

Does Levosimendan Affect Serum Ionic Calcium Levels in Cardiac Surgery As Compared To Other Inotropes – A Prospective Study

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Abstract: **PURPOSE:** To compare the different levels of ionic calcium while using levosimendan as to other inotropes in patients undergoing beating cardiac surgery.

STUDY DESIGN: Prospective randomized clinical study.

SETTING: Tertiary referral centre.

MATERIALS AND METHODS: Fifty patients undergoing Coronary Bypass Grafting off pump were enrolled in this study from January 2011 to June 2011. Comparative analysis of serum ionic calcium levels was made by routine blood gas analysis between a group of 25 patients who were given levosimendan and 25 patients in whom other standard inotropes were used. Preoperative ionic calcium was within normal limits.

STATISTICAL ANALYSIS: The results obtained were tabulated and compared using student t test. The volume of calcium gluconate required to maintain ionic calcium levels in normal limits in patients on levosimendan was significantly higher ($P < 0.01$) when compared to patients on other inotropes.

RESULTS: In patients on levosimendan, the mean amount of calcium gluconate required to maintain ionic calcium levels normal (1.10 – 1.26 mmol) was 4.69cc compared to 0.93cc in patients on other inotropes.

CONCLUSION: Levosimendan is a novel calcium sensitizer with inodilator properties which stabilizes interaction between ca and troponin c by binding to troponin c in ca dependent manner. Hence larger amounts of calcium gluconate is needed to keep serum ionic calcium levels within normal limits while using levosimendan.

Key words: levosimendan, ionic calcium

I. Introduction

Recent upsurge in referral of patients with high perioperative risk or compromised left ventricular failure for cardiac surgery has led to an increase of pharmacologic support in the form of vasodilator and inotropic therapy to achieve improvement of tissue perfusion in the perioperative period or to support weaning from cardiopulmonary bypass⁽¹⁾. Levosimendan is a novel inodilator agent which enhances myocardial performance without changes in oxygen consumption. The combination of positive inotropic and vasodilator effects of levosimendan relates to its calcium sensitizing and potassium channel opening effects. Levosimendan has been proposed in recent past to be noninferior and may have some advantages to standard inotropes⁽²⁾. Over the years, significant preclinical and clinical evidence has revealed beneficial pleiotropic effects of levosimendan and its long lived metabolite OR-1896⁽³⁾. Levosimendan is a pyridazole dinitrate derivative with linear pharmacokinetics and a relatively shorter half life although its active metabolite, OR-1896 has a half life of 70 to 80 hours accounting for a prolonged effect⁽⁴⁾. Levosimendan belongs to a new class of inotropes called calcium sensitizers that share invitro properties of calcium sensitization and phosphodiesterase inhibition. It stabilizes interaction between calcium and troponin c by binding to troponin c in a calcium dependent manner improving inotropy without adversely affecting lusitropy⁽⁵⁾. Hence comparatively larger amounts of ionic calcium have to be replaced in the form of calcium gluconate to maintain serum calcium levels in peri and post-operative periods while using levosimendan. This study compares difference in the amount of calcium gluconate injected in peri and post operative periods while using levosimendan as to other standard inotropes.

II. Materials And Methods

This comparative study was conducted in A.J Institute of Medical Sciences and Research Centre, a tertiary referral centre in South India from January 2011 to June 2011. Procedures involved were in accordance with the ethical standards of the institutional committee on human experimentation. A total number of 50 patients undergoing Coronary Artery Bypass Grafting off pump were included randomly using CONSORT method. Patients on cardiopulmonary bypass were excluded in the study. 25 patients who were randomly chosen were taken as control and standard inotropes like adrenaline, dobutamine and milrinone were used.

Levosimendan was used as an inodilator in rest of 25 patients. Preoperative ionic calcium levels were within normal limits in all the cases. Ionic calcium was determined every fourth hourly in both test and control groups during peri and post operative period by routine arterial blood gas analysis. The amount of calcium gluconate to maintain ionic calcium within normal limits was tabulated.

III. Results And Observations

Of the total of 50 patients 25 were chosen as test and 25 as control group randomly. In the test group 19 were male and 6 females, 18 were males and 7 females in the control. Mean age of the test was 57.0 +/- 9.6yrs and of the control was 58.4 +/- 8.7 yrs. Mean preoperative calcium was 1.22 +/- 0.09 in control and 1.21 +/- 0.12 in test group.

(Table 1. Demographic characteristics of the studied groups)

Routine blood gas analysis was done in all the cases which were taken up for surgery since ionic calcium was in normal limits (1.10 -1.26 mmol/L). Arterial blood gas analysis was done in perioperative period and fourth hourly during postoperative period, the results of which have been tabulated below.

(Table 2. Volume of calcium gluconate needed to maintain normal levels of ionic calcium, Fig 1)

The above variables were tabulated in the form of student – t test. The amount of calcium gluconate injection required to maintain ionic calcium levels within normal limits are significantly higher while using levosimendan than while usage of other standard inotropes ($p < 0.01$).

IV. Discussion

Acute cardiovascular dysfunction occurs perioperatively in more than 20% of cardio-surgical patients yet current acute heart failure classification is not applicable to this period. Indicators of major perioperative risk include unstable coronary syndromes, decompensated heart failure, significant arrhythmias and valvular disease. Clinical risk factors include history of heart disease, compensated heart failure, cerebrovascular disease, presence of diabetes mellitus, renal insufficiency and high risk surgery. Aggressively preserving heart function is a major goal. Volatile anaesthetics and levosimendan seem to be promising cardioprotective agents⁽⁶⁾. Traditionally, perioperatively used inotropic agents like epinephrine, dobutamine and milrinone are limited by significant increases in myocardial oxygen consumption, proarrhythmias and neurohormonal activation. Levosimendan a new inodilator for the treatment of decompensated heart failure has shown promise in elective therapy of cardiac surgery, patients with high preoperative risk or compromised left ventricular function as well as in rescue therapy of patients with difficult weaning from cardiopulmonary bypass⁽²⁾. After open chest cardiac surgery, ventricular function remains depressed (myocardial stunning) catecholamines improve ventricular function by increasing intracellular calcium ions. In parallel oxygen consumption is increased, so that hitherto intact myocardium is jeopardized⁽⁷⁾. Levosimendan is a unique therapeutic agent that increases myocardial contractility without increasing oxygen consumption or ATP demands, decreasing preload or afterload. It increases myocyte contractility by stabilizing troponin C rather than by increasing intracellular calcium⁽⁸⁾.

Levosimendan is a calcium sensitizer, directly stabilizes calcium induced conformation of troponin C. It leads to a positive inotropic effect without impairing diastolic relaxation and causing cytosolic Ca^{+2} ion overload⁽⁹⁾. It improves myocardial contractility and increases systemic pulmonary and coronary vasodilatation. It seems to be an effective choice for preventing left ventricular failure in high risk patients with severe left ventricular dysfunction compared with patients receiving dobutamine and milrinone⁽¹⁰⁾. Two large double blind randomized trials demonstrated favourable haemodynamic effects improved tolerability and a possible mortality benefit over dobutamine and placebo in patients who had acute symptoms of failure and required inotropic therapy. Levosimendan appears to be an effective inodilator devoid of detrimental effects of conventional inotropes⁽⁵⁾.

Its inotropic mechanism is based on calcium sensitization of myofilaments and its vasodilator actions are related to the opening of ATP dependent K channels. Since inotropic action doesn't require an increase in cytosolic free calcium, it is less arrhythmogenic than conventional parenteral beta agonist inotropes or phosphodiesterase III inhibiting drugs. Due to the calcium dependent binding of the drug to troponin C, levosimendan unlike some other calcium sensitizing drugs doesn't prolong diastolic relaxation of the myocytes but acts in synergy with the intramyocellular Ca^{+2} levels⁽¹¹⁾.

V. Conclusion

Levosimendan is a new inodilator agent that improves myocardial contractility by increasing the sensitivity of troponin c to calcium which usage in cardiac surgery has been growing in recent years. Levosimendan is effective in high risk cases during cardiac surgery especially during intraoperative and pumpremoval period⁽¹²⁾. It leads to a positive inotropic effect without impairing diastolic relaxation and causing

cytosolic ca^{+} ion overload. Hence significantly larger amounts of calcium gluconate is needed to maintain normal ionic calcium levels in patients while using levosimendan as compared to other inotropes. Ours is a novel attempt in this sort of comparative study as very few studies have been reported in literature till date.

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Table 1. Demographic characteristics of the studied groups

	TEST	CONTROL
Number	n = 25	n = 25
Age, mean +/- SD (range)	57.0+/-9.6 (41-76 yrs)	58.4+/-8.7(40- 74 yrs)
Sex no (%) Male	19 (76%)	18 (72%)
Sex no (%) Female	6 (24%)	7 (28%)
Weight	62.6+/-9.9 (50 – 84kg)	62.8+/-6.7(48 – 73kg)
Pre-op Calcium	1.21+/-0.12	1.22+/-0.09

Table 2. Volume of calcium gluconate required to maintain normal ionic calcium levels

Volume of ca gluconate	Test (in mmol/l)	Control(in mmol/l)
Intra-op	6.15	1.40
Post-op 4hrs	4.60	1.15
8hrs	6.35	1.20
12hrs	6.35	1.10

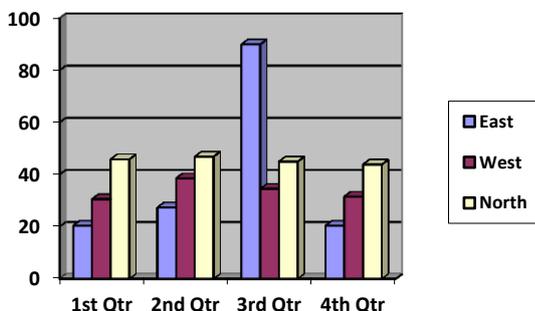


Fig 1 Bar diagram depicting volume of levosimenden & other inotropes

