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Research Article

Effect of Levosimendan and Milrinone Combination in Chronic Kidney Disease Patients Who Underwent Cardiac Surgery

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Abstract

Background: The effect of levosimendan use in chronic kidney disease (CKD) patients who underwent cardiac surgery has been investigated in a small number of subjects. Our purpose of this study was to investigate the hemodynamic effects of perioperative levosimendan in combination with milrinone administration in CKD patients underwent cardiac surgery and with poor left ventricle.

Methods: 164 CKD patients (the mean age = 56 yrs) with poor left ventricle and a high pulmonary artery hypertension were included in this study. Mean creatinine clearance was lower than 30-59 mL/min/1,73 m² (moderate to severe renal impairment). Levosimendan and milrinone were administered to 84 patients (study group; SG). The remaining 80 patients treated with placebo (placebo group; PG). We compared cardiac output (CO), cardiac index (CI), systemic vascular resistance (SVRI), pulmonary vascular resistance (PVR), myocardial enzymes, and tumor necrosis factor alpha (TNF-alpha) immediately after surgery and at 2 h, 6 h, 12 h, and 24 h after operation.

Results: No significant difference in operative mortality between groups was observed (6.3% vs. 7.7%, P=0.76). The SG showed lower rates of postoperative low-cardiac output syndrome (LCOS) (29.3% vs. 41.6%, P=0.001), and arrhytmia (26.8% vs. 44.6%) (P=0.01). CO and CI values were significantly higher in SG after the end of 6 h. PVR values were significantly low in SG (P=0.034). The amount of inotropic requirement was low in SG (P= 0.002). The laboratory analyses showed that c-TnI and TNF-alpha levels were low in SG (P= 0.0001). Compared to preoperative period, higher mean LVEF was found in both groups in the postoperative period, but the mean increase in LVEF in SG was higher than in the PG (11.70±2.39 vs. 6.2±1.30) (P<0.001).

Conclusion: The use of levosimendan plus milrinone significantly improved hemodynamics in CKD patients with poor left ventricle who underwent cardiac surgery. Duration of ICU and hospitalization were decreased significantly with inodilators treatment. Therefore, we suggest the use of levosimendan and milrinone combination in per- and postoperative period in cardiac surgery patients with CKD and poor left ventricle.

Keywords: Poor left ventricle, Chronic kidney disease, Levosimendan, Milrinone, Cardiac surgery.

Kalp Cerrahisi Geçiren Kronik Böbrek Hastalığı Hastalarında Levosimendan ve Milrinon Kombinasyonunun Etkisi

Öz

Amaç: Levosimendan kullanımının etkisi kalp ameliyatı geçirmiş kronik böbrek hastalığı (KBH) hastalarında az sayıda denekte araştırılmıştır. Bu çalışmanın amacı, kalp cerrahisi geçirmiş ve sol ventrikülü zayıf olan KBH hastalarında milrinon uygulaması ile kombinasyon halinde perioperatif levosimendan'ın hemodinamik etkilerini araştırmaktı.

Method: Bu çalışmaya, sol ventrikülü zayıf ve pulmoner arter hipertansiyonu yüksek olan 164 KBH hastası (ortalama yaş = 56 yıl) dahil edildi. Ortalama kreatinin klerensi 30-59 mL/dak/1,73 m²'den düşüktü (orta ila şiddetli böbrek yetmezliği). 84 hastaya (çalışma grubu; SG) levosimendan ve milrinon uygulandı. Kalan 80 hasta plasebo ile tedavi edildi (plasebo grubu; PG). Kardiyak output (CO), kardiyak indeks (CI), sistemik vasküler direnc (SVRI), pulmoner vasküler direnç (PVR), miyokardiyal enzimler ve tümör nekroz faktörü alfa (TNF-alfa) ameliyattan hemen sonra ve 2. , 6. , 12. ve 24. saatte karşılaştırdık.

Bulgular: Gruplar arasında operatif mortalite açısından anlamlı bir fark gözlenmedi (%6.3'e karşı %7.7, P=0.76). SG, daha düşük postoperatif düşük kalp debisi sendromu (LCOS) (%29.3'e karşı %41.6, P=0.001) ve aritmi (%26.8'e karşı %44.6) (P=0.01) gösterdi. CO ve CI değerleri 6 saatin sonunda SG'de anlamlı olarak daha yüksekti. SG'de PVR değerleri anlamlı derecede düşüktü (P=0.034). SG'de inotropik gereksinim miktarı düşüktü (P= 0.002). Laboratuvar analizleri SG'de c-TnI ve TNF-alfa düzeylerinin düşük olduğunu gösterdi (P= 0.0001). Ameliyat öncesi dönem ile karşılaştırıldığında, ameliyat sonrası dönemde her iki grupta da ortalama LVEF daha yüksek bulundu, ancak SG'de LVEF'deki ortalama artış PG'den daha yüksekti (11.70±2.39'a karşı 6.2±1.30) (P<0.001).

Sonuç: Kalp cerrahisi geçiren sol ventrikülü zayıf olan KBH hastalarında levosimendan ve milrinon kullanımı hemodinamiyi önemli ölçüde iyileştirdiği saptandı. İnodilatör tedavi ile yoğun bakım ve hastanede kalış süresi önemli ölçüde azaldı. Bu nedenle KBH ve ejeksiyon fraksiyonu düşük sol ventrikülü olan kalp cerrahisi hastalarında postoperatif ve peroperatif dönemde levosimendan ve milrinon kombinasyonunun kullanılmasının gerekliliği görüldü.

Anahtar Kelimeler: düşük ejeksiyon fraksiyonlu sol ventrikül, Kronik böbrek hastalığı, Levosimendan, Milrinone, Kalp cerrahisi.

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1. Introduction

A number of inotropic agents increases the intracellular cyclic adenylate monophosphate levels, which induces the increase in calcium release from the myocardium. Calcium accumulation gives rise to elevated myocardial oxygen consumption can result in myocardial deterioration during inotrope infusion (Hasenfuss et all., 1987) Several substrates are also utilized and have profound depression effects on myocardium due to high oxygen consumption during extracorporeal circulation (ECC). Substrate utilization is a key factor determining the oxygen consumption of the myocardial cells (Opie et all., 1991, Bersin et all., 1994, Eichhorn et all., 1994). Therefore, optimal myocardial function after cardiac surgery cannot provide in number of patients peroperatively. Observational data in chronic kidney disease (CKD) patients with poor left ventricle suggest that the use of epinephrine is associated with worse clinical outcomes such as serious ventricular arrythmia (Heringlake et all., 2007). Despite to levosimendan use is contraindicated in CKD patients, there are limited number of investigations have been published, recently. Our previous research showed that levosimedan use increased significantly ventricular functions in hemodialyses patients (Atalay et all., 2016). Also, the authors suggested levosimendan use in ESRDPs in case reports and clinical articles (Puttonen et all., 2007, Lobo Martínez et all., 2011, Papadopoulos et all, 2010). Lobo et collegues reported a succesfull result using LS in ESRD patient with severe myocardial dysfunction resistant to inotropic support (Lobo et all., 2011). Marked clinical and echocardiographic improvement without any side effect has been detected by the authors (Atalay et all., 2016, Lobo et all., 2011, Papadopoulos et all., 2010). Papadopoulos et all. showed that successfull use of levosimendan/norepinephrine combination in 13 chronic kidney disease patients undergoing hemodialyses with impaired myocardial contractility.

Milrinone, as a phosphodiesterase (PDE) III inhibitor agent, is an alternative of traditional inotropic support (Atalay et all., 2016). Besides acting as positive inotropic drugs, PDE inhibitors also acts as vasodilator via inhibiting PDE in vascular smooth muscle cells (Puttonen et all, .2007). Previous studies reported no adverse metabolic effects when the patients were treated with PDE III inhibitors, and their pre-emptive use was indicated to be beneficial on renal tubular injury markers (Lobo Martínez et all., 2011). Compared to dopamine and adrenaline, milrinone use cause less increased myocardial oxygen consumption or heart rate (Papadopoulos et all., 2010). Moreover, studies including patients with impaired left ventricular function undergoing coronary artery bypass graft (CABG) surgery reported that milrinone may decrease the postoperative myocardial ischemia and infarction incidence (Kikura et all., 2003). On the other side, levosimendan, as a new calcium sensitizer agent that exerts its activities by binding to cardiac troponin-C (cTn) in a calcium dependent manner without affecting myofibrillar ATPase. According to a previous investigation, levosimendan and milrinone stabilize the calcium-induced conformational change of cTn. These agents do not impair relaxation of intact paced isolated failing human myocardium (Parissis et all., 2007 Haikala et all., 1995, Hasenfuss et all., 1995, Végh et all., 1995, Lilleberg et all., 1995). Milrinone was also suggested to be administered to patients with pulmonary artery hypertension combined with myocardial dysfunction after ECC (Öztekin et all., 2007).

Based on these properties, we hypothesized that combinatorial use of levosimendan and milrinone in CKD patients with left ventricular dysfunction would result in improved postoperative cardiac function after open heart surgery.

2. Material and Method

We randomly selected 164 CKD patients with pulmonary artery hypertension who underwent cardiac surgery. This research has been performed between December 2008 and July 2015 after obtaining local ethics committee approval. All patients gave their written informed consents before enrolling. All patients had coronary artery disease with severe mitral and/or aortic valve disease. The inclusion criteria were LVEF lower than 0.40, a systolic pulmonary artery pressure (sPAP) was mo.re than 50 mmHg. On the other hand, exclusion criteria were known allergy to levosimendan or milrinone, redo operations, chronic obstructive pulmonary disease, severe hepatic, or end-organ disorders.

A nurse prepared the placebo, thereby ensuring that operation and ICU team were blinded to the group assignment. Study group (SG) patients were administered with a levosimendan (Simdax; Orion Pharma, Espo, Finland) bolus at a dose of 10 μg/kg for 30 minutes that was followed by a 24-h infusion at a rate of 0.05 μg/kg/min. Milrinone was administered as a half dose of bolus (25 μg/kg) immediately after weaning from ECC, and it continued at a dose of 0.5 μg/kg/min. for 24 hours later. Placebo group (PG), on the other hand, received the placebo drug, which was prepared to look-alike to levosimendan and milrinone combination and contained water-soluble vitamin concentrate (10 ml vitamin diluted in 500 ml 5% glucose solution).

2.1. Surgery

Anesthesia and cardiopulmonary bypass (CPB) procedures were performed according to our clinical practice. For hemodynamic monitoring in the operating room, a pulmonary artery catheter (Criticath; Becton-Dickinson, USA.) was inserted. On admission to the operating theatre and thereafter, the goals and means of hemodynamic support were to keep the pulmonary capillary wedge pressure (PCWP) of 12–18 mm Hg with fluid administration and the mean arterial pressure between 50 and 70 mmHg. We carefully gave attention to provide the cardiac index > 1.8 - 2.2 L/min/m² with dobutamine administration.

Hemodynamic measurements including mean arterial pressure (MAP), CI, CO, PVR and systemic vascular resistance index (SVRI) were made before induction of anesthesia. These values were calculated immediately after weaning from ECC, and at postoperative 2 h, 6 h, 12 h, and 24 h in the ICU. Cardiac enzyme analyses were calculated preoperatively (T0), and immediately after the release of aortic cross-clamp, and at postoperative 1 h, 6 h, 12 h, 24 h and 48 h. Blood gas measurements including mixed venous saturation, and hematocrit were taken in ICU every 6 h. Echocardiography was performed at baseline and prior to discharged.

2.1. Statistical methods

Data were analyzed by using SPSS for Windows statistical software (version 13.0, Inc., Chicago, IL, USA). Timepoint-wise comparisons were conducted with the T-test. Mann–Whitney U-

test was employed to analyze the cumulative doses of vasoactive medication comparisons between the groups and data were presented as mean ± standard deviation (SD). Data for normally distributed continuous variables were presented as mean values ± SD. Demographic characteristics and peri-operative variables of the patients, as well as the calculated values from the analyses, were compared by using independent samples t-test for continuous variables while categorical variables were analyzed by using either Chi-square test or Fisher's exact test. Categorical variables were expressed as numbers and percentages. Differences within groups were evaluated by using paired-samples t-test. P values lower than 0.05 was considered statistically significant.

3. Results

The patients' demographics and preoperative medications are summarized in Table 1. The charecteristics of the patients, preoperative medication, LVEF and PAP were comparable. No difference was found when compared to EuroSCORE. In patients with severe mitral or aortic valve stenosis, mechanical or bioprosthetic valve replacement was performed. We performed valvular plasty in patients with mitral and/or aortic valve insufficiency. The charecteristics of surgical procedures in both groups have been summarized in Table 2. Intraoperative and postoperative properties including intraaortic balloon pump (IABP) use and inotropic infusion are indicated in Table 3. No differences were observed between groups when preoperative MAP, SVRI, CI, and heart rate (HR) were compared. Intraoperative and postoperative data including HR, CO, CI, cardiac enzyme, and TNF-alpha levels at various intervals have been shown in Table 4.

Table 1. *Demographic data of the patients.*

Characteristics	SG N=84	PG N=80	p-value
Age (years)	59,6±9,7	55,5±6,9	0,90
Male/Female	52/32	47/33	0,79
BSA (m^2)	1,80±0,12	1,87±0,09	0,84
Functional Capacity (NYHA)	3,1±0,4	3,2±0,3	0,90
Pre-operative EF (%)	41,8±0,4	3,2±0,3	0,95
Pre-operative sPAP (mmHg)	41,2±14,2	42,8±12,1	0,90
Medication			
Calcium channel inhibitors	44	42	
Antiarrhythmicagents (N)	13	4	
Platelet aggregation inhibitors (N)	84	80	
Nitrates (N)	59	56	

BSA: body surface area, EF: ejection fraction, NYHA: New York Heart Association, PAP: Pulmonary arterial pressure.

Table 2*. Surgical procedures in both groups.*

Surgery type	SG	PG
CABG+MVR	27	25
CABG+AVR	24	28
CABG+AVR+MVR	8	10
CABG+ Mitral repair	18	10
CABG+ Aortic repair	9	5
CABG+ AVR+MP+TP	4	2

AVR: Aortic valve replacement, **CABG**: Coronary artery bypass grafting, **MP:** Mitral plasty, **MVR:** Mitral valve replacement, **TP**: Tricuspid plasty.

Table 3. *Intraoperative and postoperative data.*

Features	SG	PG	p-value
XC period (min)	88.7 ± 56.4	69.2 ± 26.8	0.779
CPB period (min)	115,4 ±62,8	89,4 ±33,2	0,884
Operation time (min)	219,5±83,2	155,0±49,4	0,424
Need for inotropic drug*	19 (55.8%)	24 (80%)	**0,012**
Need for IABP*	2 (5.8%)	6 (20%)	0,0021
Mortality	1 (2.8%)	2 (6%)	0,63
Postoperative exploration	1	2	0,084
Low cardiac output*	6 (10.7%)	15 (50%)	0,0001
Acute renal failure	2	4	0,078
Lenght of stay in ICU (h)	43,6 ±2,1	57,5 ±1,3	0,0001
Lenght of stay at hospital* (d)	13,2 ±2,4	16,8 ±1,5	0,0001
Arrhytmia*	6,5 ±4,8	11 ±3,4	0,036

CPB; Cardiopulmonary bypass, **IABP;** Intra-aortic balloon counterpulsation, **ICU;** Intensive care unit, **XC:** Cross-clamp;

Table 4. *Heart rate, cardiac index and enzymes levels at various time intervals*

Time	Group	HR	CI	CK-MB	c-Tro-I	CO (L/min)
Baseline	SG	77.13±5.4	2.09±0.20	17.4±8.2	0.90±1.09	2.11±0.20
	PG	69.83±7.4	2.03±0.18	16.26±6.1	0.87±1.05	2.06±0.22
After weaning from ECU	SG	95.41±3.8	3.19±0.22	34.12±11.20*	3.91±1.90*	2.54±0.20
	PG	89.61±2.7	2.43±0.27	56.10±9.08*	3.60±0.90*	2.36±0.24
1 hour	SG	98.33±6.0	3.29±0.2*	37.24±8.70*	5.90±1.73*	3.54±0.24*
	PG	96.2±8.2	2.32±0.2	55.12±10	4.64±0.19	2.66±0.54
6 hours	SG	93.23±5.9	3.22±0.3*	36.01±6.2*	6.70±1.01*	3.34±0.04*
	PG	91.47±6.0	2.46±0.1*	51.12±6.19	3.90±0.96	2.86±0.30
12 hours	SG	90.63±5.4	3.45±0.3*	28.07±7.20*	5.90±2.04*	3.88±0.12*
	PG	98.23±8.2	2.5±0.2	46.08±5.0	2.86±1.03	3.01±0.70
24 hours	SG	87.22±5.0	3.66±0.2*	19.08±3.77*	3.86±0.96*	3.64±0.20*
	PG	89.32±4.9	2.6±0.2	29.20±7.1	1.90±0.77	2.26±0.54

CI: cardiac index(L/min./m²), **CK-MB:** Creatin Kinase Myocardial Band, **CO:** Cardiac out-put (L/min.), **ECC:** Extracorporeal circulation, **HR:** heart rate. *P<0.05

Table 5. *MAP, CVP, and SVRI measurements at various time intervals*

Time	Group	MAP	CVP	SVRI
Baseline	SG	66.93±7.0	9.2±1.1	1855±134
	PG	62.30±7.1	10.09±1.11	1796±145
After weaning from ECC	SG	58.93±5.5	8.3±2.1	**1558±139***
	PG	56.93±3.2	7.9±3.1	1690±189
1 hours	SG	74.90±6.0	10.01±1.44	**1518±145***
	PG	71.85±4.7	8.6±1.56	1499±145
6 hours	SG	71.93±8.2*	11.20±1.93	**1581±121***
	PG	56.93±2.8	7.23±1.81	1673±111
12 hours	SG	78.93±5.4*	8.2±1.1	**1459±124***
	PG	56.93±5.1	6.67±1.1	1666±111
24 hours	SG	70.43±9.3	9.2±1.1	**1399±136***
	PG	65.93±7	7.2±1.1	1126±115

CVP: Central venous pressure, **MAP:** Mean arterial pressure, **SVRI:** systemic vascular resistance index (dyn/s/cm¯5). *P<0.05

Preoperative TNF-alpha levels were similar in both SG and PG (1.90±2.03 pg/ml and 2.04±2.97 pg/ml, respectively) (P>0.05). In SG and PG at 2 h, the mean TNF-alpha levels were 21.23±7.10 pg/ml, and 38.1±9.1 pg/ml, respectively (P=0.001). In PG, at 6 h, 12 h, and 24 h after surgery, TNF-alpha levels were 44.22±13.3, 56.2±7.2, and 48.7±11.0 pg/ml, respectively. For the same time periods, in SG, the mean serum TNF-alpha levels were 33.10±12.1 pg/ml, 38.6±9.4 pg/ml, and 41.07±8.95 pg/ml. at 6, 12 and 24 hour after surgery. Comparisons of serum TNF-alpha levels for three timepoints revealed significant differences between the groups (P=0.01) (Fig. 1.).

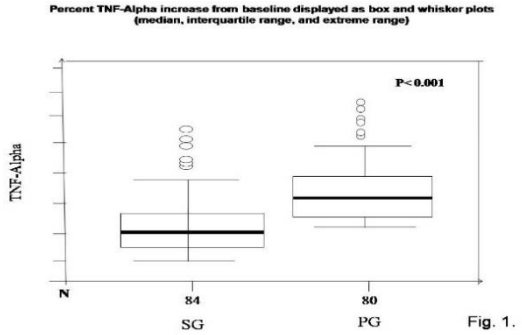

Figure 1*. exhibits that TNF-alpha blood levels in different times. The mean level of TNF- alpha increased significantly in placebo group.*

The SVRI was lower, CO and CI were higher in SG compared with PG (P<0.01). A trend towards lower SVRI values in SG compared to the PG in the immediate postoperative period. In the early postoperative period, CI and LVEF did not change in placebo group. These levels were significantly higher in study group.

Intraoperative characteristics of both groups including duration of cross-clamp, CPB time, dose of inotropic administered to the patients, and the duration of ICU stay are documented in table III. Statistical differences were found for requirement of inotropic drugs and IABP insertion. The amount of inotropic drug use use (dobutamine and/or noradrenaline) was higher in the PG (P=0.001).

The intensive care unit stay and tracheal intubation time was statistically significant in PG (43.6 h vs 57.5 h) (P<0.01). Total hospital stay was significantly low in SG (9.20 d vs 16.80 d) (P<0.001). Significant differences that were in favor of SG were recorded for cardiac enzyme levels, CO and CI (intraoperative and postoperative data are summarized in table 3). Postoperative CI and CO values of SG at 1 h, 6 h, 12 h and 24 h were significantly high in SG.

Intragroup comparisons showed that CO and CI significantly increased regarding the baseline values in SG (P=0.001). Statistically significant differences that were in favor of SG were recorded for preoperative values (table 4). The SG showed lower rates of low postoperative CO (26.3% vs. 63.3%, P=0.014) and arrhytmia (16.3% vs. 44.6%, P=0.021). The heart rate, CI and myocardial enzymes levels at various time intervals have been summarized in table 4.

Compared to the preoperative period, both SG and PG had higher mean LVEF in the postoperative period, but the mean increase in LVEF was higher in SG than PG (8.88±2.39 vs. 4.31±1.23) (P<0.001). Moreover, no significant difference in operative mortality was observed between groups (6.3% vs. 7.7%, P=0.679) (Fig. 2 and 3.). cTp-I values in different times have been shown in Fig. 4.

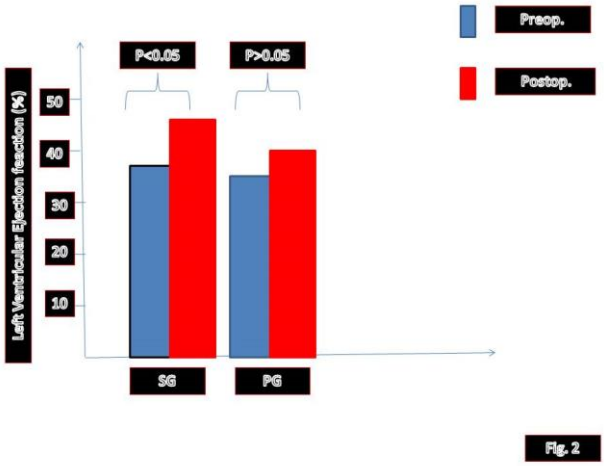

Figure 2. *shows that preoperative and postoperative comparison of LEVF in both groups. LVEF was found elevated significantly in SG.*

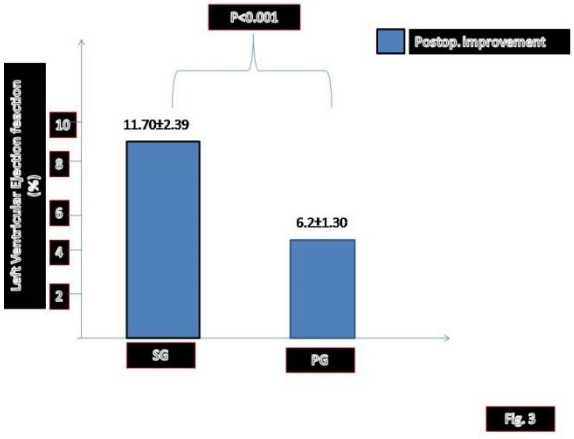

Figure 3. *demonstrates that significant postoperative improvement of LVEF in study group.*

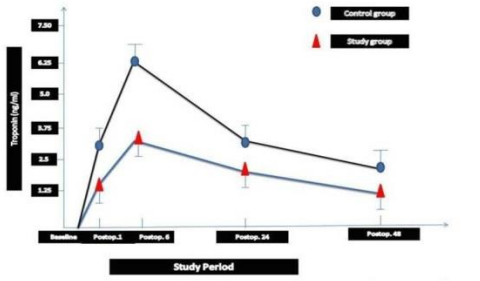

Figure 4*. exhibits that blood c-TnI values in both groups during 48 h intervals. c-TnI concentrations among groups measured immediately after surgery, and at 1 h, 6 h, 24 h and 48 h following the surgical procedures. A significant difference was found when we compared between groups.*

The mean basal PAP was 41.2 ± 16.2 mmHg in SG and 42.8 ± 12.1 mmHg in PG (P>0.05). Postoperatively, PAP measurement was low in SG compared to that in PG (P= 0. 0034). PAP was more decreased in SG over time after operations. Immediately after surgery, the mean PAP value was calculated as 26.40±16.50 mmHg and 33.34±6.40 mmHg in SG

and PG, respectively (P<0.05). When we compared pulmonary vascular resistances after surgery, it was low in SG compared to those in PG. The decrease in PVR over time was marked in SG (PVR:432.4±340.4dyne/s/cm^{-}5 vs PVR:218.7±163.2 dyne/s/cm^{-}5 (P<0.05). MAP, central venous pressure, and SVRI measurements at various time points are summarized in table V. In PG, SVRI was higher immediately after surgery than that in SG (Table V). Baseline and postoperative values were calculated as 1681.2 ± 422.6 dyne/s/cm^{-}5 in SG and 1039.2 ± 354.2 dyne/s/cm^{-}5 in PG (P=0.001).

4. Discussion

To our knowledge, levosimendan in combination with milrinone use has not previously been investigated in CABG concomitant with valve surgery in patients with impaired left ventricle. Our study clearly demonstrated that utilization of levosimendan and milrinone in CABG patients who required heart valve surgery with myocardial impairment undergoing on-pump may be reduce the level of cardiac troponin release, sPAP, and PVRI. Also, our investigation showed that levosimendan administration for preconditioning of left ventricle prior to surgery, and milrinone infusion increased myocardial performance including LVEF, CO and CI peroperatively. Combination of these drugs significantly decreased the duration of intubation, and improved post operative left ventricular stroke work index. In addition, our research revealed that bolus doses of levosimendan and milrinone followed by continuous maintenance administration for about 24 hours post-operatively, could reduce the serum level of c-TnI and TNF-alpha which have been evidences of myocardial ischemia and inflammatory effects of CPB in CABG operations.

To achieve adequate hemodynamic status, the incidence of inotropic drugs (two or more) use is proportionally higher in patients undergoing CABG concomitant with valve surgery when compared to CABG alone in patients with impaired left ventricle. Ischemia-reperfusion during surgery leads to depleted of high energy phosphates, overloaded intracellular calcium levels, and free radical generation (Papadopoulos et all., 2010, Kikura et all., 2003). Risk factors associated with need for inotropic support includes low ejection fraction, congestive heart failure, emergency operation, prolonged duration of CPB and aortic clamping. Therefore, prior to our research we hypothesised that to reduce postoperative mortality and morbidity we used milrinone and levosimendan as inodilator agents, in our risky patients.

Vegh and Lilleberg showed that in a dog model of model acute heart failure induced by ligation of the left anterior descending artery, levosimendan use improved coronary blood flow and myocardial contractility (Hasenfuss et all., 1995, Végh et all., 1995, Lilleberg et all., 1995). In general, recovery of myocardium after one hour after the termination of CPB and continues until 24 hours post-surgery (Oztekin et all., 2007). Our study results are parallel to Veghs' study.

To induce hemodynamic improvement 30-70% of patients have been required inotropic agent(s) peroperatively (Breisblatt et all., 1990). To provide this lethal condition levosimendan has been suggested in previous studies (Hernandez et all., 2009, Nijhawan et all., 1999, Labriola et all., 2004). Previous studies showed that levosimendan improved hemodynamics and enhanced the right ventriculo-pulmonary vascular coupling due to increased contractility and reduced right ventricular afterload in models of acute RV dysfunction in animals (Hein et all., 2009, Missant et all., 2007). In contrast to previous investigation (Cavusoglu et all., 2009), our study showed that peroperative pulmonary artery presure decreased significantly with the use of inodilators combination. We believe that rigt ventricular effects should be investigate in many cases with impaired bi-ventricular heart failure.

Pharmacokinetic properties of levosimendan's metabolites, especially the molecule known as OR-1896, are implicated in the prolonged effects of levosimendan (Cavusoglu et all., 2009). OR-1896 has the same pharmacodynamic profile of levosimendan, with a half-life and activity period of 80 hours and 2 weeks, respectively. Compared to PG, lower rates of postoperative low CO (26.3% vs. 46.9%) and arrhytmia (16.3% vs 24.6%) were found in SG. In both groups LVEF increased significantly in postoperative period, but the mean increase in LVEF in SG was higher than PG (8.88±2.39 vs 4.31±1.23). To provide appropriate CI, 34 % of patients in SG and 56 % of patients in PG required additional inotropic, respectively These values were parallel to postoperative cardiac enzyme release in both groups. Additional inotrope and/or vasopressor administration requirement was more frequent in PG.

According to previous studies, phosphodiesterase inhibition causes increased cAMP levels, and thus elevated clearance of cytosolic calcium by endoplasmic reticulum ATPase pump, leading to accelerated myofilament relaxation (Hein et all., 2009, Missant et all., 2007). Previously, it was shown that levosimendan pretreatment enhanced microcirculation and coronary artery flow, as well as enhanced cardiac performance and neurohormonal activation, in patients with advanced heart failure outcomes in CABG operation (Hein et all., 2009, Missant et all., 2007).

The positive effects of levosimendan on ventricular function and arrhythmias and cyclic nucleotide levels during ischemia/reperfusion have shown in a pig model by Du Toit et al. (Álvarez et all., 2006). In our published study, we showed supraventricular antiarrhytmic effect of levosimendan in CABG surgery (Du Toit et all., 2001). Ericssson et collegues previously showed that levosimendan facilitated weaning from cardiopulmonary bypass and decreased the mortality undergoing CABG with impaired left ventricular function (Eriksson et all., 2009).

European Milrinone Multicenter Trials Group exhibited that milrinone consumes myocardial oxygen (Eriksson et all., 2009). Karlsberg et collegues suggested milrinone use for the management of the patients with heart failure and pulmonary congestion following myocardial infarction (Karlsberg et all., 1996). Feneck study demonstrated that phosphodiesterase III inhibition using milrinone has positive and vasodilator effects in patients with heart failure and open-heart surgery (Feneck et all., 2001). Thus, previous milrinone studies showed that it improved hemodynamic profile in off-pump-CABG operations.

De Hert et al. showed in their study that cardiac surgery patients with a low preoperative EF, stroke volume was better maintained when the patients were administered with dobutamine and levosimendan combination (De Hert et all.,

2007). Jörgensen et al. and Malliotakis study showed the positive effects of levosimendan on left ventricular relaxation and filling pressure in patients with left ventricular hypertrophy due to aortic stenosis (Malliotakis et all., 2007, Jörgensenet all., 2008). Cohen et all. demonstrated that natriuretic peptide in response to levosimendan treatment was in association with improved survival in patients with severe acutely decompensated heart failure (Cohen et all., 2009). In Lobato (Lobato et all., 2000) and Kikura study (Kikura et all., 1997) did show that milrinone improved left ventricular compliance after open heart surgery. In contrast to previous research, Hadadzadeh and colleagues did not detect any significant difference between their patients who were administered with milrinone in terms of inotropic drug support requirement, myocardial ischemia, duration of inotropic drug support, and morbidity rate (Hadadzadeh et all., 2013).

5. Conclusions

As we know that NYHA class III and IV condition, longer aortic cross clamp and CBP time are increased morbidity and mortality rate, and requirement the higher dose inotropic agents use after open heart surgery. According to our results, in CABG patients with impaired myocardium who required concomitant valv surgery, the use of preoperative LS and peroperative milrinone administration facilitated weaning from CPB in patients with impaired left ventricle. Peroperative treatments with drug combination shortened the dose of inotropic administration and IABP after surgery. The use drugs combination significantly decreased the duration of tracheal intubation, hospitalization, and postoperative LOS. Duration of inotropic use was significantly lower in our patients administered with levosimendan in combination with milrinone as alternative to other inotropic drugs.

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