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Research Article / Araştırma

Effects of Iloprost and Nitroglycerin in Mitral Valve Patients with Pulmonary Hypertension

Pulmoner Hipertansiyonlu Mitral Kapak Hastalarında İloprost ve Nitrogliserin Etkileri

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ABSTRACT

Objectives: Pulmonary hypertension (PHT) is one of the important factors determining the prognosis in the postoperative period, especially in mitral valve patients. We aimed to compare the two treatments (iloprost and nitroglycerin [NTG]) applied at the exit of cardiopulmonary bypass in mitral valve patients with PHT who will be operated in our center.

Methods: Sixty patients with a mean pulmonary artery pressure (PAP) ≥25 mmHg were randomized to receive postoperative IV iloprost (Group: 1, n=30) or IV NTG (Group: 2, n=30). Basal hemodynamic parameters (heart rate, systolic blood pressure, central venous pressure, PAP, and pulmonary capillary wedge pressure [Pcwp]) were recorded before and after treatment in both groups (T_0). After induction of anesthesia; patients in Group-I were started on Iloprost at 1 ng^{-1} kg^{-1} min, and NTG at 0.5–1 μg^{-1} kg^{-1} min in patients in Group-II. The same parameters were recorded after cardiopulmonary bypass (T_1), postoperative 1st h (T_2), postoperative 12th h (T_3), and postoperative 24th h (T_4).

Results: Mean pulmonary arterial pressure, pulmonary arterial systolic, and diastolic pressure and PcwP were compared and no statistically significant difference was found between the groups at the time of T_0 measurement (p>0.05). Statistically significantly lower pressures were found in favor of Iloprost at T_1, T_2, T_3, and T_4 measurement periods (p<0.05).

Conclusion: Iloprost and NTG are two effective agents that can treat postoperative PHT in mitral valve surgery. The fact that iloprost causes more specific and significant vasodilation in the pulmonary vascular area, decreases pulmonary vascular resistance without significantly lowering Systemic vascular resistance, and provides significant improvement in Cardiac output and Cardiac index suggest that iloprost is a more effective agent than NTG.

Keywords: Iloprost, mitral valve surgery, pulmonary hypertension

ÖZ

Amaç: Pulmoner hipertansiyon özellikle mitral kapak hastalarında postoperatif dönemde prognozu belirleyen önemli faktörlerden biridir. Bu çalışmada, merkezimizde ameliyat edilecek pulmoner hipertansiyonlu mitral kapak hastalarında kardiyopulmoner baypas çıkışında uygulanan iki tedavinin (iloprost ve nitrogliserin) karşılaştırılması amaçlandı.

Yöntem: Ortalama pulmoner arter basıncı ≥25 mmHg olan 60 hasta postoperatif intravenöz iloprost (Grup 1, n=30) veya intravenöz nitrogliserin (Grup 2, n=30) verilmek üzere randomize edildi. Her iki grupta tedavi öncesi ve sonrası bazal hemodinamik parametreler (kalp hızı, sistolik arter basıncı, santral venöz basınç, pulmoner arter basıncı, pulmoner kapiller uç basıncı) kaydedildi (T_0). Grup 1'deki hastalara 1 ng/kg/dakikadan iloprost, grup 2'deki hastalara ise 0,5-1 µg/kg/dakikadan nitrogliserin anestezi indüksiyonundan sonra başlandı. Aynı parametreler kardiyopulmoner baypas sonrası (T_1), postoperatif birinci saat (T_2), postoperatif 12. saat (T_3) ve postoperatif 24. saat (T_4) kaydedildi.

Bulgular: Ortalama pulmoner arter basıncı, pulmoner arter sistolik ve diyastolik basıncı ve pulmoner kapiller uç basıncı karşılaştırıldı ve T_0 ölçüm zamanında gruplar arasında istatistiksel olarak anlamlı fark görülmedi (p>0,05). T_1, T_2, T_3 ve T_4 ölçüm süreçlerinde iloprost lehine istatistiksel olarak anlamlı derecede basınçlar düşük bulundu (p<0,05).

Sonuç: İloprost ve nitrogliserin mitral kapak cerrahisinde postoperatif dönemde görülen pulmoner hipertansiyonu tedavi edebilen iki etkili ajandır. İloprostun pulmoner yatakta daha spesifik ve anlamlı vazodilatasyon yapması, sistemik vasküler direnci belirgin bir şekilde düşürmeden pulmoner vasküler direnci azaltması, kalp debisi ve kalp indeksinde belirgin iyileşme sağlaması, nitrogliserine oranla iloprostun daha etkili bir ajan olduğunu düşündürmektedir.

Anahtar sözcükler: İloprost, mitral kapak cerrahisi, pulmoner hipertansiyon

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Introduction

Pulmonary hypertension (PHT) refers to the hemodynamic outcome of many diseases rather than describing a disease. PH is defined as an increase in mean pulmonary artery pressure (mPAP) of ≥25 mmHg at rest.[1–3] PHT is a clinical outcome that determines the prognosis in the post-operative period, which is frequently seen in patients with mitral valve disease.[4]

Right ventricular failure, which increases mortality and morbidity, may develop after cardiopulmonary bypass (CPB) in valvular diseases with PHT.[5] In this case, auxiliary methods such as inotropic and vasodilator agents, intra-aortic balloon pump support, right ventricular assistive devices, and extracorporeal membrane oxygenation can be applied.

In recent years, developments in intensive care and the use of different inotropic and vasodilator agents have enabled the patient group considered to be high risk or inoperable to be operated with acceptable morbidity and mortality.

These agents are inhaled nitric oxide, routinely used nitroglycerin (NTG) infusion and less frequently used prostaglandins, and intravenous phosphodiesterase 5 inhibitors.[6–9]

In our study, we planned to compare the hemodynamic and mechanical effects of two different treatments (iv NTG infusion and iv iloprost infusion, a stable prostaglandin analog) after CPB in mitral valve patients with PHT who will be operated on in our center.

Methods

Our study included 60 patients who were operated due to mitral valve disease in our center between January and June 2022 and whose mean PAP was above 25 mmHg. After obtaining the hospital ethics committee permission and informed consent from all patients; the cases were randomly divided into two groups as iloprost infusion group (Group I, 30 cases) and NTG infusion group (Group II, 30 cases). Patients in Group-I were started with Iloprost (Shering, Germany) at a dose of 1 ng^{-1} kg^{-1} min, and patients in Group-II were started with 0.5–1 μg^{-1} kg^{-1} min dose of NTG (Perlinganit, Schwarz Pharma, Germany) after anesthesia induction. The patients in both groups were monitored for routine cardiac surgery anesthesia [5-lead-ECG, peripheral oxygen saturation (SPO_2), radial arterial catheterization, Bispectral Index (BIS)]. In the induction of anesthesia; propofol at a dose of 2–4 mg/kg, fentanyl at a dose of 5 mcgr/kg and rocuronium at a dose of 1 mg/kg were used.

A Swan-Ganz catheter (7.5 F, Edwards Lifesciences Corporation, USA) was inserted through the internal jugular vein to monitor pulmonary arterial pressure. Propofol, fentanyl, and sevoflurane (2%) were used for the maintenance of anesthesia. Patients were sedated with propofol 2 mg/kg/h for the first 6 h postoperatively until adequate hemodynamic stabilization was achieved. The patients were ventilated with 40% O_2. Tidal volume was adjusted to 6–8 ml/kg, respiratory rate was adjusted to generate arterial carbon dioxide and arterial pH approximately 30–35 mmHg and 7.40, respectively.

In the stable period after anesthesia induction (T_0), after CPB (T_1), post-operative 1st h (T_2), post-operative 12th h (T_3), and post-operative 24th h (T_4) follow-ups, heart rate (HR), blood pressures (SAP; DAP; MAP), central venous pressure (CVP), pulmonary artery systolic pressure (PSP), pulmonary artery diastolic pressure (PDP), mean mPAP, and pulmonary capillary wedge pressure (Pcwp) were monitored and hemodynamic parameters were calculated in these intervals using the Fick method.

Fick method; Cardiac output (CO)=VO_2/CaO_2-CvO_2 (L/min).

Cardiac index (CI)=KD/BSA(L/min/m^2), pulmonary vascular resistance (PVR)=80x(MPA-PCWP)/CO(dyn.sn.cm^{-5}), Systemic vascular resistance (SVR)=80× (MAP-CVP)/CO (dyn.sn.cm^{-5}), oxygen consumption (VO_2) was calculated from special tables prepared according to age, gender, and HR. (CO: Cardiac output, VO_2: Oxygen consumption, C(a-v)O_2: Arterial-venous oxygen content difference, CI: Cardiac index, BSA: Body surface area, PVR: Pulmonary vascular resistance, SVR: Systemic vascular resistance, MAP: Mean arterial pressure, MPAP: Mean pulmonary arterial pressure, CVP: Central venous pressure, PCWP: Pulmonary capillary wedge pressure).

Statistical Analysis

While evaluating the findings obtained in the study, SPSS 28.0.1 for Windows was used for statistical analysis. In the analysis of the study data, in addition to descriptive statistical methods (Mean, Standard deviation), Paired-t test was used for the parameters showing normal distribution, and Wilcoxon Signed-Rank test for the cases that did not show normal distribution. The results were evaluated at the 95% confidence interval and the significance level of $p<0.05$.

Results

The distribution of the patients according to their characteristics is shown in Table 1. There was no difference between the two groups in terms of age, weight, gender, and body surface area. In hemodynamic evaluation, no significant difference was found in terms of HR in both groups at any time ($p>0.05$). The comparison in terms of blood pressures (SAP, DAP, and MAP) and the obtained results are summarized in Table 2. While there was no significant

Table 1. Patient characteristics

	Group I (n=30) (Iloprost)	Group II (n=30) (NTG)	p
Age (years)	48.4±12.9	51.3±3.09	0.130
Weight (kg)	68.0±7.26	64.5±2.01	0.115
Sex (F/M)	20/10	16/14	–
BSA (m^2)	1.70±0.09	1.68±0.111	0.2178

P<0.05; NTG: Nitroglycerin; F: Female; M: Male; BSA: Body surface area.

Table 2. Comparison of SAP, DAP and MAP values of the groups

	Group I (n=30) (Iloprost) Mean±SD	Group II (n=30) (NTG) Mean±SD	p
T_0 (after anesthesia induction)			
SAP	126.1±15	123.7±12.75	0.5694
DAP	68.0±9.52	65.4±2.45	0.4283
MAP	81.9± 9.08	84.7± 7.24	0.4216
T_1 (after CPB)			
SAP	121.1±13.3	117.7±11.70	0.4936
DAP	64.0±4.86	66.7±9.44	0.3795
MAP	80.9±8.31	82.8±7.28	0.4939
T_2 (postop. 1st h)			
SAP	121.1±16.0	118.8±9.46	0.5892
DAP	69.5±8.63	66.4±7.64	0.2550
MAP	80.5±7.04	79.2±7.52†	0.502
T_3 (postop. 12th h)			
SAP	12.5±15.4†	117.6±11.13	0.3164
DAP	60.5±7.42†	64.9±5.11	0.0888
MAP	74.6±10.21†	81.1±5.50	0.0866
T_4 (postop. 24th h)			
SAP	114.6±17.6	123.1±8.26	0.0819
DAP	67.3±7.76	67.8±5.31	0.8236
MAP	80.6±10.69	80.7± 7.81	0.9464

Significant at the p<0.05 level when the two groups were compared; When the two groups were compared, p<0.01 was highly significant; †: Significant at p<0.05 level when compared with in-group baseline values; P<0.01 highly significant when compared with in-group baseline values; SAP: Systolic arterial pressure; DAP: Diastolic arterial pressure; MAP: Mean arterial pressure; SD: Standard deviation; NTG: Nitroglycerin.

difference between the groups in any period, the pressure values at the post-operative 12th h in the iloprost group were found to be significantly lower than the baseline value (p<0.05). The CVP values in both groups were lower in the NTG group at all measurement times, but were not statistically significant.

Pulmonary artery systolic pressure, PDP, mPAP, and Pcwp values are shown in Table 3. While there was no statistically significant difference between the groups at T_0 measurement time (p>0.05), pressure differences at T_1, T_2, T_3, and T_4 measurement times were statistically significantly lower in favor of Iloprost (p<0.05).

Table 3. Comparison of PSP, PDP, MPAP, and PCWP values of the groups

	Group I (n=30) (Iloprost) Mean±SD	Group II (n=30) (NTG) Mean±SD	p
T_0 (after anesthesia induction)			
PSP	54.3±13.48	53.1±4.50	0.0625
PDP	32.5±11.36	34.1± 5.04	0.0819
MPAP	31.7±10.46	30.7± 4.52	0.2428
PCWP	24.5±8.17	24.9±3.72	0.3164
T_1 (after CPB)			
PSP	34.4±4.45†	40.8±11.04†	0.0295*
PDP	22.6±9.28†	27.2±5.31†	0.0378*
MPAP	22.3±8.07†	27.7±2.74	0.0253*
PCWP	14.9±4.15†	17.7±2.96†	0.0434*
T_2 (postop. 1st h)			
PSP	33.1±4.05†	41.4±9.75†	0.0210*
PDP	22.5±6.74	25.2±3.93†	0.0744
MPAP	18.7±7.97†	24.5±3.56	0.0280*
PCWP	14.9±3.45†	16.1± 2.77	0.0105*
T_3 (postop. 12th h)			
PSP	32.9±3.74†	38.9±8.44†	0.0347*
PDP	18.6±6.00	20.7±4.24†	0.2421
MPAP	18.2±7.55†	23.7±3.79†	0.0121*
PCWP	14.1±2.27†	14.8±2.37†	0.0333*
T_4 (postop. 24th h)			
PSP	31.6±10.04†	37.1±3.11†	0.0255*
PDP	15.7±6.09†	19.5±3.40†	0.0151*
MPAP	18.4±6.72†	21.9±3.91†	0.0396*
PCWP	12.6±2.50††	14.7±2.12†	0.3280

*: Significant at the p<0.05 level when the two groups were compared; When the two groups were compared, p<0.01 was highly significant; †: Significant at p<0.05 level when compared with in-group baseline values; P<0.01 highly significant when compared with in-group baseline values; CPB: Cardiopulmonary bypass; PSP: Pulmonary artery systolic pressure; PDP: Pulmonary artery diastolic pressure; MPAP: Mean pulmonary arterial pressure; PCWP: Pulmonary capillary wedge pressure; SD: Standard deviation; NTG: Nitroglycerin.

When in-group values are compared with baseline values;

In Group I; All pressures at time T_1, pressures other than PDP at time T_2 and T_3 and pressures at time T_4 were significantly lower than T_0 (p<0.05). Especially the decrease in Pcwp at T_4 time was found to be statistically significant (p<0.01).

In Group II; Although pressure values at T_1, T_2, T_3 and T_4 measurement times were higher than Group I, all pressure measurements were significantly lower than the values at T_0 in the intragroup evaluation, except for mPAP at T_1 and T_2 times and Pcwp at T_2 times (p<0.05).

Changes in CO and CI in both groups were not statistically significant at T_0 and T_1 measurement times (p>0.05),

Table 4. Comparison of CO and CI values of the groups

	Group I (n=30) (Iloprost) Mean±SD	Group II (n=30) (NTG) Mean±SD	p
T_0 (after anesthesia induction)			
CO	3.00±0.645	2.87±0.346	0.0833
CI	1.78±0.454	1.60±0.212	0.092
T_1 (after CPB)			
CO	3.17±0.512	2.98±0.297	0.2421
CI	1.88±0.348	1.78±0.210†	0.3211
T_2 (postop. 1st h)			
CO	3.34±0.494†	3.06±0.430†	0.0423*
CI	1.98±0.347†	1.83±0.292†	0.021*
T_3 (postop. 12th h)			
CO	3.47±0.469†	3.07±0.409†	0.0252*
CI	2.05±0.331†	1.83±0.253†	0.041*
T_4 (postop. 24th h)			
CO	3.53±0.526††	3.32±0.501†	0.019*
CI	2.09±0.366†	1.97± 0.306†	0.032*

*: Significant at the p<0.05 level when the two groups were compared; When the two groups were compared, p<0.01 was highly significant; †: Significant at p<0.05 level when compared with in-group baseline values; P<0.01 highly significant when compared with in-group baseline values; CO: Cardiac output, CI: Cardiac index; SD: Standard deviation; NTG: Nitroglycerin.

but CO and CI were significantly higher in the iloprost group than in the NTG group in the measurements at T_2, T_3, and T_4 (p<0.05).

When the intragroup values in both groups were compared, the CO and CI values at the T_2, T_3, and T_4 measurement times were significantly higher than the T_0 and T_1 values (p<0.05). This elevation was particularly significant in the T_4 measurement of the iloprost group (p<0.01) (Table 4). There was no significant difference in SVR and PVR values in both groups at T_0 measurement time. At T_1, T_2, T_3, and T_4 measurement times, PVR was statistically significantly lower in the iloprost group than in the NTG group (p<0.05) (Fig. 1). When both groups were evaluated in terms of SVR, there was no significant difference in other measurement times except T_3 measurement time (p>0.05) (Fig. 2). At T_3 measurement time, the SVR value in the iloprost group was significantly lower than in the NTG group (p<0.05).

There was no difference between the groups in RVSWI and LVSWI values in both groups, at T_0, T_1, and T_4 measurement times. At the time of T_2 and T_3 measurement, RVSWI was significantly lower in the NTG group than in the iloprost group (p<0.05). When in-group values were compared, LVSWI was significantly higher than T_0 only at the time of T_4 measurement in both groups (p<0.05). There was no significant difference between the two groups in arterial and pulmonary venous blood gases (p>0.05).

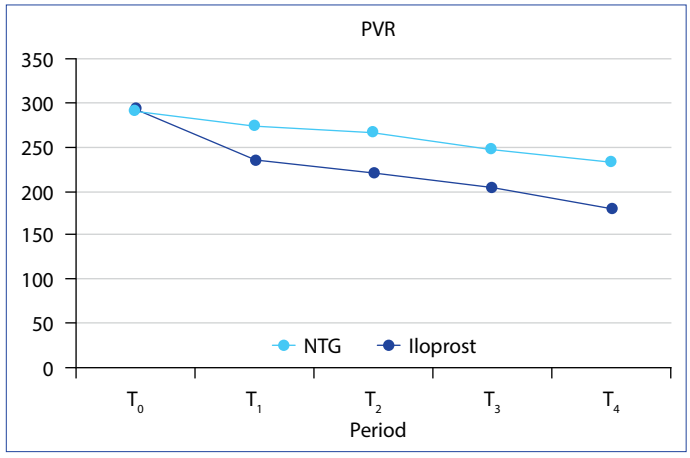

Figure 1. Pulmonary vascular resistance.

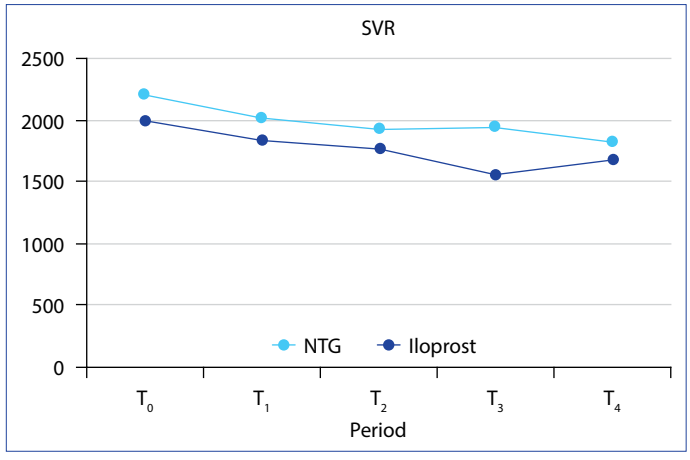

Figure 2. Systemic vascular resistance.

Discussion

PHT refers to the hemodynamic outcome of many diseases rather than describing a disease. PHT is one of the factors determining the prognosis in the postoperative period, especially in mitral valve patients.[4] In mitral valve diseases developing PHT and congestive heart failure, right ventricular failure may develop after CPB, which increases mortality and morbidity.[5] In the treatment of PHT, which developed in the preoperative period and continues to a large extent in the postoperative period, intravenous agents are one of the commonly used treatment methods. Two of the most important of these agents are NTG and prostaglandins, which have been used for many years. Iloprost, a stable prostaglandin analog, stands out among prostaglandins due to its advantages.

In our study, we observed that both Iloprost and NTG had no effect on HR when used from the CPB exit to the postoperative 24th h. We see that there are conflicting results in the literature in different studies conducted in different patient groups. In the study of Moertl et al.,[10] in which

they compared the short-term effects of levosimendan and prostaglandin E1 in decompensated heart failure, they could not detect a significant change in the prostaglandin E1 group, although a significant increase in HR was observed in the levosimendan group. Hulsmann et al.[11] divided 68 patients with chronic heart failure awaiting transplantation into two groups as awaiting elective transplantation and those awaiting urgent transplantation. Right heart catheterization was performed before and after PGE1 infusions.

Janjindamai et al.[12] reported that the use of intravenous iloprost in their study in newborns with severe persistent PHT did not cause a statistically significant difference in blood pressure and HR. The reason for the difference in the effect on HR may be that studies have been conducted in different patient groups. Due to the systemic vascular resistance-lowering effect of both Iloprost and NTG, and especially due to diuretic therapy used for heart failure, negative fluid balance in patients may cause an increase in HR. In our study, no significant difference was observed between groups and within groups. Receiving similar responses in both groups may be due to the fact that there was no difference between the groups. Both Iloprost and NTG reduce post-operative PMP.

This effect appears immediately after CPB and lasts up to the postoperative 24th h. The most significant effect was the severely significant decrease in Pcwp observed at the post-operative 24th h in the iloprost group ($p<0.001$). There was no significant difference between the groups in the CVP, SAP, DAP, and MAP measurements made during this period. This demonstrates the sensitivity of the pulmonary vascular field to the agents used, especially iloprost.

Although this effect is also in NTG, the effect is more pronounced in iloprost. Considering the sensitivity of venous system to the NTG at low doses, a decrease in CVP was expected, especially in the NTG group. Although there was a decrease, it did not reach a significant level. Mandal et al.[13] found a decrease in both systemic and pulmonary pressures, SvO_2 and CVB when IV NTG was used. When iNTG and dobutamine were used in combination, they only detected a decrease in pulmonary pressures (mPAP, PVRI) and did not detect any decrease in CVP. In the study of Goyal et al.[14] using iNTG on 19 children with congenital heart disease with PHT; systolic, diastolic, and mean pulmonary arterial pressure and PVRI decreased significantly, whereas HR, systolic arterial pressure, diastolic arterial pressure, mean arterial pressure, PCWP, CVP, and SVRI did not change. The results of this study are similar to the results of our study.

Fattouch et al.[15] in their study using iPGI2, iNO, IV nitroprussid for PHT developing after mitral valve replacement; While iPGI2 reduced PVR (–50%), TPG (–64%) and mPAP (–20%), it did not significantly change PCWP. It has also been reported that iPGI2 increases CO and SV. Similar results were obtained in iNO (PVR [–45%], TPG [–62%], and mPAP [–19%]).

Compared to NTG, Iloprost significantly lowers PVR after CPB ($p<0.05$), and CO and CI measurements made during this period were significantly higher ($p<0.05$) in the iloprost group. This suggests that iloprost is a better alternative to NTG. This increase in CO and CI is probably due to decreased right ventricular load.

In a prospective randomized controlled study conducted by Winterhalter et al.[16] in 253 high-risk cardiac patients, 20 mcgr iloprost and placebo were compared and it was found that iloprost decreased RV afterload and increased CI.

Tavares-Silva et al.[17] evaluated the reversibility of PHT with vasoreactivity test in patients awaiting heart transplantation using levosimendan (0.1 µg/kg/min), iNO (40 ppm), and inhaled iloprost (14–17 µg). According to the results of the study; levosimendan, iNO and inhaled iloprost decreased the PAP and transpulmonary gradient and increased the Cardiac index. Antoniou et al.[18] evaluated the hemodynamic effects of using iNO (10 ppm) plus inhaled iloprost (10 mcgr) in patients who developed PHT and right ventricular dysfunction after cardiac surgery in another study. Significant reductions in pulmonary vascular resistance (PVR) and mean pulmonary arterial pressure (mPAP) were detected, while increases in cardiac index (CI) and venous blood oxygen saturation (PvO_2) were detected. In our study group, it was seen that iloprost significantly increased RVSWI. This increase is especially evident at the 1st and 12th h postoperatively. This finding is also compatible with the literature.[11,15,17,19] Pulmonary vasodilator drugs can decrease arterial oxygen partial pressure by increasing flow and shunting to poorly perfused areas of the lung. They also increase the alveolo-arterial oxygen gradient by solving hypoxic pulmonary vasoconstriction during the treatment of pulmonary vasoconstriction.[1,3,8,12] However, this effect can be masked because of the CO-increasing effect, especially in prostaglandin, as oxygen supply and use are more effective.

In our study, it is seen that there is no significant difference in the measurements made from both arterial and pulmonary venous blood gases, both within the group and between the groups. Fattouch et al.[15] showed that inhaled iloprost and NO are more effective than nitroprusside for the treatment of PHT after mitral valve replacement.

Since the use of iloprost in the treatment of primary PHT covers a long period of time, it is stated that systemic side effects such as jaw pain, leg pain, headache, diarrhea, decrease in systemic arterial pressure, ventilation/perfusion mismatch may be seen due to IV use.[20] However, IV iloprost is more effective than NTG in the treatment of secondary PHT that persists for a while after mitral valve replacement. In our study, it reduced the pulmonary pressures quite effectively without adversely affecting the systemic pressures, especially in the late postoperative period such as the 12th and 24th h.

As a result; iloprost and NTG are two effective agents that can treat PHT seen in the postoperative period of mitral valve surgery. It suggests that iloprost is a more effective agent than NTG, with its more specific and significant arterial vasodilation in the pulmonary vascular area, its reduction in PVR without significantly lowering SVR, its significant improvement in CO and CI, and its positive effects on RVSWI. Complications that occur in long-term IV use are not seen in early-term use after open heart surgery. Due to the side effects seen in IV use, the inhaled form has been used recently. In shorter-term use, IV use is preferred in mitral valve surgery as a cost-effective application.

Disclosures

Ethics Committee Approval: Ethics Committee Approval : The study was approved by the SBU Dr. Siyami Ersek Hospital Ethics Committee (Date : 15.06.2020,No: 0124).

Informed Consent: Written informed consent was obtained from all patients.

Peer-review: Externally peer-reviewed.

Conflict of Interest: None declared.

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Authorship Contributions: Concept – M.Ş, T.K.; Design – M.Ş, T.K.; Supervision – T.K.; Fundings – M.Ş, T.K.; Materials – M.Ş.; Data collection &/or processing – M.Ş.; Analysis and/or interpretation – T.K.; Literature search – M.Ş, T.K.; Writing – M.Ş.; Critical review – T.K.

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