antiinflammatory [2,3] and antiapoptotic effects [2].

Belletti, et al. [4] evaluated inotropic and vasopressor drugs in a meta-analysis of 177 trials involving 28,280 septic subjects and reported that the only agent to ameliorate mortality was levosimendan.

Zangrillo, et al. [4] performed a meta-analysis of severe sepsis and septic shock using levosimendan. A total of 246 patients in 7 studies were studied in the meta-analysis. According to standard inotropic treatment, there was a significant decrease in mortality in the levosimendan group (47% in the levosimendan group and 61% in the control group). In the levosimendan group, blood lactate level decreased significantly and cardiac index and total amount of infused liquid were significantly higher. According to standard inotropic treatment, levosimendan has been shown to reduce mortality in cases of severe sepsis and septic shock.

In a meta-analysis involving 3470 patients with severe sepsis and septic shock, Belletti, et al. [5] reported that levosimendan (odds ratio 0.17, 95% confidence interval 0.05-0.6), dobutamine (odds ratio 0.30, 95% confidence interval 0.9-0.99) epinephrine (odds ratio 0.35, 95% confidence interval 0.13-0.96), vasopressin (odds ratio 0.37, 95% confidence interval 0.16-0.89) and norepinephrine plus dobutamine (odds ratio 0.4, 95% confidence interval 0.11-0.96) and Rank analysis suggested that levosimendan is the best treatment option.

Hajjej, et al. [6], compared the effects of levosimendan and dobtaminin on skeletal muscle extracellular fluid concentrations of glucose, lactate, pryvate and glycerol in 20 septic cases. Levosimendan has been found to increase the pryvate concentration and lactate clearance relative to dobutamine, and to decrease the ratio of lactate/fructate. Reported that levosimendan improved cellular metabolic effects in septic shock cases.

Memiş, et al. [7], examined 30 patients who were diagnosed with septic shock. They investigated the effects of levosimendan and dobutamine added to dopamine treatment on liver function. According to dobutamine group, levosimendan group showed significant increase in systolic, diastolic and mean arterial pressure. They found that adding levosimendan to the dopamine treatment increased splanchnic perfusion.

Morelli, et al. [8], compared the effects of dobutamine and levosimendan on microcirculation in septic shock cases. They found that levosimendan increased micro circular blood flow in sublingual small and medium diameter vessels.

Hasslacher, et al. [9] studied polymorphonuclear cells from healthy volunteers that incubated in levosimendan. The respiratory burst after N-formyl-Met-leu-Phe (fMLP) and phorbol 12-myristate 13-acetate (PMA) stimulation were evaluated by fluorescent staining. Cell adhesion molecule expression and apoptosis of polymorphonuclear cells were evaluated by flow cytometry. In vivo, levosimendan has been shown to have effects on acute heart failure (n = 16) and septic heart failure (n = 9). They found that levosimendan

suppressed respiratory burst activity in fMLP and PMA-stimulated ploymorphonuclear cells, depending on the dose. They found that levosimendan did not affect apoptosis and polymorphonuclear cell adhesion molecule formation. In vivo, a significant decrease (45%) in PMA-induced oxidative burst and a significant decrease in fMLP-stimulated oxidative burst (49%) were observed in patients with acute heart failure after 2 hours of levosimendan therapy. In cases of septic shock, levosimendan significantly reduced the oxidative burst in stimulated polymorphonuclear cells with unexplained (48%) and fMLP (46%) and PMA (43%). As a result, they reported that levosimendan showed immunoregulatory effect by reducing oxidative burst in polymorphonuclear cells.

Wang, et al. [10] examined the anti-inflammatory effects of levosimendan in septic mice. They found that levosimendan improved left ventricular function without altering heart rate and thus corrected hypotension significantly. They found that they reduced lung damage and lowered blood proinflammatory and chemotactic cytokine levels. They stated that they significantly increased the survival rate of mice. They found that RA inhibited the formation of proinflammatory and chemotactic cytokines in endotoxin-stimulated RAW265.7 macrophages. Inhibit the Rho kinase signaling pathway. They also reported that the serum high mobility group box 1 level in the sepsis decreased.

Erbüyün, et al. [11], have reported that levosimendan reduces inflammatory cytokine production by reducing the formation of transforming growth factor TGF-β2 and Smad1, Smad2 and Smad3.

Wagner, et al. [12], found that levosimendan increased left ventricular ejection fraction and myofibrillar calcium sensitivity in septic rats

Schellekens, et al. [13] examined the effects of levosimendan on oxidative and inflammatory pathways on the diaphragm in mechanically ventilated endotoxemic rats. Mechanical ventilation and endotoxemia have found that inducible nitric oxide synthase in the diaphragm increases mRNA and interleukin 1β, interleukin 6 but decreases interleukin 10 levels. They found that Levosimendan significantly lowering the concentration of 4-hydroxy-2-nonenal protein significantly and reduced INOS mRNA by decreasing nitrosylated proteins significantly. They reported that levosimendan partially reduced nitrosative and oxidative stress.

In conclusion, the positive effects of levosimendan on hemodynamic and inflammatory responses in sepsis have been shown clinically and experimentally. However, there is a need for more extensive clinical and experimental work to prove these beneficial effects.

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