Study of the Effect of Levosimendan (A novel inotropic calcium-sensitizing agent) on Cardiac Performance In patients Undergoing on-Pump CABG

(Randomized Controlled prospective study)

Thesis

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By

Ahmad Ibrahim El-Sonbaty

M.B.B.ch- M.Sc. of Anesthesia

Under supervision of

Prof. Dr. Adel Abdel Fattah Saleh MD

Professor of Anesthesia
Faculty of Medicine
Cairo University

Prof.Dr. Hesham Salah Khedr

Professor of Anesthesia
Faculty of Medicine
Cairo University

Dr. Tamer Osama Azab

Assistant Professor of Anesthesia
Faculty of Medicine
Cairo University

Dr. Tarek Awad Mary

Lecturer of Anesthesia
Faculty of medicine
Cairo university

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Abstract

Objective: levosimendan is a new calcium sensitizer with inodilatory properties. There is growing clinical experience with levosimendan given to cardiac surgical patients. The aim of this study was to evaluate the effects of intra-operative use of different doses of levosimendan versus known inotrope e.g. adrenaline; in surgical patients with compromised left ventricular function.

Design: randomized controlled prospective study.

Setting:cairo university hospital.

Participants: patients undergoing cardiac surgery fulfilled our inclusion criteria.

Methods: thirty cardiac patients divided in three groups. group A (n=10) was received levosimendan as 30 mcg/ kg as loading dose over 5 min followed by 0.3 mcg/kg/min till the end of surgery, group B (n=10) was received levosimendan as 12 mcg/ kg as loading dose over 5 min followed by 0.05 mcg/kg/min till the end of surgery and control group (n=10) in which inotropic support e.g. adrenaline used only if needed.

Results: continuous levosimendan infusion increased cardiac index, stroke volume index significantly in both group A and B compared with control group. Pulmonary wedge pressure and mean arterial pressure systemic vascular resistance index significantly decreased in group A compared to both control group and group B which required vasoconstrictor support; noradrenaline (0.05µg/kg/min) in four patients. Pulmonary wedge pressure and mean arterial pressure systemic vascular resistance index showed modest change in group B compared control group. Heart rate showed significant increase in group A compared to

control group and group B . Ejection fraction showed significant improvement in both group A and group B over control group but there was insignificantly changed between the two groups of levosimendan. These hemodynamic effects of levosimendan persisted postoperatively. Five patients in control group needed intropic support i.e. adrenaline.

Conclusion: levosimendan can be used for intraopertive inotropic support for cardiac surgical patients avoiding Side effects of conventional inotropes. Although higher doses may carry more favorable effects on hemodynamic variables but these changes were not significantly different from those with lower doses, in addition, higher doses may be associated with unfavorable effects which may need to be corrected for patient interest.

Keywords: levosimendan, calcium sensitizers, inotropic agents, cardiac surgery, impaired ventricular function.

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ACE inhibitor……...Angotensin Converting Enzyme inhibitor.

ACT……..Activated clothing time.

ANP……..Atrial natriuretic peptide.

ATP……..Adenosine TriPhosphate

AUC…… Area under the plasma concentration-time curve.

AVP…… Arginine vasopressin.

Ca^{2+}.....Calcium.

CABG……..Coronary artery bypass grafting.

CAD…….Coronary Artery Disease.

cAMP……...Cyclic Adenosine MonoPhophate.

CK-MB……Creatine kinase MB subunit.

CHF……..Congestive Heart Failure.

CI……..Cardiac Index.

CL_{tot} …….Total clearance.

Cmax……Maximum plasma concentration.

CO……Cardiac Output.

CPB…… ..CardioPulmonary Bypass.

CVP……..Central Venous Pressure

CYP …….Cytochrome P.

DAG ……Diacylglycerol.

DOB…….Dobutamine.

ECG……..ElectroCardioGraphy.

EDA …….End diastolic area.

EDC ……..End- diastolic circumference.

EDV……...End Diastolic Volume.

EF……...Ejection fraction.

ESV……...End Systolic Volume.

GTP……...Guanidine triphosphate.

Hct…….……Hematocrite.

HR…….Heart rate.

Ht…….……..Height.

IP_3……...Inositol 1.4, 5-triphosphate.

K^+……...Potasium.

LS……...Levosimendan.

LV……...Left Ventricle.

LVAD…….Left ventricular assist device.

MAP……....Mean Arterial Pressure.

MAP……Mean arterial pressure.

Mg^{2+}…….Magnesium.

MPAP……. …….Mean Pulmonary Arterial Pressure.

MVO_2.....Myocardial Oxygen demand.

Na^+…….....Sodium.

NYHA ……..New York Heart Association.

O_2……..Oxygen.

$PaCO_2$……Arterial carbon diaoxide tension.

PaO_2…….Arterial oxygen tension.

PAP…….....Pulmonary Artery Pressure.

PCWP…….....Pulmonary Capillary Wedge Pressure.

PDE III…….....PhophDiEsterase III.

PET……...Positron emission tomography.

PGE_1……..Prostaglandin E_1.

PH……. Acid-base balance.

PTCA…….Percutaneous trans-lumenal coronary angiography.

PVR……Pulmonary Vascular Resistance.

PVRI……Pulmonary Vascular Resistance Index.

RAP……..Right Atrial Pressure.

RV…….Right Ventricle.

RyR2…….Ryanodine receptor type 2.

SD …….……..Standard deviation.

SERCA2……...Sarcoplasmic endoplasmic reticulum calcium adenosine triphosphatase isoform 2

SR…….Sarcoplasmic reticulum.

SVI…….... Stoke volume index.

SVR……...Systemic Vascular Resistance.

SVRI…….Systemic vascular resistance index.

TEE……...Transesophageal echocardiography.

TnC……...Troponin C.

TnI…….....Troponin I.

TnT……...Troponin T.

V_d ……Volume of distribution.

Wt…….……Weight.

Introduction

Despite advanced techniques of myocardial protection, ischemia during aortic cross-clamping and reperfusion of previously hypoperfused areas of myocardium lead to a variable degree of stunning and, frequently requires inotropic support to reverse depressed contractility. This fall in cardiac output, referred to as ‘postoperative low cardiac output syndrome’, contributes to postoperative morbidity and mortality.

Most of the currently available inotropic drugs enhance myocardial contractility by increasing concentrations of intracellular calcium, which leads to an increase in myocardial oxygen consumption [(1)].

Levosimendan is a new calcium-sensitizing agent that has been developed for the treatment of decompensated heart failure. This agent sensitizes troponin C to calcium in a manner that is dependent on calcium concentration, thereby increasing the effects of calcium on cardiac myofilaments during systole, and improving contraction at a low energy[(2,3)]. Levosimendan also leads to vasodilatation through the opening of ATP-sensitive potassium channels[(4)]. By these inotropic and vasodilatory actions, levosimendan increases cardiac output without increasing myocardial oxygen demand.

Previous randomized trials have established the favorable hemodynamic effects of intravenously administered levosimendan in patients with severe heart failure.[(5,6)] Following 6–24 hours of levosimendan infusion, hemodynamic parameters improved; improved survival was also seen up to 180 days after the infusion.[(5)] However, these trial results did not include patients with impaired left ventricular function having undergone cardiac surgery.

Other small-scale studies have demonstrated that levosimendan improved cardiac output and decreased afterload after cardiopulmonary bypass in patients with normal preoperative left ventricular (LV) function[7,8]. These results indicate a potential clinical role for levosimendan in cardiac surgical patients. However, these studies excluded patients with pre-existing LV systolic dysfunction.

Therefore, the efficacy and safety of levosimendan in the immediate postoperative care period for high-risk patients with impaired cardiac function has not been well established.

Aim of the work and scope of thesis : The aim of this study is to test the hypothesis that, levosimendan enhances cardiac performance after cardiopulmonary bypass (CPB), without arrythmogenic effects. The goals of the present study are to determine whether levosimendan in two doses regimen improves hemodynamic functions in patients undergoing on-pump CABG and determine if the all effects of levosimendan are dose-dependent or the difference in effects of the two doses are not significant.

PERIOPERATIVE VENTRICULAR DYSFUNCTION

PHYSIOLOGICAL CONSIDERATIONS OF MYOCARDIAL CONTRACTION:

MECHANISM OF MYOCARDIAL CONTRACTION:

Myocardial cells contract as a result of the interaction of two overlapping, rigid contractile proteins, actin and myosin. These proteins are fixed in position within each cell during both contraction and relaxation. Dystrophin, a large intracellular protein, connects actin to the cell membrane (sarcolemma). Cell shortening occurs when the actin and myosin are allowed to fully interact and slide over one another (Figure 1). This interaction is normally prevented by two regulatory proteins, troponin and tropomyosin; troponin is composed of three subunits, troponin I (TnI), troponin C (TnC), and troponin T (TnT). Troponin is attached to actin at regular intervals, whereas tropomyosin lies within the center of the actin structure. An increase in intracellular calcium concentration (from about 10^{-7} to 10^{-5} mol/L) promotes contraction as calcium ions bind troponin C. The resulting conformational change in these regulatory proteins exposes the active sites on actin that allow interaction with myosin bridges (points of overlapping). The active site on myosin functions as a magnesium-dependent ATPase whose activity is enhanced by the increase in intracellular calcium concentration. A series of attachments and disengagements occur as each myosin bridge advances over successive active sites on actin. Adenosine triphosphate (ATP) is consumed during each attachment. Relaxation occurs as calcium is actively pumped back into the sarcoplasmic reticulum by a Ca^{2+}–Mg^{2+}-ATPase; the resulting drop in intracellular calcium concentration allows the troponin–tropomyosin complex to again prevent the interaction between actin and myosin[(9)].