Clinical Effect of Iloprost on Pulmonary Artery Hypertension After Mitral Valve Surgery

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ABSTRACT

Introduction: Pulmonary arterial hypertension (PAH) is an important risk factor for increased mortality and morbidity during mitral valve surgery. In this study, we analysed the haemodynamic effects of the prostaglandin analogue iloprost in patients with PAH.

Patients and Methods: We retrospectively analysed patients with PAH who were undergoing mitral valve surgery and had received intravenous iloprost therapy at our hospital from 1 January 2003 to 31 March 2013. Systemic and pulmonary arterial pressures were measured with catheterisation. The haemodynamic parameters were administered preoperatively and at 0 hours and 24 hours postoperatively.

Results: A total of 135 patients had undergone mitral valve operations, of whom 78 patients were administered iloprost during the study period. Of all the cases, 29.9% were male and the average patient age was 54.45 ± 12.48 years. A comparison of the preoperative, hour 0 and hour 24 baseline parameters showed that pulmonary artery pressure and blood pressure statistically significantly decreased at postoperative hour 24 ($p< 0.05$). Age, preoperative EF and revisions were found to be statistically significant risk factors for mortality ($p< 0.0001$). Pulmonary pressures did not affect mortality and were not classified as risk factors.

Conclusion: Iloprost treatment might improve postoperative outcomes in patients with high pulmonary arterial pressures and with decreasing pulmonary arterial pressures in the early postoperative period. Treatment with iloprost during the mitral valve replacement decreases high pulmonary arterial pressures and the perioperative mortality risk.

Key Words: Mitral valve surgery; cardiopulmonary bypass; iloprost; pulmonary hypertension

Mitral Kapak Cerrahisinde İloprost Kullanımının Pulmoner Arter Hipertansiyonu Üzerine Klinik Etkisi

ÖZET

Giriş: Mitral kapak cerrahisinde artmış pulmoner arter basıncı artmış mortalite ve morbidite için önemli bir risk faktörüdür. Biz bu çalışmada, prostaglandin analoğu iloprostun, pulmoner arteryel hipertansiyonu (PAH) olan hastalardaki hemodinamik etkilerini araştırdık.

Hastalar ve Yöntem: Çalışmamızda hastanemizde 01.01.2003-31.03.2013 tarihleri arasında mitral kapak cerrahisi uygulanan ve PAH nedeniyle intravenöz iloprost tedavisi uygulanan hastalar retrospektif olarak incelendi. Hastaların sistemik ve pulmoner arter basınçları kateter aracılığıyla elde edildi. Elde edilen preoperatif, postoperatif 0. ve 24. saatteki hemodinamik değerler incelendi.

Bulgular: Bu periyotta 135 hastaya mitral kapak replasmanı uygulanmış olup, 78 hastaya PAH nedeniyle iloprost tedavisi verilmişti. Hastaların %29.9'u erkek olup hastalar ortalama 54.45 ± 12.48 yaşında idi. Preoperatif değerler ile postoperatif 0 ve 24. saat sistemik ve pulmoner basınçlar karşılaştırıldığında; postoperatif 24. saatte pulmoner arter basıncının ve kan basıncının istatistiksel olarak anlamlı derecede azaldığı görüldü ($p< 0.0001$). Yaş, preoperatif ejeksiyon fraksiyonu ve revizyon mortalite açısından anlamlı risk faktörü olarak belirlendi ($p< 0.0001$). Pulmoner basınçlar mortalite açısından risk faktörü olarak bulunmadı.

Sonuç: Yüksek pulmoner arter basınçlı hastalarda iloprost tedavisi postoperatif erken dönemde pulmoner arter basıncını düşürerek hastanın iyileşmesine katkı sağlar. Mitral kapak replasmanı esnasında iloprost tedavisi pulmoner arter basıncını düşürerek, peroperatif mortalite riskini azaltır.

Anahtar Kelimeler: Mitral kapak cerrahisi; kardiyopulmoner baypas; iloprost; pulmoner hipertansiyon

Cite this arcticle as: *Selçuk ÜN, Orhan G, Taşdemir Mete M, Temur B, Bayer Erdoğan S, Uğur M, Sargın M, Aykut Aka S. Clinical effect of iloprost on pulmonary artery hypertension after mitral valve surgery. Koşuyolu Heart J 2019;22(3):182-7.*

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Submitted: 29.03.2019
Accepted: 01.08.2019

INTRODUCTION

Severe pulmonary arterial hypertension (PAH) is associated with increased perioperative and long-term mortality and morbidity in mitral valve surgery[1-3]. In severe PAH, the mortality of mitral valve replacement (MVR) can be as high as 31%[4,5]. This has caused some surgeons to avoid MVR in patients with severe PAH.

Discoveries regarding the pathological mechanisms underlying PAH has paved the way for novel treatments. Endothelin receptor antagonists, prostacyclin analogues and phosphodiesterase-5 analogues are examples of such new drugs used to relieve PAH[6-8]. Iloprost, a prostacyclin analogue (a derivative of prostaglandin-I2) that is metabolised from endogenous arachidonic acid through the cyclooxygenase pathway, plays a significant role in regulating the pulmonary vascular tone[9]. It acts by activating soluble adenylatecyclase in the muscle cells of the vessels. This results in vascular relaxation and decreased Pulmonary vascular resistance (PVR). Taking into account these advantages, iloprost might be used to regulate pulmonary hypertension during cardiac surgery.

In our study, we aimed to retrospectively assess the haemodynamic effects of iloprost during the initiation of cardiopulmonary bypass (CPB) in open-heart surgery in the patients who have PAH with mitral valve disease. We also evaluated the factors that might influence the haemodynamic parameters during peroperative iloprost infusion.

PATIENTS and METHODS

We retrospectively analysed the patients who had undergone mitral valve surgery from 1 January 2003 to 31 March 2013 at our hospital. We included the patients who were administered intravenous iloprost infusion to treat mitral valve disease and PAH. The study was approved by the Institutional Review Board. Demographic and clinical information (including echocardiographic reports), preoperative and postoperative drug administration records and follow-up details were collected by reviewing past medical records.

All the patients received the routine protocols from the surgical and anaesthesiology teams for MVR. A 7F pulmonary artery catheter (PV2047, VoLEF Catheter PACC 947, Pulsion Medical Systems AG) was inserted into the pulmonary artery. All surgeries were performed with a full median sternotomy and on cardiopulmonary bypass by the same surgeon. Cardiac arrest was obtained by anterograde cold blood cardioplegia. The size and type of implanted prosthetic valves were recorded along with the need for concomitant aortic or tricuspid intervention.

Routine haemodynamic variables, heart rate (HR), mean arterial pressure (MAP), mean pulmonary arterial pressure (MPAP), central venous pressure and pulmonary capillary wedge pressure were collected for analysis. PVR and systemic vascular resistance (SVR) were derived by standard formulas. Cardiac output was measured using a 7F thermodilution pulmonary artery catheter during expiration. In preoperative echocardiography, the mean pulmonary artery pressure was higher than 25 mmHg in all the patients who received iloprost treatment. The effects of intravenous iloprost on haemodynamic at postoperative hour 0 and hour 24 were recorded and analysed.

After the operation, all patients were transferred to the intensive care unit (ICU). Narcotic analgesics and nitro-glycerine infusion were administered to all the patients to stabilise the haemodynamic and make extubation possible. Inotropic agents were administered if deemed necessary by the presiding physician. Warfarin treatment was started at the 1st postoperative day.

Statistical Analysis

IBM SPSS version 20.0 software (Statistical Package for Social Sciences) for Windows was used to analyse the data. Categorical variables were defined as frequency and percentage, while continuous variables were defined as mean and standard deviation. The normal distribution of data was evaluated with the Kolmogorov-Smirnov analysis. The ttest was used for independent groups that fit into normal distribution and the Kruskal-Wallis analysis, Mann-Whitney U test, and Chisquare tests were used for data that did not fit into normal distribution. Correlation of data was measured with the correlation coefficient; risk analysis was done with logistic regression and ROC analysis. The results were evaluated with a confidence interval of 0.95 and significance was accepted at $p< 0.05$.

RESULTS

There were 135 patients who underwent mitral valve intervention and 78 of them were administered intravenous iloprost therapy in the study period. The demographic and surgical data are presented in Table 1.

Table 1. Demographics and peroperative data

Parameter	Value
Age (years)	54.45 ± 12.48
Male (%)	29.9
Preoperative LVEF (%)	51.25 ± 10.61
Atrial fibrillation (%)	18.4
Cross-clamp time (minutes)	89.48 ± 41.45
CPB duration (minutes)	128.73 ± 52.64
MVR (%)	36
MVR + Tricuspid DeVega Annuloplasty (%)	38
MVR + CABG (%)	10
MVR + AVR + Tricuspid DeVega Annuloplasty (%)	16

AVR: Aortic valve replacement; CABG: Coronary artery bypass grafting; CPB: Cardiopulmonary bypass; MVR: Mitral valve replacement.

Table 2. Comparison of preoperative, early postoperative and postoperative 24th hour pulmonary artery pressures

Variable		Mean ± SD	Statistical evaluation	p
PAP_d	Preop	21.73 ± 5.33	Preoperative-Hour 0	0.002
	0	20.74 ± 4.4	Preoperative-Hour 24	0.0001
	24	15.87 ± 4.86	Hour 0-Hour 24	0.0001
MPAP	Preop	28.19 ± 11.73	Preoperative-Hour 0	0.915
	0	28.06 ± 9.64	Preoperative-Hour 24	0.001
	24	22.3 ± 8.64	Hour 0-Hour 24	0.0001
PAP_s	Preop	60.28 ± 23.23	Preoperative-Hour 0	0.0001
	0	55.59 ± 18.68	Preoperative-Hour 24	0.0001
	24	40.75 ± 14.27	Hour 0-Hour 24	0.0001

MPAP: Mean pulmonary arterial pressure, PAP_d: Diastolic pulmonary arterial pressure, PAP_s: Systolic pulmonary arterial pressure.

Table 3. Comparison of preoperative, early postoperative and postoperative 24th hour systemic blood pressures

Variable		Mean ± SD	Statistical evaluation	p
SBP	Preop	133.9 ± 20.91	Preoperative-Hour 0	< 0.001
	0	106.7 ± 12.03	Preoperative-Hour 24	< 0.001
	24	103.64 ± 14.23	Hour 0-Hour 24	< 0.001
DBP	Preop	78.06 ± 9.51	Preoperative-Hour 0	< 0.001
	0	59.48 ± 9.1	Preoperative-Hour 24	< 0.001
	24	57.16 ± 11.47	Hour 0-Hour 24	< 0.001
MAP	Preop	95.01 ± 11.75	Preoperative-Hour 0	< 0.001
	0	91.35 ± 9.96	Preoperative-Hour 24	< 0.001
	24	82.39 ± 11.59	Hour 0-Hour 24	< 0.001

DBP: Diastolic blood pressure; MAP: Mean arterial pressure; SBP: Systolic blood pressure.

Table 4. Risk factors for mortality

						95% CI	
	B	S.E.	Wald	Sig.	OR	Lower Limit	Higher Limit
Age	0.013	0.002	37.697	0.0001	0.987	0.983	0.991
Preoperative EF	0.011	0.003	17.347	0.0001	1.011	1.006	1.016
Redo	0.567	0.068	70.329	0.0001	0.567	0.497	0.648
Cross-clamp	0.005	0.001	51.355	0.0001	0.995	0.994	0.996
Revision	1.403	0.07	5.4	0.02	4.067	3.546	4.664
Inotropic support	20.26	1163.47	0.000	0.986	-	-	-

EF: Ejection fraction.

When comparing preoperative, hour 0 and hour 24 baseline haemodynamics, we found that pulomary artery pressure (PAP) (sPAP, dPAP, mPAP) and blood pressure (SBP, DBP, MAP) were significantly decreased at postoperative hour 24 ($p< 0.05$) (Table 2, 3). HR and serum transaminase levels were found to increased, however, this difference did not reach statistical significance ($p> 0.05$).

Table 5. Significant risk factors for increased mortality

						95% CI	
	B	S.E.	Wald	p	OR	Lower Limit	Higher Limit
Age	0.239	0.074	10.381	0.001	1.270	1.098	1.469
Preoperative EF	0.295	0.063	22.226	0.0001	1.344	1.188	1.519
Revision	1.428	0.062	522.26	0.0001	4.171	3.690	4.715

EF: Ejection fraction.

Early postoperative mortality (at postoperative 1 month) was 8%. In the analysis of mortality, redo surgery, cross-clamp time and inotropic support were not found to be risk factors for increased mortality (p> 0.05). However, age, preoperative EF and revisions were found to be significant risk factors for mortality (p< 0.05) (Table 4). Age and preoperative EF also emerged as risk factors for mortality as continuous variables. Cut-off points were determined as 36.5 years for age and 40% for EF. Being above 36.5 years of age, having an EF lower than 40% and having undergone surgical revision were found to be statistically very significant risk factors (Table 5). Pulmonary pressures did not emerge as risk factors that affected mortality.

DISCUSSION

In this study, we aimed to evaluate the effectiveness of iloprost treatment in patients with increased pulmonary artery pressure who had undergone mitral valve surgery. Our results encourage the use of iloprost during mitral valve surgery.

Existence of pulmonary hypertension is an important factor for increased postoperative mortality and morbidity in mitral valve surgery. PAH can be fatal in the early postoperative follow-up period. Severe PAH has been linked with high mortality in some studies, while others have found no increased risk[10,11]. Pre-existing pulmonary hypertension might be aggravated as a result of ischaemia-reperfusion injury after CPB along with the activation of inflammatory processes and vasoconstrictor mechanisms. Systemic inflammatory responses and associated impaired endotheliumdependent vasodilatation may result in high pulmonary blood pressure that leads to PAH[12]. This situation increases right ventricle afterload that may not be tolerated by an impaired right ventricle (RV) and acute right ventricular failure may occur[13]. Therefore, treatment of PAH and RV dysfunction relies heavily on pharmacological interventions to achieve pulmonary vasodilation[14].

Iloprost has been reported as an effective treatment modality in acute right ventricular failure, after valvular surgery and pulmonary thrombo-endarterectomy[15-18]. However, no randomised controlled trial testing the use of intravenous iloprost treatment to prevent RV failure in mitral valve surgery cases with pulmonary hypertension has been published to date. There is also no dose response curve defined in the current studies. In our study, we investigated the effect of intravenous iloprost (1 mg/kg/minute), which was started at the end of CPB and continued until 24 hours postoperatively in patients with pulmonary hypertension who were undergoing mitral valve surgery. We found that intravenous iloprost treatment prevents acute pulmonary hypertensive crisis in the postoperative period and decreases pulmonary arterial pressures in the early postoperative period. Decrease in pulmonary pressures was evident right after CPB and was most prominent at the 24th postoperative hour.

Intravenous administration of vasodilators almost invariably produces systemic vasodilatation and causes arterial hypotension, which, particularly in the haemodynamically unstable patient, further jeopardises RV function by reducing coronary perfusion and causing deterioration of ventricular interdependence[14,19,20]. Therefore, nonselective intravenous vasodilators have limited postoperative use in cardiac surgery. Inhaled vasodilators have been shown to be an effective method due to their selective pulmonary vasodilatory action[21]. Sablotzki et al.[22] reported that there were no side effects of iloprost inhalation, including a decrease in systolic BP and SVR or impaired cardiac functions. Inhaled iloprost treatment might be an alternative to nitrous oxide (NO) for acute right heart failure following transplantation with a 23.5% reduction in PVR and a 24% increase in cardiac index without any changes to the SVR[23]. Inhaled and intravenous iloprost have been compared for their haemodynamic effects and the use of intravenous iloprost was found to be limited in patients with chronic heart failure due to its negative effects on blood pressure and HR. However, in studies and case presentations comparing intravenous and inhaled iloprost, similar responses in pulmonary pressures were reported. A slightly greater decrease in PAP with inhaled iloprost was observed, however, an increased and more expensive dosage was needed and side effects such as tachyphylaxis were more frequent[24]. The most important disadvantage of inhaled iloprost treatment is its relative duration of action with 30-60 minutes of haemodynamic

effects persisting after each inhalation. Moreover, special equipment is necessary to administer this treatment to intubated patients. Reduced practicality and less duration of action of iloprost shifted the attention on to intravenous iloprost infusions. Due to its reduced cost and increased action, we opted to use intravenous iloprost in our study.

The use of prostacyclin and its analogues provides beneficial effects for the management of PAH[24-26]. Hsao-Hsun Hsu et al.[28] reported an opacity in the pulmonary artery that was associated with reperfusion-related pulmonary oedema. This oedema resolved rapidly, the duration of intubation was shortened, and the recovery of pulmonary tissues was faster after 3 days of intravenous iloprost treatment following pulmonary thromboendarterectomy. Theodoraki et al.[15] stated the beneficial effects of iloprost using post-CPB echocardiographic examination and haemodynamic parameters. Vasodilation is not only effect of iloprost treatment, as iloprost also affects pulmonary vascular remodelling[29]. In patients where mechanical ventilation and inhaled NO did not produce an adequate response, intravenous iloprost infusion was able to reduce pulmonary hypertension and PVR and eventually reverse postoperative hypoxia[28]. Studies show that intravenous iloprost frequently causes systemic vasodilation and arterial hypotension. Systemic hypotension is a dose-limiting factor, since pulmonary selectivity is decreased during intravenous administration[30]. Systemic vasodilation, which could limit the use of intravenous iloprost, can be remedied with close haemodynamic monitoring and dose adjustment. In our study, at the end of CPB and at the postoperative 24th hour, our patients' HRs were found to be progressively increasing. We believe this is a response of intravenous iloprost to the reduced SVR and illuminates another disadvantage. However, this increase in the HRs did not force us to stop the iloprost treatment. We observed that intravenous iloprost decreased both systemic and pulmonary vascular pressure, but these effects could be reversed with successful management using vasoconstrictor agents, such as noradrenaline.

The operative mortality rate in patients with severe PAH undergoing MVR has been reported to be up to 31%[4,5]. Recent studies have confirmed improved outcomes and lower mortality rates (2.3-10%) as a result of better myocardial preservation and improved postoperative care[1,16,17]. Myocardial preservation, improved anaesthetic technique and better postoperative management have considerable impacts on improving the outcome of MVR in patients with severe PAH. In our study, the overall mortality rate was 8%, which is a great outcome as compared to the previous works. While evaluating the ICU period and the late-stage complications of our patients, we observed that there was no mortality due to pulmonary hypertension. We did not observe any other side effects of iloprost, such as chin pain, syncope, flushing, or catheter infection. Within the scope of these findings, it can be concluded that these complications do not occur in open-heart surgery because shorter durations of infusions are used as compared to those used during PPH and PAH surgeries.

The study has some limitations. Firstly, it was not a randomised prospective study. It lacked the data of the control group that was not treated with iloprost. We analysed our data retrospectively in patients with mitral valve disease accompanied by PAH. Our results encourage the use of iloprost treatment for PAH patients. Further randomised control studies with larger groups are needed in the future to verify our results.

The procedural risk of overall mortality in MVR is 4-8%. Increased pulmonary artery pressures have been one of the most well-known risk factors for mortality during mitral valve surgery, as well as any kind of open-heart surgery. Treatment with iloprost during the operative period seems to decrease the effect of high pulmonary pressures on mortality after MVR. Patients with high pulmonary pressures may benefit from iloprost treatment during cardiac surgery, as a decrease in pulmonary arterial pressures can be achieved preoperatively. Decrease of the pulmonary arterial pressures will improve the postoperative outcomes of patients with PAH.

CONFLICT of INTEREST

The authors reported no conflict of interest related to this article.

AUTHORSHIP CONTRIBUTIONS

Concept/Design: ÜS, GO
Analysis/Interpretation: ÜS, MM, BT
Data Acquisition: BT, SE
Writting: ÜS, MU
Critical Revision: MU, MS, SA, GO
Final Approval: All of authors

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