Atlas of Science
another view on science
http://atlasofscience.org

Levosimendan to reduce mortality in cardiac surgery (CHEETAH trial)

Over the past decade, there was a significant decline of mortality after cardiac-surgery. Although the average perioperative mortality for elective procedures currently is 1% to 2%, the rate of major complications remains high. Low-cardiac-output syndrome (LCOS, a situation where all organs suffers due to an insufficient flow of blood arriving from the heart) is the most common and the most serious complication, associated with short- and long-term mortality, and healthcare resource utilization. Mortality among patients who develop LCOS after cardiac surgery can exceed 20%.

The management of patients with LCOS after cardiac surgery is debated. None of the drugs currently used have randomized evidence to support its use to improve clinical relevant outcomes such as mortality. Old inotropic agents are possibly associated with higher risk of death.

Levosimendan is a relatively new drug which is widely used to treat chronic and acute heart failure in different clinical settings. Levosimendan has a triple mechanism of action that may explain the improvement in clinically relevant outcomes observed so far. By binding to cardiac troponin C, it enhances myofilament responsiveness to calcium, thereby increasing myocardial contraction without increasing myocardial oxygen consumption. In addition, levosimendan activates sarcolemmal adenosine triphosphate–dependent potassium channels which are important mediators of ischemic and pharmacological cardioprotection. Nevertheless, only single-center trials support the use of levosimendan to treat LCOS after cardiac surgery.

We are conducting the first large double-blind, placebo-controlled, multicenter, randomized trial (CHEETAH trial) to determine whether levosimendan significantly improves survival in patients with postoperative myocardial dysfunction following cardiac surgery. The study is supported by a grant of the Italian Ministry of Health (RF-2009-1519827). Patients undergoing cardiac surgery with LCOS within 24 hours from surgery will receive either continious levosimendan (0.05-0.2 μg/[kg min]) or placebo infusion for 24-48 hours. LCOS will be defined as the need for high inotropic support or perioperative use of intraaortic balloon pump. The study drug infusion will be continued for 24-48 hours or until discharge from the intensive care unit (ICU) if this occurs earlier. This is a pragmatic study where levosimendan or placebo is added to the best available treatment in the operating room or in the ICU environment with the definition of best available treatment left to the decision of each single center to increase external generalization in case of positive results.

In the present study, we will primarily test the hypothesis that levosimendan would reduce 30-day mortality in cardiac surgery patients with perioperative LCOS. Secondary end points include mortality at 1 year, mechanical ventilation, acute renal failure, adverse events, and length of ICU and hospital stay. A composite end point of survival and/or need for renal replacement therapy will be evaluated as well.

The trial has 3 characteristicsthat make it interesting for all cardiovascular specialists. The written consent is signed by all patients who undergo cardiac surgery, and only patients that meet inclusion criteria are randomized. Second, the present is a uniquely pragmatic study aiming to show if levosimendan added to

the best available treatment can reduce mortality in patients who undergo LCOS after cardiac surgery. Third, the study enrolls both patients immediately after weaning from cardiopulmonary bypass and in the first 24 hours.

In conclusion, our trial will give important insights into the pathophysiology and management of LCOS after cardiac surgery. It will also help to determine whether levosimendan in the early treatment of postsurgical LCOS improves survival and reduces ICU stay.

Giovanni Landoni [1,2], ***Vladimir V. Lomivorotov*** [3], ***Gabriele Alvaro*** [4], ***Rosetta Lobreglio*** [5], ***Antonio Pisano*** [6], ***Valery V. Likhvantsev*** [7], ***Alberto Zangrillo*** [1,2]

[1]*Department of Anesthesia and Intensive Care, IRCCS San Raffaele Scientific Institute, Milan, Italy*

[2]*Vita-Salute San Raffaele University, Milan, Italy*

[3]*Department of Anesthesiology and Intensive Care, State Research Institute of Circulation Pathology, Novosibirsk, Russia*

[4]*Anesthesia and Intensive Care, A.O.U. "Mater Domini" Germaneto, Catanzaro, Italy*

[5]*Department of Anesthesia and Intensive Care, A.O.U. Città della Salute e della Scienza, Turin, Italy*

[6]*Division of Cardiac Anesthesia and Intensive Care Unit, AORN "Dei Colli" – Monaldi Hospital, Naples, Italy*

[7]*Department of Anesthesiology and Intensive Care, Moscow Regional Clinical & Research Institute, Moscow, Russia*

Publication

A randomized controlled trial of levosimendan to reduce mortality in high-risk cardiac surgery patients (CHEETAH): Rationale and design.
Zangrillo A, Alvaro G, Pisano A, Guarracino F, Lobreglio R, Bradic N, Lembo R, Gianni S, Calabrò MG, Likhvantsev V, Grigoryev E, Buscaglia G, Pala G, Auci E, Amantea B, Monaco F, De Vuono G, Corcione A, Galdieri N, Cariello C, Bove T, Fominskiy E, Auriemma S, Baiocchi M, Bianchi A, Frontini M, Paternoster G, Sangalli F, Wang CY, Zucchetti MC, Biondi-Zoccai G, Gemma M, Lipinski MJ, Lomivorotov VV, Landoni G
Am Heart J. 2016 Jul