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Levosimendan in Pediatric Cardiac Surgery: An Evidence Based Review

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Abstract

Levosimendan (LS) is a calcium sensitizing agent with inotropic properties. It has been shown to improve cardiac function, haemodynamic performance and survival in adult with heart failure. Intraoperative administration of levosimendan during adult cardiac surgery have been shown to be beneficial. This new rescue drug also has some beneficial effects in pediatric cardiac surgery. Over the last two decades many studies have been conducted to determine the effect of levosimendan in different therapeutic settings such as heart failure, cardiogenic shock, septic shock, cardiac and non cardiac surgery. The drug has also been compared with several inotropic agents such as dopamine, dobutamine, milrinone, enoximone or as an addition to the best standard of care. Though a few reviews and meta analyses are available where adult cardiac surgical patients are concerned, only few studies exist in literature pertinent to its use in pediatric cardiac surgical patients. The aim of this review is to summarize the available evidence about the mechanism of action and use of LS in pediatric cardiac surgery.

Abbreviations: LS: Levosimendan; LCOS: Low Cardiac Output Syndrome; ATP: Adenosine Triphosphate; PDEs: Phosphodiesterases

Introduction

Levosimendan is a pyridazone- dinitrite derivative which comes under a new class of ino- dilator cum calcium sensitizers. It improves cardiac function and survival in critically ill patients. Its use during perioperative scenario in patients undergoing cardiac surgery is a subject of recent interest. Infusion of LS increases cardiac output due to an increase in stroke volume and heart rate with a fall in pulmonary capillary wedge pressure. Several observations in adult suggest that a single infusion of LS in heart failure adults have an effect lasting for 6-24 hrs and result in hemodynamic changes, symptomatic benefits and reduction in mortality and morbidity [1-3]. There are a wide range of inotropes available for the treatment of low cardiac output syndrome (LCOS) after pediatric cardiac surgery. All of them have their own benefits and disadvantages [4]. The basic aim of this review is to summarize the available evidence about the pharmacology and use of LS in pediatric cardiac surgery. We analyzed the peer reviewed publications identified through searches of Pubmed from January 1990 through December 2005. Search items included levosimendan, inotropic agents, cardiac surgery and children. Case reports and bibliographies from these references were also reviewed. The results of unpublished or ongoing trials were published from presentations at scientific meetings.

Pharmacology

Mechanism of action

The mechanism of action of LS is otherwise named as calcium sensitization. It does not increase the intracellular concentration of free calcium. It binds to the cardiac troponin C in a calcium dependent manner and stabilizes troponin C. This facilitates actin-myosin cross bridges without increasing myocardial consumption of adenosine triphosphate (ATP). Cardiac performance and contractility significantly improved with no increase in the total myocardial oxygen demand and consumption. LS is inhibits phosphodiesterases (PDEs) and in particular PDE III in human cardiac myocytes that increases calcium influx through sarcolemmal channels [5]. Inspite of structural similarity with molecules belonging to the PDF-inhibitor family, LS does not increase intracellular levels of cAMP and thus the of intracellular calcium level in a variety of experimental models. In addition to calcium sensitization, LS also stimulates ATP sensitive K+ channels that are suppressed by intracellular ATP and acts synergistically with nucleotide diphosphates [6]. This mechanism also contributes to the vasodilator action of this agent. A similar effect of this drug in cardiac myocytes may protect ischemic myocardium because the activation of ATP sensitive K+ channels would likely occur

in ischemic regions in which the intracellular ADP concentration is decreased. The cardiac performance and contractility after LS administration is significantly improved with no increase in the total myocardial energy demand and oxygen consumption. The potential for arrhythmia is also reduced as intracellular calcium levels are not raised. An additional benefit is that the stabilization effect is calcium dependent and levosimendan exert this effect during systole. It does not affect the duration of diastole thus ventricular relaxation is not impaired and additional ventricular filling and optimal coronary perfusion results. The haemodynamic effects of levosimendan were found to be higher in patients who used β blockers. Its superiority over other inotropic agents can also be evidenced with this feature [7]. Finally, LS also opens the cardiac mitochondrial ATP dependent K+ channels, a potentially cardio protective mechanism linked to the preconditioning in response to the oxidative stress [8]. LS also cause venous, arterial and coronary vasodilation by opening ATP sensitive potassium channels in smooth muscle. Dose dependent hypotension is a common phenomenon with this drug. It is also beneficial in the setting of pulmonary vasoconstriction, right ventricular dysfunction by reducing pulmonary vascular resistance.

Pharmacokinetic in children

In an open group single dose study, Turnlahti M, et al. [9] evaluated the pharmacokinetics, hemodynamic effects and safety of LS in pediatric cardiac surgical patients. After a single 12μgm/kg intravenous infusion of LS, the mean maximum concentration of the drug was 59±2.3 ng/ml in children older than 6 months of age. The drug had a rapid distribution with a mean half life of 0.24±0.07 hrs. The mean termination half life and total plasma clearance were 1.6±0.08 hrs, 3.6±1.3 ml/min/kg respectively. The terminal elimination half life in children aged 3-6 months was slower than in older children (2.3 hrs vs 1.6 hrs). The change in haemodynamics was similar to that in adult patients.

Utility in pediatric cardiac surgery

LS have pharmacologic and hemodynamic advantages over conventional inotropic agents. The perioperative use of this drug has increased over the years. Magliola R et al. [10] in a prospective study infused LS at a dose of 6 μgm/kg over 15 min period, followed by a 24 hr intravenous infusion at 0.1 μgm /kg/min to children who developed refractory post surgical low cardiac output syndrome. Only 50% of their patients responded in whom both inotropic and (A-V) DO2 score showed a reduction. There was no adverse effect related to this drug. LS was administered to seven infants weighing 2.6-6.3 kg who developed severe myocardial depression after complex heart surgery. In four children the drug was started while weaning from CPB while in otter three infants it was administered after the termination of CPB but before chest closure. All the patients received LS at a loading dose of 12 μgm /kg over 10 minutes followed by a continuous infusion of 0.2 μgm /kg/min for 24 hrs. The haemodynamic parameters as well as the lactate levels were documented during LS infusion at defined time points. The heart rate, mean arterial pressure and central venous pressure did not alter. There was an increase in central venous oxygen saturation and decrease in mean arterial lactate to a significant extent at 24 and 48 hrs compared to the base line [11]. Lechner E et al. [12] compare the effect of LS in 40 pediatric patients after corrective open heart surgery. The patients received either a 24 hr infusion of 0.1 μgm /kg/min LS or 0.5 μgm /kg/min milrinone. Both the drugs had an improved effect both on cardiac index and cardiac output without any serious adverse events. However, the improvement was gradual over a time period in LS group where was it was stable in milrinone group. The p values for heart rate, serum lactate, blood pressure, mixed venous oxygen saturation and near infrared spectroscopy were insignificant. Ricci Z and colleague administered 72 hr continuous infusion of LS at a dose of 0.1 μgm /kg/min to 32 neonates undergoing corrective surgery for congenital heart disease and compared the hemodynamics with matched neonates (31 in number) who received post CPB inotropes according to the institutional protocol [13]. A lower lactate level at 6 hr postoperative period was achieved with LS infusion. LS group had lower inotropic score ($p<0.001$) and lower incidence of postoperative low cardiac output syndrome (37%) compared to the conventional group (61%) ($p= 0.059$, or 0.38, 95% CI 0.14-1.0). One group of authors administered LS at a dose of 0.1 μgm /kg/min 24 hr before surgery and continued the infusion for 48 hr after surgery. A significant reduction in inotrope score was noticed after 72 hrs (p, 0.05). A similar trend was observed in brain natriuretic peptide (1210 to 459 pg/ml, $p<0.05$) and blood lactate level ($p<0.05$) during the period of evaluation. The authors marked it as a safe and effective drug in patients with single ventricle physiology [14]. A group of authors from a tertiary health care centre infused LS at a loading dose of 12 μgm /kg during rewarming on CPB followed by continuous infusion of 0.1 μgm /kg/min for 48 hr. 32.7% of their patients were managed with LS as a sole inotrope without any significant side effects [15].

LS infusion at a loading dose of 12 μgm gm/kg followed by 0.2 μgm gm/kg/min led to an improvement of diuresis and haemodynamics in a 3 year old child who developed cardiac failure during weaning from CPB. The authors were able to reduce the dose of analogous inotropic support (e.g. dopamine, dobutamine and adrenaline) by 6 hr and could stop all of them by 48 hrs. The authors opined that LS is a satisfactory agent in the treatment of myocardial failure in children undergoing open heart surgery [16]. In a randomized double blind clinical trial, Momeni et al. [17] reported a lower rate pressure index, an indicator of myocardial oxygen demand, at 24 and 48 hr respectively in the LS group ($p<0.001$) in comparison with the milrinone group. Although not statistically different, the troponin values in the LS group were less at 1 hr and 4 hr post

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operatively. Lactate levels were non significant. They concluded that LS is at least as efficacious as milrinone after corrective congenital cardiac surgery in neonates and infants. Pertti et al. [18] studied 484 LS delivered to 293 patients over 10 years, as administered to children with cardiac surgery (72%), cardiomyopathy (14%) and with cardiac failure (14%). The most common use of LS (94%) was when the other inotropic agents were insufficient to maintain stable haemodynamics. The results of a questionnaire concerning the perceptions of clinicians were also evaluated. Eighty- nine percent of the respondents believed LS administration postponed the need for mechanical assist device in some children with cardiomyopathy. Furthermore, 61.1% of the respondents felt that it had saved the lives of some children when the other treatments had failed and 44% thought mechanical support was totally avoided in few patients post cardiac surgery after receiving levosimendan. A single case report by Lechner et al. [19] described the beneficial effect of LS when conventional inotropes failed in a premature infant who developed post atrial switch operation heart failure. The baby had an improvement in SVR, decrease in left atrial pressure and an improvement in left ventricular function and fractional shortening. In another case report, the authors described successful use of LS in the treatment of post operative low cardiac output syndrome in a patient with congenital mitral insufficiency and severe pulmonary hypertension who was nonresponsive to enoximone infusion and inhaled nitric oxide. The ejection fraction was 30% and ScVO2 was 60 % during initiation of levosimendan therapy. The drug was substituted for enoximone and started at a dose of 0.2 μgm /kg/min for 24 hrs. The infusion of adrenaline, dobutamine and sodium nitroprusside was continued. The ScVO2 started increasing from day 3 (66.8%). However, the ejection fraction remained the same. By day 7, the EF improved to 50% and ScVO2 88.3% and he was off all the inotropes [20].

Adverse Events

LS is considered to be safe and efficacious for use in children based on extensive experimental model. However, it is generally considered that there is not enough evidence from the few existing studies done in children to warrant the routine use of LS in cardiac surgical setting. LS is well tolerated by children except some degree of hypotension and tachycardia. In a largest published study on LS in children, mortality was higher (11%) in LS group than overall mortality after cardiac surgery in children in the same study period [18]. The authors had an opinion that LS was mainly administered to the high risk patients and after the other inotropic agents were found to be insufficient to maintain stable haemodynamics.

Conclusion

In summary, LS causes a dose dependent improvement in haemodynamic and cardiac function in children undergoing cardiac surgery. The drug is well tolerated and appears to reduce morbidity. However, more randomized trials are essential to establish its' routine use in these group of children.

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