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Effect of peri-operative milrinone on pulmonary artery pressure in patients undergoing mitral valve replacement

Mitral kapak değişimi yapılan hastalarda milrinon kullanımının pulmoner basınç üzerine etkisi

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Abstract

Aim: Increased pulmonary artery pressure is associated with higher surgical risk in patients undergoing mitral valve replacement. The aim of this study was to investigate the effect of milrinone on the pulmonary artery pressures of patients with mitral valve disease (stenosis or regurgitation) who underwent mitral valve replacement surgery.

Methods: In this case-control study, 48 patients with mitral valve disease who underwent mitral valve replacement surgery were included. The patients were divided into a control group of 30, who were not administered milrinone, and a study group of 18 who received milrinone perioperatively. Systolic pulmonary artery pressures (SPAP), left ventricle ejection fractions (LVEF) and the following postoperative outcomes were recorded: low cardiac output syndrome, stroke, renal failure, bleeding, ventricular arrhythmia and mortality occurring within 30 days of surgery either in or out of the hospital.

Results: In the study group, preoperative LVEFs and postoperative low cardiac output syndrome were lower (72.0 (6.1) vs 62.5(8.4) $P<0.001$ and $P=0.007$, respectively), SPAPs were higher (45.50 (7.0) vs 55.06 (5.5), $P<0.001$), and length of stay in intensive care unit was significantly shorter (4.7 (2.2) vs 3.2 (0.5), $P=0.008$). Also, reduction in both postoperative SPAP and 30-day SPAP were significantly higher [-11.40(-13.25-(-8.63)) vs -4.42(-5.89-(-2.80)), $P<0.001$; -13.6(-15.6-(-9.75)) vs -5.56 (-7.20-(-3.30)), $P<0.001$, respectively].

Conclusion: We found that using perioperative milrinone reduces the systolic pulmonary artery pressure and lowers the rate of low cardiac output syndrome. Milrinone can be used as an effective therapy to reduce to pulmonary pressure in patients with pulmonary hypertension undergoing mitral valve replacement surgery.

Keywords: Mitral valve disease, Pulmonary artery pressure, Mitral valve replacement

Öz

Amaç: Pulmoner arter basıncının yüksek olduğu durumlarda mitral kapak değişimi operasyonlarında cerrahi risk yükselmektedir. Bu çalışmada mitral kapak hastalığı nedeniyle cerrahi tedavi uygulanan hastalarda milrinon kullanımının pulmoner basınlar üzerine etkisini araştırmayı amaçladık.

Yöntemler: Mitral kapak hastalığı nedeniyle kapak değişimi uygulanan 48 hasta çalışmaya dahil edildi. Hastalar cerahide milrinon kullanımına göre milrinon kullanılan (n=18) ve milrinon kullanılmayan (n=30) olarak ikiye gruba ayrıldı. Cerrahi sonrası 30 günlük süre içinde sistolik pulmoner arter basıncı ve sol ventrikül ejeksiyon fraksiyonları ile birlikte cerrahi sonrası mortalite, düşük kardiyak debi sendromu, inme, böbrek yetmezliği, kanama ve ventrikül aritmileri kaydedildi.

Bulgular: Milrinon kullanan grupta cerrahi öncesi sol ventrikül ejeksiyon fraksiyonu kullanmayan gruba göre daha düşükken (72,0 (6,1) vs 62,5 (8,4) $P<0,001$) sistolik pulmoner arter basınçları daha yüksekti (45,50 (7,0), 55,06 (5,5), $P<0,001$). Cerrahi sonrası milrinon kullanılan grupta düşük kardiyak debi sendromu daha az görülürken ($P=0.007$), yoğun bakımda kalış süreleri kullanmayan gruba göre daha kısaydı (4,7 (2,2) vs 3,2 (0,5), $P=0,008$). Hem cerrahi sonrası hem de 30. gün sistolik pulmoner arter basınçlarında ki düşme değerleri milrinon kullanılan grupta istatistik açıdan daha anlamlıydı [-11,40(-13,25-(-8,63)) vs -4,42(-5,89-(-2,80)), $P<0,001$; -13,6(-15,6-(-9,75)) vs -5,56 (-7,20-(-3,30)), $P<0,001$, sırasıyla].

Sonuç: Çalışmamızda milrinon kullanımı cerrahi sonrası pulmoner basınçları düşürürken düşük kardiyak debi oluşumun azalttığı gözlenmiştir. Bu sonuca göre pulmoner arter hipertansiyonu olan ve mitral kapak değişimi yapılacak hastalarda milrinon kullanımının pulmoner basınçları düşürmede etkili bir tedavi seçeneği olduğunu düşünmekteyiz.

Anahtar kelimeler: Mitral kapak hastalığı, Pulmoner arter basıncı, Mitral kapak değişimi

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Introduction

Increased systolic and diastolic pulmonary pressures are frequently seen in mitral valve disease [1]. Pulmonary hypertension (PHT) occurs due to the retrograde transmission of increased left atrial pressure. In patients with mitral valve disease, PHT indicates compensated heart failure along with left ventricular dysfunction.

Higher pulmonary artery pressure is associated with increased risk of mortality and morbidity during mitral valve surgery [2]. Medical options to decrease pulmonary vascular resistance in PHT patients undergoing cardiac surgery include nitric oxide, sildenafil, and isoproterenol, none of which have long-lasting effects [3].

Milrinone, a phosphodiesterase inhibitor, is commonly used in cardiopulmonary bypass during the weaning process to decrease the pulmonary vascular resistance [4]. It exerts inotropic effects by increasing myocardial contractility. Milrinone's advantages include lowering coronary artery resistance and increasing coronary perfusion.

In this study we aimed to investigate the effect of milrinone on postoperative outcomes in patients with mitral valve disease undergoing mitral valve replacement.

Materials and methods

We identified 48 patients with mitral valve disease (regurgitation or stenosis) who electively underwent mitral valve replacement surgery from September 2015 to July 2019. Clinical characteristics, laboratory findings, surgical details and postoperative outcomes were obtained from the patients' files. Patients with a history of kidney disease requiring dialysis, right-heart failure, poor morbidity, patients in critical preoperative state, those who had active endocarditis and concomitant aortic valve disease requiring surgical intervention were excluded from the study.

All patients were divided into two groups according to perioperative milrinone usage. The study group consisted of 18 patients who received milrinone and the control group comprised 30 patients who did not. The following postoperative outcomes were recorded: low cardiac output syndrome, stroke, renal failure, bleeding, ventricular arrhythmia, and mortality occurring within 30 days of surgery either in or out of hospital. Additionally, left ventricle ejection fraction (LVEF) and systolic pulmonary artery pressure (SPAP) within the postoperative period were recorded just before discharge from hospital-between the 5^{th}-7^{th} post-operative days and during the first month follow-up.

Echocardiographic analysis

All patients were examined with two-dimensional trans-thoracic echocardiography (TTE) before and after their surgical procedures. TTE was performed pre-operatively, between the 5^{th} and 7^{th} postoperative days (just before discharge from hospital) and one month following the surgery. A modified Simpson`s method was used to assess left-ventricular ejection fractions and Bernoulli equation by Doppler was used to measure pulmonary artery systolic pressures.

30-day mortality was considered as death within 30 days of surgery. Postoperative stroke was defined as newly occurring neurological deficit with radiological confirmation. Renal failure was defined as deterioration of kidney function requiring hemodialysis. Ventricular arrhythmia was occurrence of any ventricular arrhythmias which needed medical or electrical cardioversion, i.e., ventricular tachycardia and ventricular fibrillation. Low output syndrome was defined as a decrease in systemic perfusion secondary to myocardial dysfunction requiring inotropic agents other than milrinone or intra-aortic balloon pump implantation during the peri-operative period. Postoperative bleeding was massif drainage of blood requiring surgical revision. Length of stay (LOS) was defined by days spent in the intensive care unit (ICU) and in the hospital after surgery.

Surgical technique

All mitral valve replacement (MVR) procedures were performed with median sternotomy. Cardiopulmonary bypass was established with ascending aortic and bicaval cannulation. Cold blood cardioplegia was administered to stop and protect the heart. The mitral valve was exposed through a left atriotomy in the interatrial groove, and the anterior and posterior leaflets were excised. A mechanical or bioprosthetic valve was then implanted according to the patient's condition. Concomitant procedures included coronary artery bypass graft (CABG), cryo-ablation with maze procedure and tricuspid annuloplasty depending on indication.

Milrinone usage

All patients with high systolic pulmonary artery pressures received intravenous milrinone. A loading dose of 25 μgr/kg milrinone during weaning from cardiopulmonary bypass was followed by a maintenance dose of 0.25 μgr/kg/min administered for 24 hours following the operation.

Statistical analysis

Statistical tests were performed with SPSS version 16 (SPSS Inc., Chicago, IL, USA). Continuous variables were presented as mean (standard deviation), and categorical variables were shown with percentages. Either the Student's t-test or the Mann-Whitney U test was used to compare parametric values between the two groups. Chi-square test was used to compare categorical variables.

Results

Among 48 patients, 18 (37.5%) were males and 30 (62.5%) were females. Table 1 shows the demographic, clinical and laboratory characteristics of the population. Preoperative LVEFs were lower (72.0 (6.1) vs 62.5(8.4) $P<0.001$) and SPAPs were higher in the study group (45.50 (7.0) vs 55.06 (5.5), $P<0.001$). The operative details of the patients, which are presented in Table 2, did not differ among groups.

While mortality and other complications were similar, postoperative low cardiac output syndrome was significantly lower ($P=0.007$) and length of stay in the intensive care unit was significantly shorter in the study group (4.7 (2.2) vs 3.2 (0.5), $P=0.008$).

Reductions in both postoperative SPAP and 30-day SPAPs were more significant in patients who received milrinone [-11.40(-13.25-(-8.63)) vs -4.42(-5.89-(-2.80)), $P<0.001$; -13.6(-15.6-(-9.75)) vs -5.56 (-7.20-(-3.30)), $P<0.001$, respectively] (Table 3).

Table 1: Baseline characteristics of the study population

Variable	Control group (n=30)	Study group (n=18)	*P*-value
Age (years)	63.3 (9)	64.6 (11)	0.654
Female n (%)	18 (60%)	12 (67%)	0.644
Male n (%)	12 (40%)	6 (33%)	0.644
History of COPD n (%)	6 (20%)	2 (11%)	0.424
Hypertension n (%)	12 (40%)	10 (56%)	0.295
Diabetes mellitus n (%)	5 (17%)	4 (22%)	0.633
Current smoking n (%)	9 (30%)	2 (11%)	0.132
Type of additional surgery			
Ablation n (%)	3 (10%)	4 (22%)	0.245
Tricuspid annuloplasty	5 (17%)	5 (28%)	0.359
CABG	4 (13%)	4 (22%)	0.424
Preop-NYHA > 2 n (%)	8 (27%)	7 (39%)	0.376
Postop-NYHA > 2 n (%)	1 (3%)	1 (6%)	0.728
Postop-30-day-NYHA > 2 n (%)	3 (11%)	1 (6%)	0.545
Post-op LCOS (%)	22 (73%)	6 (33%)	0.007
Postop-Ventricular Tachycardia n (%)	3 (10%)	3 (17%)	0.499
30-day mortality n (%)	2 (7%)	1(6%)	0.878
Dialysis requirement (%)	3 (10%)	1 (7%)	0.590
Stroke n (%)	1 (3%)	1 (6%)	0.709
Postoperative bleeding n (%)	1 (3%)	1 (6%)	0.709

COPD: Chronic obstructive pulmonary disease, CABG: Coronary artery bypass graft, LCOS: Low cardiac output syndrome, NYHA: New York Heart Association

Table 2: The laboratory findings of study population

Variable	Control group (n=30)	Study group (n=18)	*P*-value
BMI ((kg/m^2))	22.2 (1.4)	22.7 (1.7)	0.321
SCr (mg/dl)	1.06 (0.2)	1.04 (0.2)	0.825
Glucose (mg/dl)	107.2 (15.4)	105.6 (12.4)	0.712
WBC ($\times 10^3/\mu L$)	7.42 (1.0)	7.84 (1.5)	0.242
Hemoglobin (g/dl)	11.3 (1.3)	11.9 (1.8)	0.208
CPB time (min)	97 (15)	101 (17)	0.416
X-Clamp time (min)	73 (11)	75 (10)	0.675
Los ICU	4.7(2.2)	3.2 (0.5)	0.008
Los overall	11.8 (3.9)	9.6 (1.4)	0.024

BMI: Body mass index, SCr; Serum creatinine at admission, WBC: White blood cell, CPB: Cardiopulmonary bypass, ICU: Intensive care unit, Los: Length of stay

Table 3: Echocardiographic findings of study population

Variable	Control group (n=30)	Study group (n=18)	*P*-value
Preoperative LVEF (%)	50.40 (4.8)	44.22 (6.2)	<0.001
Postoperative LVEF (%)	43.07 (3.9)	42.60 (4.9)	0.716
30^{th} day LVEF (%)	49.48 (2.7)	47.24 (4.5)	0.046
Preoperative PASP (mmHg)	45.50 (7.0)	55.06 (5.5)	<0.001
Postoperative PASP (mmHg)	41.25 (4.8)	44.00 (3.6)	0.048
30. day PASP (mmHg)	40.4 (3.8)	42.29 (2.7)	0.083
ΔLVEF* (postop-preop)	-7.3 (-10.2-(4.4))	-2.4 (-3.6-(-1.4))	0.001
ΔLVEF* (30^{th} day-preop)	-7.3 (-10.2-(4.4))	-2.4 (-3.6-(-1.4))	0.001
ΔLVEF* (30^{th} day-postop)	5.8 (4.2-8.8)	4.6 (3.4-5.8)	0.250
ΔPASP* (postop-preop)	-4.42(-5.89-(-2.80))	-11.40(-13.25-(-8.63))	<0.001
ΔPASP* (30^{th} day-preop)	-5.56 (-7.20-(-3.30))	-13.6(-15.6-(-9.75))	<0.001
ΔPASP* (30^{th} day-postop)	-1.17(-1.92-(-0.30))	-1.67(-2.81-(-0.36))	0.746

LVEF: Left ventricle ejection fraction, PASP: Pulmonary artery systolic pressure, these values were presented by median with inter-quartile range (25th and 75th percentile)

Discussion

This study showed that perioperative milrinone administration reduces postoperative SPAP and LCOS occurrence in patients with pulmonary hypertension undergoing mitral replacement surgery.

Pulmonary hypertension is a common sequel of mitral valve disease and is associated with poor prognosis during surgical repair or replacement [5,6]. Chronically elevated left atrial pressure causes alveolar stress, and pulmonary vascular remodeling due to elevation of pulmonary vascular resistance accounts for the pathophysiological mechanism underlying PHT in mitral disease [1]. Increased pulmonary vascular resistance (PVR) is detrimental to cardiac output in postoperative cardiac-surgery patients.

The treatment of increased pulmonary vascular resistance has not been fully established due to the lack of selectivity of drugs for pulmonary vasculature. Many agents, such as dobutamine, norepinephrine, levosimendan, nitric oxide and nitroglycerin, were used to relieve pulmonary hypertension during cardiovascular surgery [7-10]. However, these inotropic drugs have possible systemic or cardiac side effects, like arrhythmia and increased myocardial oxygen consumption resulting in cardiac ischemia and renal failure [11,12].

Milrinone, a phosphodiesterase inhibitor, exerts positive inotropic effects by increasing cyclic adenosine monophosphate in the myocardium, thereby increasing stroke volume. It is widely used in cardiac surgery during the weaning process from cardiopulmonary bypass [13]. The drug is also commonly used in congenital cardiac surgery or in patients with heart failure [14,15]. Milrinone is also a potent pulmonary vasodilator that reduces pulmonary vascular resistance, for which reason it is particularly preferred in patients with low cardiac output and higher pulmonary artery pressure undergoing cardiac surgery.

Only a couple of studies have previously examined milrinone in pulmonary hypertension occurring during mitral valve surgery. Oztekin et al. [16] reported that using milrinone caused significant reduction in pulmonary artery pressure, central venous pressure and pulmonary capillary wedge pressure in patients with mitral valve stenosis and PHT undergoing mitral valve replacement. They also found that it facilitated weaning from cardiopulmonary bypass with less side effects. Wang et al. [17] showed that mean pulmonary artery pressure and PVR were significantly reduced by the administration of milrinone in the same population. In our study, postoperative SPAP had similarly reduced in the study group at the first postoperative week and month.

Previous studies have shown that compared with dobutamine, milrinone causes greater reduction in left and right ventricular filling pressures owing to greater reduction in vascular resistance, which makes it superior to dobutamine in the treatment of low cardiac output syndrome following cardiac surgery [18]. We similarly found that the occurrence of postoperative LCOS reduced with milrinone administration.

In our study, pre-operative LVEF were lower and SPAP was higher in patients who received milrinone. Although postoperative mortality and morbidity were similar in both groups, we found that in the study group, systolic pulmonary artery pressures reduced significantly during the postoperative week and remained low at one-month follow up.

Limitation

The retrospective and unicentered nature as well as the small sample size were the primary limitations of this study. The exact measurement of the pulmonary artery pressure is performed by right heart catheterization; however, we assessed pulmonary pressures with echocardiography. Further research is needed to evaluate the effects of milrinone following MVR in patients with mitral valve disease.

Conclusion

Milrinone effectively reduces SPAP and LCOS and appears to be an alternative promising approach in addressing the problem of pulmonary hypertension in patients undergoing mitral valve replacement surgery.

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