Original Article

Comparison of levosimendan and nitroglycerine in patients undergoing coronary artery bypass graft surgery

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ABSTRACT

Background: Levosimendan a calcium ion sensitizer improves both systolic and diastolic functions. This novel lusitropic drug has predictable antiischemic properties which are mediated via the opening of mitochondrial adenosine triphosphate-sensitive potassium channels. This action of levosimendan is beneficial in cardiac surgical patients as it improves myocardial contractility, decreases systemic vascular resistance (SVR), and increases cardiac index (CI) and is thought to be cardioprotective. We decided to study whether levosimendan has any impact on the outcomes such as the duration of ventilation, the length of Intensive Care Unit (ICU) stay, and the hospital stay when compared with the nitroglycerine (NTG), which is the current standard of care at our center. **Materials and Methods:** Forty-seven patients undergoing elective coronary artery bypass surgery were randomly assigned to two groups receiving either levosimendan or NTG. The medications were started before starting surgery and continued until 24 h in the postoperative period. Baseline hemodynamic parameters were evaluated before beginning of the operation and then postoperatively at 3 different time intervals. N-terminal fragment of pro-brain natriuretic peptide (NT-proBNP) levels were also measured in both groups. **Results:** In comparison to the NTG group, the duration of ventilation and length of ICU stay were significantly less in levosimendan group ($P < 0.05$, $P = 0.02$). NT-proBNP level analysis showed a slow rising pattern in both groups and a statistically significant rise in the levels was observed in NTG group ($P = 0.03$, $P = 0.02$) in postoperative period when compared to levosimendan group of patients. **Conclusion:** Levosimendan treatment in patients undergoing surgical revascularization resulted in improved CI, decreased SVR and lower heart rate. And, thereby the duration of ventilation and length of ICU stay were significantly less in this group of patients when compared with NTG group.

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INTRODUCTION

Myocardial dysfunction, a frequent complication after open heart surgeries performed under cardiopulmonary bypass (CPB) is mediated by ischemia and reperfusion injuries. Myocardial preservation with cold primed potassium rich cardioplegia prevents ischemia by causing electromechanical arrest of the heart in diastole and by reducing the myocardial oxygen consumption. However, many patients still develop myocardial dysfunction requiring pharmacological or mechanical circulatory support during weaning off CPB and/or afterward in the postoperative period in the Intensive Care Unit (ICU), accounting for increased morbidity and mortality.[1,2]

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Levosimendan, a calcium ion sensitizer with a unique mechanism of action has been used in patients with poor left ventricular function undergoing coronary revascularization and in acute heart failure situations.[3,4] It has a positive inotropic[5] and anti-stunning effects mediated by calcium sensitization of contractile proteins.[6] By opening of the adenosine triphosphate (ATP)-sensitive potassium (K-ATP) channels, levosimendan imparts additional vasodilatory[7] and anti-ischemic properties.[8] The K-ATP channel being an important mediator of cardioprotection,[8] levosimendan may offer beneficial effect in situations of myocardial stress.

NTG has been in use in the patients undergoing surgical coronary revascularization since long with proven benefits.[9] However, its effect is not predictable when used as an infusion for a longer period of time due to tachyphylaxis.[10] Further, additional inotropic support is required in many patients in the immediate postoperative period.

MATERIALS AND METHODS

Following approval of Hospital Research Ethics Committee and obtaining written informed consent, 47 adult patients undergoing elective on-pump coronary artery bypass graft surgery (CABG) were enrolled for this study. The patients were randomly allocated to levosimendan (Group L) (Simenda Injection Manufactured by Lupin Ltd. India) and nitroglycerine (NTG) (NTG Injection Manufactured by Unimed Technologies Ltd. India) (Group N) groups. This study was conducted in Cardiothoracic and Vascular Surgery operating room and ICU, All India Institute of Medical Sciences between January 2013 and January 2014. Inclusion criteria were age >18 years and normal ejection fraction (ejection fraction >50%) undergoing 1st time on pump CABG. Exclusion criteria included cardiac failure, unstable angina, associated valvular heart disease, diabetes mellitus treated with sulfonilureas, renal dysfunction (preoperative serum creatinine >1.5 mg/dl), abnormal liver function (serum aspartate aminotransferase or alanine aminotransferase >100 IU/L) and significant chronic obstructive pulmonary disease (forced expiratory volume in 1 s <50% of the predicted value or <2 L), history of prior CABG or recent MI within the previous month.

In the operation theater, patients were monitored with electrocardiogram, invasive blood pressure, pulse oximetry, nasopharyngeal temperature, pulmonary artery catheter (PAC), arterial blood gas, urine output, and capnography. The mean arterial pressure (MAP) and heart rate (HR) were maintained at 80–100 mmHg and 60–80/min respectively in both the groups at all points of time prior to initiation of CPB. After the induction of anesthesia and tracheal intubation, a continuous thermodilution PAC (CCO-PAC, Edwards Lifesciences, Irvine, CA, USA) was inserted in the right internal jugular vein under sterile conditions and the baseline hemodynamic data such as cardiac index (CI), systemic vascular resistance (SVR), and pulmonary capillary wedge pressure (PCWP) were recorded. The aim was to maintain the CI, SVR, and PCWP near normal at all points of time. The study drug levosimendan or NTG was administered as a slow intravenous (iv) infusion through the central venous port of a PAC before starting the operation. Hypotension, defined as MAP <60 mm Hg was treated by iv fluid or phenylephrine boluses of 50 μg, similarly, hypertension was treated with boluses of fentanyl, midazolam or metoprolol. As per the standard protocol, CPB was established after systemic heparinization and coronary artery bypass operation was performed under mild hypothermia (32°C) using one left internal mammary artery (LIMA) and one to three vein grafts obtained from lower limbs. CPB was discontinued following rewarming up to 36°C of nasopharyngeal temperature. After surgery, all patients were shifted to ICU and electively ventilated and sedated with propofol infusion at 1 mg/kg/h. Upon meeting the extubation criteria (CI >2.5 L/min/m^2, hemodynamic stability, no significant arrhythmias, hemoglobin >10 g/dl, no signs of excessive bleeding [>100 ml/h], peripheral temperature exceeded 33°C, urine output >0.5 ml/kg/h, adequate response to command, arterial oxygen saturation by pulse oximetry [SpO_2] >95% at a fraction of inspired oxygen concentration [FiO_2] <0.6, pH >7.3, arterial carbon dioxide tension [$PaCO_2$] <40 mm Hg and adequate respiratory effort) the patients were extubated.

The patients were shifted to the wards when they fulfilled the following eligibility criteria SpO_2 >95% at a FiO_2 <0.5 by face mask, adequate hemodynamic stability with no arrhythmias, chest tube drainage <50 ml/h, urine output >0.5 ml/kg/h, and no inotropic or vasopressor therapy. The criteria for discharging the patients from hospital were hemodynamic stability without arrhythmias, the presence of clean, dry wounds, no pyrexia, and no difficulty in bowel and bladder movements, ambulating and eating independently.

Drug administration

The study drug levosimendan was started at 10 mcg/kg over 10 min as a loading dose through CCO-PAC followed by an infusion at 0.1 mcg/kg/min in Group L and continued up to 24 h in the ICU. Similarly, in Group N, NTG was started at 0.5 mcg/kg/min. The drugs were started prior to skin incision after the baseline hemodynamic parameters were recorded from PAC and continued post-CPB in the ICU for 24 h. Post-CPB in odds ratio and in the ICU inotropic support epinephrine infusion at 0.05–0.1 mcg/kg/min was commenced if MAP <65 mm Hg with CI <2 L in the presence of PCWP of 15 and HR of 70–110 in NTG group and norepinephrine infusion at 0.05–0.1 mcg/kg/min was used for MAP <65, SVR <800 dynes/s/cm^{-5} and a CI >3l/m/m^2 in Group L. Seven patients from Group N and 10 patients from Group L received epinephrine and norepinephrine infusions, respectively, and all these patients (n = 17) were excluded from the study [Figure 1].

Blood samples for an N-terminal fragment of pro-brain natriuretic peptide (NT-proBNP) levels were drawn in ethylenediaminetetraacetic acid vials and were estimated at 3 different time points by immunoassay (Alere Triage R NT-proBNP kits, Alere Inc. Waltham, MA, USA). T1 was before starting the study drugs, T2 at 12 h and T3 at 24 h post CABG in the ICU. Hemodynamic measures were recorded at 4 different time points, before starting the study drugs (T1), at 6 h (T2), at 12 h (T3), and at 24 h (T4) in the ICU.

Outcomes

The outcomes such as duration of ventilation, the length of ICU stay, and the length of hospital stay were observed in this study.

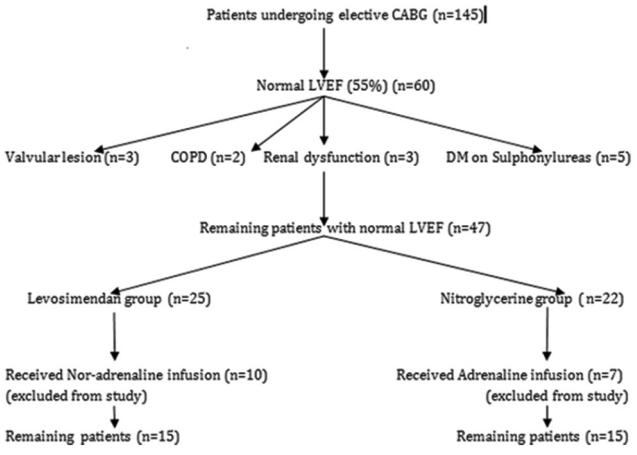

Figure 1: Consort diagram of the study

Analysis

Patient demographics, hemodynamics, and NT-proBNP levels were reported as mean ± standard deviation. The above data were analyzed by independent Student's *t*-test between two groups, whereas repeated measures analysis was done with paired samples *t*-test to compare the values within the same group at 4 different time points. All the categorical variables were analyzed using Fisher's exact test. $P < 0.05$ was considered statistically significant. All the data were analyzed by SPSS version 21.0 (IBM SPSS Statistics, Version 21.0. Armonk, NY: IBM Corp. USA).

RESULTS

In this study, we enrolled 47 consecutive patients divided into two groups - Group L (n = 25) and Group N (n = 22). After excluding, 17 patients who required inotropes and vasopressors [Figure 1] (seven from NTG group and 10 from levosimendan group), each group had 15 patients. The data from all 30 patients were included in the statistical analysis. The two groups were comparable with respect to demographic and intraoperative data [Table 1]. No significant difference was observed in CPB time, aortic cross-clamp time and number of vessels grafted [Table 1].

Table 2 summarizes postoperative results and clinical outcomes. The length of ICU stay and duration of ventilation were significantly less in Group L ($P = 0.02$ and $P < 0.05$). However, there was no difference in hospital stay between both groups [Table 2].

Table 3 shows hemodynamic variables (HR, MAP, PCWP, CI, and SVR) measured at various time intervals in both groups. No significant difference in baseline hemodynamic values was seen between the groups [Table 3]. The CI measured at T2, T3, and T4 after surgery was significantly higher in Group L ($P = 0.03$, $P = 0.02$, $P < 0.05$) [Table 3] and SVR measured at T2 andT3 were significantly lower in Group L ($P = 0.02$, $P = 0.04$) [Table 3] when compared with the values at same time points in Group N. And also there was significant decrease in SVR at T2, T3, and T4 compared with the T1 values within both groups individually [Table 3]. The CI was significantly higher at T4 when compared to T1 in both groups independently [Table 3].

Table 4 depicts the NT-proBNP levels in both groups. The NT-proBNP levels rose in both the groups post-CPB but the rate of rise was statistically significant in

Group N ($P = 0.03$, $P = 0.02$) when compared with Group L. The rise of NT-proBNP within the Group L was less than the rise within the N group ($P = 0.02$, $P = 0.04$).

There were no postoperative adverse cardiovascular events/complications such as myocardial infarction, life-threatening arrhythmias, pulmonary edema, and major neurological deficit in both groups. Intra-aortic balloon counterpulsation was not required for any of the patients in both groups. Re-exploration for significant postoperative bleeding was performed in two patients (one in each group) [Table 2].

Table 1: Baseline demographic and surgical data in both groups

Parameters	Group L (*n*=15)	Group N (*n*=15)	*P* value
Age	63.60±11.31	61.20±12.17	0.72
Sex (male)	10	11	0.50
Weight (Kgs)	74.8±9.0	75.4±13.0	0.57
Height (cms)	165.9±8.3	166.4±7.9	0.90
Ejection fraction%	57±3.5	56.8±2.0	0.80
CPB duration (mins)	75.8±6.5	75.5±6.4	0.71
ACC duration (mins)	47.5±8.8	46.7±5.5	0.87
Number of grafts	3±1	3±1	0.92

CPB: Cardiopulmonary bypass, ACC: Aortic cross clamp

Table 2: Post-operative results: Data expressed as mean±standard deviation

Parameters	Group L (*n*=15)	Group N (*n*=15)	*P* value
Thirty day mortality	0	0	>0.05
Ventilation duration (hrs.)	6.3±1.5	8.5±1.8	<0.05
ICU stay (hrs.)	33.3±7.1	43.3±14.2	0.02
Hospital stay (days)	12.3±1.8	12.0±1.7	0.77
Re-exploration (*n*)	1	1	>0.05

DISCUSSION

In this study, we have shown that levosimendan may be superior to NTG as far as left ventricular systolic and diastolic functions (significant increase in postoperative CI, a decrease in SVR, lower HR, and less rise in NT-proBNP levels in Group L when compared to Group N) are concerned. This could be seen from a significant reduction in ventilation duration, the length of ICU stay and earlier extubation in Group L.

Despite the use of contemporary cardioprotective strategies, variable degrees of myocardial stunning occur after cardiac surgery, and this may result in postoperative myocardial dysfunction. Myocardial stunning represents a prolonged postischemic contractile dysfunction of myocardium salvaged by reperfusion.[11] Studies have demonstrated contractile dysfunction over first few hours after myocardial revascularization that generally resolves spontaneously over 24–48 h.[12] During the period of transient myocardial dysfunction, there is a need to improve the myocardial function, so inotropic agents are chosen for hemodynamic support. Unlike regularly used inotropes, levosimendan improves myocardial contractility primarily by enhancing myocardial contractile protein sensitivity to calcium without increasing its intracellular concentration. This

Table 3: Haemodynamic variables at different time intervals (Data expressed as mean±standard deviation)

Parameters	Group	T1	T2	T3	T4
HR (beats/minutes)	L	64.3±8.2	69.6±7.4[a]	70.0±8.6[b]	67.3±8.1
	N	64.1±8.5	81.2±8.8	80.67±8.8	82.8±9.8
P value		0.97	0.001	0.002	<0.001
MAP (mmHg)	L	84.1±5.6	86.1±6.5	83.1±4.8	82.9±4.4
	N	84.1±5.3	84.1±7.4	84.2±5.2	84.1±5.4
P value		0.95	0.48	0.75	0.49
CI (ml/min/square meter)	L	3.1±0.7	3.2±0.7	3.3±0.7	3.4±0.5[c]
	N	2.6±0.7	2.6±0.6	2.6±0.6	2.9±0.3[c]
P value		0.09	0.03*	0.02*	<0.001
SVR	L	1221.1±390.1	1116.8±318.1[a]	1116.7±311.8[b]	1101.9±307.1[c]
	N	1489.3±383.4	1391.1±361.2[a]	1369.7±350.2[b]	1277.3±311.1[c]
P value		0.06	0.02*	0.04*	0.10
PCWP (mmHg)	L	13.7±1.9	13.3±1.9	13.1±0.9	12.8±0.9
	N	14.3±1.4	13.4±1.1	13.6±0.9	12.7±0.8
P value		0.29	0.82	0.13	0.82

HR: Heart rate, MAP: Mean arterial pressure, CI: Cardiac index, SVR: Systemic vascular resistance, PCWP: Pulmonary capillary wedge pressure; [a]*P*<0.05 between T1 and T2 within the group; [b]*P*<0.05 between T1 and T3 within the group; [c]*P*<0.05 between T1 and T4 within the group; **P*<0.05 between the two groups

Table 4: N-terminal fragment of pro-brain natriuretic peptide levels at T1, T2, T3. Data expressed as mean±standard deviation

Time interval	Group L (*n*=15)	Group N (*n*=15)	Remarks
T1	432.28±216.69	505.12±283.13	*P*>0.05
T2	466.57±66.34	987.5±593.6	[a](*P*=0.02), [#](*P*=0.03)
T3	536.57±112.26	1216.62±711.54	[b](*P*=0.04), [#](*P*=0.02)

[a]*P*<0.05 between T1 and T2 within the group, [b]*P*<0.05 between T1 and T3 within the group, [#]*P*<0.05 between the two groups

action does not result in an increase in myocardial oxygen consumption.[13,14] Levosimendan acts by direct binding with protein-C, thereby increasing the affinity of troponin-C for calcium. A lack of calcium sensitization under low calcium concentration (i.e., during diastole) has been shown to prevent worsening of diastolic dysfunction in patients with heart failure. Levosimendan causes vasodilatation, which has been attributed to activation of K-ATP channels and decreasing the sensitivity to calcium.[15,16] An increase in coronary blood flow and reduction in coronary vascular resistance have been reported.[17]

Many studies have indicated that early use of levosimendan induces protection against subsequent ischemic stress through its K-ATP channel opening properties.[8] The opening and stimulation of mitochondrial K-ATP channel are an important mediator which protects the heart against ischemia-reperfusion damage,[18] decreases myocardial infarct size,[19] does ischemic preconditioning,[20] and enhances recovery of stunned myocardium.[21] Clinical use of levosimendan has shown to improve cardiac performance in left ventricular failure.[22,23]

Our study confirmed the benefits of the early use of levosimendan in on-pump CABG patients by improving the hemodynamics and maintaining a steady level of NT-proBNP and with this the outcome advantages (reduced length of ICU stay). Our findings are similar to the results observed in recent studies,[4] strengthening the conclusion that the observed increase in CI produced by levosimendan probably the result of combined action of reduced SVR (LV afterload) and a modest increase in myocardial contractility. Levosimendan has a fast onset of action (due to short elimination half-life of 1 h) but its effects are long lasting due to its active metabolite OR-1896 (has a long elimination half-life of 70–80 h). This long half-life of OR-1896 maintains the drug's efficacy for up to 9 days after 24 h infusion.[24] This along with its less arrhythmogenic property makes it superior over other traditional inotropes.[25] Data suggest that this effect might be related to anti-inflammatory and anti-apoptotic properties.[8] Owing to its K-ATP channel opening properties, levosimendan produces vasodilatation and causes potentially significant hypotension. Use of nor-epinephrine (as a vasoconstrictor) infusion has been recommended in many studies to counter the hypotension induced by levosimendan.[4]

Despite the proven benefit of NTG after CABG,[9] it has got its own limitations, of which tolerance is most important. The mechanism of tolerance has been extensively investigated.[10] To overcome this disadvantage, we compared NTG with levosimendan to assess the later's efficacy as a lusitropic agent and thereby making it an alternative to NTG in patients undergoing on-pump CABG. Kivikko *et al*.[25] in their review opined that tolerance was absent with levosimendan, despite 48 h of infusion and that the cardiac performance improved with no increase in oxygen consumption. Another theoretical possible disadvantage of application of NTG is that it can affect pulmonary gas exchange in the early postoperative period by stealing the pulmonary blood flow to areas of less ventilation (antagonizing effect on hypoxic pulmonary vasoconstriction).[26] This is particularly seen after on-pump cardiac surgeries where early postoperative hypoxemia is not uncommon. Because of this, the time on tracheal intubation gets prolonged, and ICU stay becomes longer. Moreover, the third disadvantage with NTG is that it is purely a vasodilator having no inotropic action. In early postoperative period due to the myocardial contractile dysfunction, some amount of inotropic support is required alongside with NTG for the heart to recover from myocardial stunning effect. NTG has advantages in early postoperative period because of its antihypertensive action (as vasoconstriction plays a major role in causing hypertension).[27] NTG, a coronary vasodilator, prevents spasm of LIMA, and it helps in uniform rewarming of the patient before terminating the CPB. Despite all these advantages, we in the current study could demonstrate that NTG is inferior to levosimendan in patients undergoing on-pump CABG. The hemodynamics (higher CI, lower SVR, and lower HR) were better maintained with levosimendan than NTG and the outcomes such as ventilation duration and length of ICU stay were shorter with levosimendan. Adrenaline was used as inotrope at 0.05 mcg/kg/min by other studies to support the MAP if it decreases while the patient is on NTG infusion.[27]

NT-proBNP has been used as one of the biochemical markers for risk stratification with coronary artery disease.[28] NT-proBNP reliably detects both systolic and diastolic dysfunction in patients undergoing CABG under CPB.[29] Since the rise of NT-proBNP levels was less in Group L, it was justified to say that levosimendan had a beneficial effect on both systolic and diastolic function which was correlated clinically from improved hemodynamic parameters such as increased CI and decreased SVR. Though NT-proBNP levels were expected to fall 24 h postsurgery, the biochemical picture was opposite. The half-life of NT-proBNP is considered to be 60–120 min,[30] suggesting that meaningful changes in hemodynamics could be reflected by this test theoretically every 12 h. Thus, NT-proBNP concentrations lag behind the clinical picture, given its longer time for clearance.

CONCLUSION

Early treatment with levosimendan (before skin incision) with bolus and then continuous infusion in patients undergoing on-pump CABG surgery resulted in earlier extubation, reduction in ventilation duration and a shorter length of ICU stay. Thus levosimendan can be used as an alternative to routine NTG, though at a higher cost. More studies are required to find out if the same beneficial clinical outcomes are achieved in patients undergoing high-risk cardiac surgery.

Limitations

The current study has a small sample size. A bigger sample size is necessary to prove the superiority of levosimendan over NTG. Echocardiographic evaluation in postoperative period could have been done to assess the systolic and diastolic functions. Other biochemical markers could have been tested to detect any myocardial injury/or any new onset of myocardial ischemia/infarction.

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Conflicts of interest

There are no conflicts of interest.

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