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Original Article

Effect of Treprostinil on the Early Postoperative Prognosis of Patients with Severe Left Heart Valvular Disease Combined with Severe Pulmonary Hypertension

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Objective: To investigate the effect of treprostinil on the early postoperative prognosis of patients with severe left heart valvular disease combined with severe pulmonary hypertension (PAH).

Methods: A retrospective study including 55 patients with severe left heart valvular disease combined with severe PAH who underwent left heart valve replacement in our hospital between January 2019 and May 2019 was conducted. Patients were divided into two groups (treprostinil group and control group), and the clinical data of patients in the two groups were compared and analyzed.

Results: Compared with the preoperative status, the mean postoperative pulmonary artery pressure (mPAP) in both groups was significantly lower. Compared with the control group, the treprostinil group had a significantly lower mPAP. Moreover, the postoperative mechanical ventilation time, intensive care unit (ICU) stay, and hospital stay of the treprostinil group were significantly shorter than those of the control group. There were no serious drug-related side effects in either group.

Conclusions: Treprostinil can improve the early postoperative prognosis of patients with severe left heart valvular disease combined with severe PAH undergoing prosthetic valve replacement.

Keywords: treprostinil, postoperative effect, valvular disease, pulmonary arterial hypertension

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Introduction

Heart valvular disease is one of the most common heart diseases.[1)] In China, there is still a large number of patients with severe left heart valve disease who seek medical treatment only when they have symptoms.[2,3)] For severe left heart valvular disease, surgical prosthetic valve replacement is a direct and effective treatment that improves the patient's cardiac function and clinical symptoms. Pulmonary hypertension (PAH) is a common complication in patients with severe left heart valve disease.[4-6)] During the process of prosthetic valve replacement, the release of inflammatory factors and vasoactive substances and endothelial damage aggravate the patient's existing PAH, which may affect the prognosis of patients with left heart valvular disease, especially for those with severe

PAH. As a stable prostacyclin analogue, treprostinil can dilate blood vessels, inhibit platelet aggregation and inhibit the proliferation of smooth muscle cells.[7-9] Present clinical studies have shown that treprostinil is safe and effective for the treatment of PAH.[10-12] Through a literature search, few studies have focused on using treprostinil as the treatment for early postoperative PAH in patients with severe left heart valvular disease undergoing prosthetic valve replacement. Therefore, we performed this retrospective study to determine whether treprostinil use should be recommended in the clinical setting.

Materials and Methods

This study was approved by the ethics committee of our university. All patients and their relatives were informed of the content of the study and provided formal written informed consent.

Considering the pathophysiological changes in left heart valvular disease and referring to patient data in China and the literature, we set the following inclusion criteria in our study for severe left heart valvular disease: (1) New York Heart Association (NYHA) class III-IV and/or ejection fraction >0.4; (2) cardiothoracic ratio ≥0.60 and/or left ventricular end diastolic diameter ≥65 mm on echocardiography; (3) combined with mild–moderate (Child-Pugh grade B) hepatic dysfunction; (4) with mild–moderate renal insufficiency (preoperative creatinine ≥133 μmol/l); (5) double left heart valvular replacement; (6) emergency surgery; (7) with coronary artery disease and/or other malformations that need to be treated at the same time; and (8) repeated heart surgery.

We selected 55 patients who received left heart prosthetic valve replacement in our hospital from January 2019 to May 2019. These patients were included in the same period in our hospital, and they were treated by surgeons and anesthesiologists with the same skill sets. The inclusion criteria in this study were adult patients meeting at least one or more of the above-mentioned criteria combined with preoperative severe PAH diagnosed by echocardiography (assessed by transthoracic echocardiography [TTE], pulmonary artery systolic pressure >70 mmHg). The enrolled patients ranged from 32 to 70 years old, with an average age of 50.4 ± 9.2 years. There were 28 females and 27 males. The preoperative cardiac function was classified according to the NYHA system; 27 cases were level III, and 3 cases were level IV. Data on the etiology of the valvular disease, associated atrial fibrillation, and tricuspid regurgitation are shown in **Table 1**. Mitral valve replacement (MVR) was performed in 33 patients, aortic valve replacement (AVR) in 3 patients, and double valve replacement (MVR + AVR) in 19 patients. Patients included in this study had no concurrent coronary artery disease or other cardiac malformations requiring simultaneous correction, no emergency surgery, no history of heart surgery, and no hepatorenal failure. All patients were divided into the treprostinil group (n = 28) and the control group (n = 27) according to whether treprostinil was used. The choice of different anti-PAH drugs was based on the experience of the surgeons and anesthesiologists. The other relevant clinical data of the patients are listed in **Table 1**.

After routine preoperative treatment (no other anti-PAH drugs were used in either group preoperatively), the patients underwent open-heart surgery under general anesthesia, endotracheal intubation, and cardiopulmonary bypass. Intraoperative insertion of the Swan-Ganz catheter was performed. Cardiac output, mean pulmonary artery pressure (mPAP), pulmonary artery wedge pressure, and other data were recorded. The catheter remained inserted while the patient was in the intensive care unit (ICU) until the endotracheal tube was removed. The parameters of the anesthesia machines were set to intermittent positive pressure ventilation; the tidal volume was 6–8 mL/kg, 10–12 times/min; and the oxygen concentration was 40%. Cardiopulmonary bypass was routinely established, and blood cardioplegia was delivered to all patients.

After completing left heart prosthetic valve replacement, a DeVega tricuspid annuloplasty was performed using a modification of DeVega's technique for those patients with moderate-to-severe tricuspid regurgitation, and tested for tricuspid function by injecting saline into the right ventricle. Then closing the right atriotomy, rewarming, blood transfusion, and other measures, the postoperative vital signs of the patients were relatively stable. Treprostinil was injected via an intravenous infusion pump, starting at 1.25 ng/kg/min and gradually increasing to 10.0–15.0 ng/kg/min for maintenance in the treprostinil group. The dosage was adjusted according to changes in hemodynamics. In addition, milrinone (PKU Health Care Corp, Ltd., Chongqing, China) was administered via an intravenous infusion pump at a dose of 0.5–0.75 μg/kg/min in the control group. The other routine treatments were the same in both groups. The hemodynamics of patients at 1, 2, and 4 hours after using treprostinil or milrinone are recorded in **Fig. 1** and **2**. Then, the use of anti-PAH drugs was continued during the ICU and hospital stays. The

Table 1 General clinical information in both groups

Items	Group T	Group C	P value
Age (year)	48.2 ± 5.0	52.1 ± 6.2	0.753
Gender (M/F)	14/14	13/14	0.891
Weight (kg)	61.7 ± 11.2	63.2 ± 13.8	0.621
Body surface area (m^2)	1.52 ± 0.33	1.53 ± 0.37	0.912
Disease history (year)	10.2 ± 3.2	10.3 ± 3.5	0.876
NYHA class			
I	2	2	0.940
II	10	11	
III	14	13	
IV	2	1	
Etiology			
Rheumatic	24	22	0.530
Degenerative	3	2	
Others or uncertain	1	3	
Valve lesion type			
Mitral stenosis	9	8	0.949
Mitral insufficiency	2	3	
Mitral stenosis and insufficiency	6	5	
Aortic lesion	1	2	
Mitral and aortic lesion	10	9	
Tricuspid regurgitation			
Mild	4	7	0.319
Moderate	18	12	
Severe	6	8	
Cardiothoracic ratio	0.61 ± 0.09	0.63 ± 0.08	0.907
Pulmonary hypertension (mmHg) (measured by TTE)	87.6 ± 15.2	85.6 ± 13.3	0.716
Ejection fraction (%)	55.8 ± 16.5	52.4 ± 12.6	0.668
Atrial fibrillation	26	24	0.609
Left atrial thrombosis	5	4	0.760
Diabetes mellitus	5	7	0.469
Liver insufficiency	3	3	0.962
Renal insufficiency	4	3	0.724
Chronic obstructive pulmonary disease	2	2	0.970
Pulmonary infection	5	5	0.949

NYHA: New York Heart Association

dosage of catecholamine was the same in both groups. The relevant data pertaining to the aortic cross-clamp time, cardiopulmonary bypass time, operative time, postoperative mechanical ventilation time, ICU stay, and hospital stay are recorded in **Table 2**. Early postoperative complications, such as low cardiac output syndrome, malignant arrhythmia, brain complications, bleeding, severe infection, progressive severe liver and kidney impairment and drug-related side effects, were also documented. Before discharge, all patients underwent TTE examinations, and the relevant data are shown in **Table 2**.

Measurement data are represented as the mean ± standard deviation, and those data were tested for the normality of their distributions and analyzed with independent-samples t-tests. Categorical data were analyzed using the chi-square test by SPSS 22.0. (IMB corp., Armonk, NY, USA). A $p < 0.05$ was defined as statistically significant.

Results

There were no significant differences in the following clinical data between the two groups: age, sex, weight, and preoperative pulmonary artery pressure status ($P > 0.05$). According to the data measured by the SwanGanz catheter, the postoperative mPAP values were significantly lower than the preoperative values in both groups ($P < 0.05$). Compared with the control group, the treprostinil group experienced a significantly greater decrease in the mPAP after the operation ($P < 0.05$). However, there was no

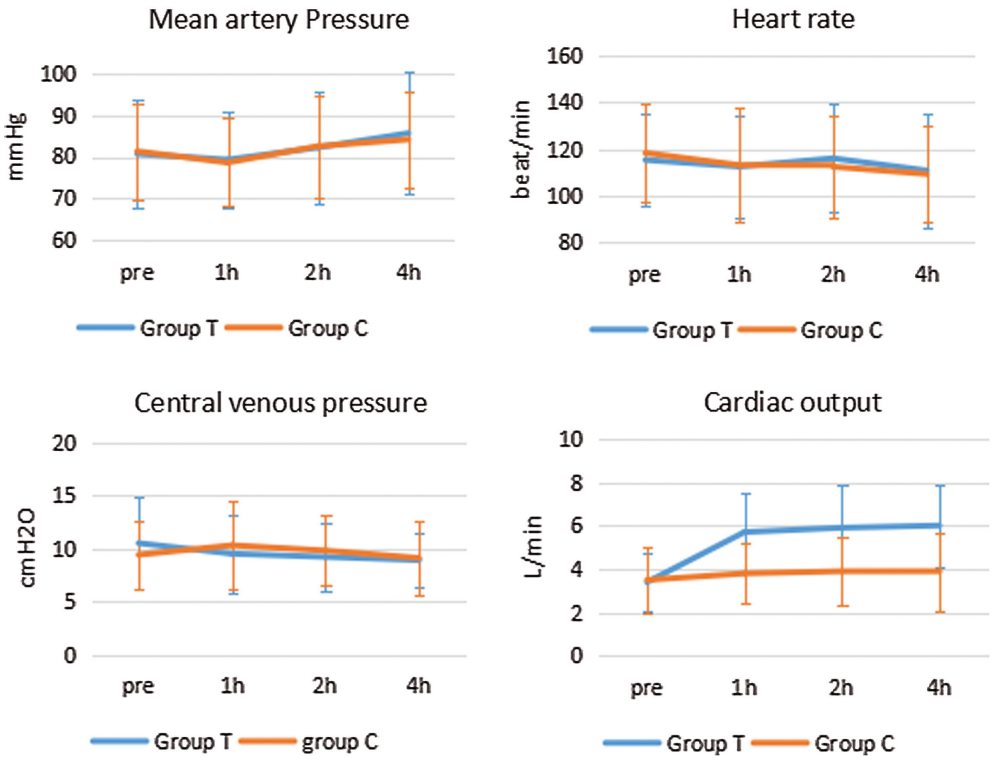

Fig. 1 The comparison of perioperative mean pulmonary artery pressure, heart rate, and central venous and pressure cardiac output measured by the SwanGanz catheter between the two groups.

significant difference between the two groups in other hemodynamic indicators monitored during the operation (**Fig. 1** and **2**). Compared with the preoperative TTE results, lower levels were also shown in the postoperative TTE examinations in both groups. The mPAP measured by TTE was significantly lower in the treprostinil group compared with the control group. Moreover, the postoperative mechanical ventilation time, ICU stay, and hospital stay of the treprostinil group were significantly shorter than those of the control group. There were no drug-related side effects in either group.

Discussion

In developing countries, severe valvular disease is still one of the most common diseases treated by cardiac surgery.[1)] Studies have shown that the incidence and prevalence of valvular disease are high in China, and rheumatic and degenerative valvular diseases are the main types.[2,3,13)] Severe left heart valvular disease is clinically characterized by mitral and/or aortic valve lesions, often associated with severe PAH. Patients with left heart valvular disease are in a state of high load for a long time, which causes myocardial cell changes, such as deformation, necrosis and fibrosis; deteriorated cardiac contraction function; and structural and functional changes in the heart, resulting in left heart failure. In addition, hypoxia and internal environmental changes may lead to pulmonary vascular remodeling and PAH. Severe PAH, in turn, aggravates left heart valvular disease.[5,14-16)]

Prosthetic valve replacement is an effective method for the treatment of left valve disease, but severe PAH may affect the prognosis of patients.[6)] Briongos and his team concluded that both preoperative PAH and significant tricuspid regurgitation were associated with postoperative persistent PAH. Valve replacement should be planned before the development of PAH.[17)] Yang and his colleagues found that mitral valve surgery could be performed with acceptable 30-day mortality for patients with moderate to severe PAH in a retrospective study, but they also noted that long-term survival was impaired by moderate to severe PAH.[18)]

As a targeted drug for the treatment of PAH, treprostinil has been used clinically in adult patients.[19)] Treprostinil is a long-acting and stable prostacycline analogue that causes pulmonary and circulatory vasodilation, inhibition of platelet aggregation, and inhibition of smooth muscle cell proliferation. Treprostinil has a high affinity for PGI2, PGE2, and PGD2 receptors but a low affinity

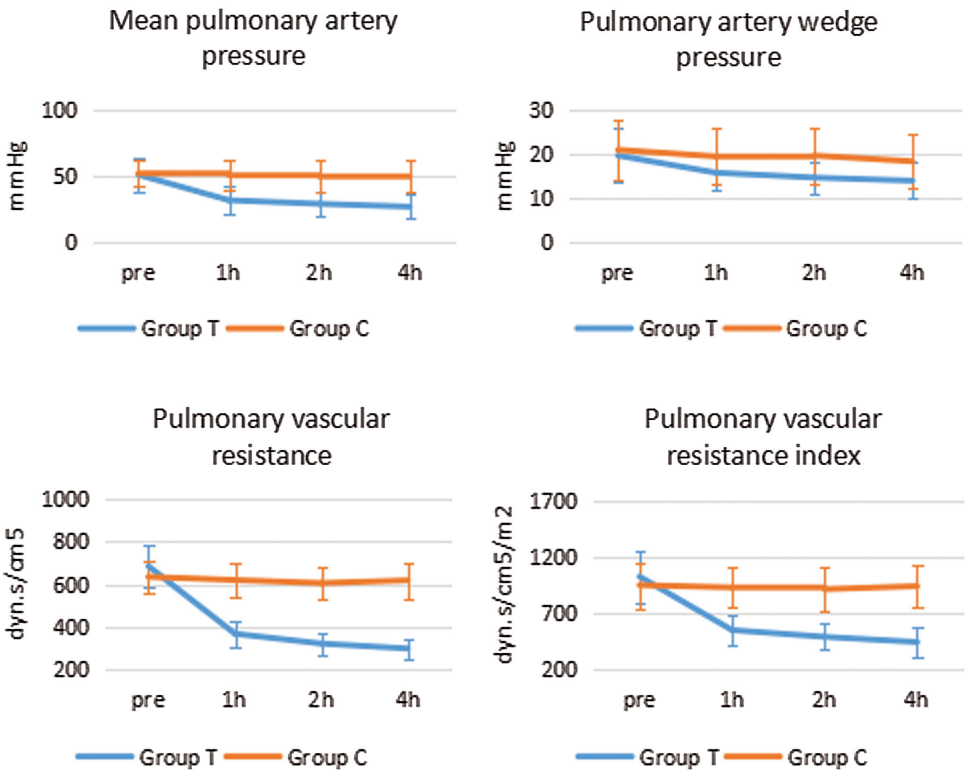

Fig. 2 The comparison of perioperative mean pulmonary artery pressure, pulmonary artery wedge pressure, pulmonary vascular resistance, and pulmonary vascular resistance index measured by the SwanGanz catheter between the two groups.

for vasoconstrictor receptors. It is also believed that the vasodilation and anti-proliferation effects of treprostinil are mediated by peroxisome proliferator activation receptors. Treprostinil can be administered via the subcutaneous, intravenous, inhalational or oral routes, and all four administration methods have achieved good efficacy and safety in the treatment of adult PAH patients. Richter et al.[20] reported preliminary evidence supporting the procedural safety of the insertion of a fully implantable pump for patients with severe PAH. Benza et al.[21] concluded that continuous intravenous treprostinil for 1 year appears to be safe and effective in PAH patients, including those transitioned from intravenous epoprostenol in their 1-year open-label trial. Many studies have concluded that treprostinil has advantages over other prostacyclins.[22,23] Simonneau and his colleagues concluded that long-term subcutaneous infusion of treprostinil was an effective treatment with an acceptable safety profile in patients with PAH.[24] Richter et al.[25] and his team concluded that intravenous treprostinil administered via a pump in advanced PAH patients was associated with a very low risk of bloodstream infections but that this therapy needed standardization and should be offered only in specialized PAH centers. Due to the limitations of the current data, there have been few studies on the use of treprostinil after left heart valvular disease-related PAH.

At present, there is no uniform standard for the dosage of treprostinil, and studies have shown a dose-dependent effect of the drug. In this study, we started with the dosage of 1.25 ng/kg/min, which is recommended in the instructions for treprostinil, and the maintenance dosage was gradually increased to 10.0–5.0 ng/kg/min. El-Kersh and his teams reported their experience with inpatient rapid titration of intravenous treprostinil. Their experience suggested that the median maximum dose achieved was 20 ng·kg·min and that the median uptitration interval of 6 days was safe and tolerable.[26] Wang et al.[27] reported that the rapid titration of intravenous treprostinil was initiated at 1.25 ng/kg/min and increased to an effective dosage of 10 ng/kg/min with increases in 1.25–2.5 ng/kg/min every 3 hours. Then, they adjusted the dosage to a median maximum dosage of 15 ng/kg/min (interquartile range, 15–20 ng/kg/min) over a median uptitration period of 34 hours (24–41 hours) for 17 parturients with severe PAH. Their results showed that rapid uptitration of intravenous

Table 2 Comparison of clinical data between the two groups

Items	Group T	Group C	P value
Operative time (min)	125.8 ± 30.5	130.5 ± 28.2	0.653
Aortic cross-clamp time (min)	35.2 ± 13.6	40.3 ± 10.8	0.712
Cardiopulmonary bypassing time (min)	76.8 ± 18.9	79.3 ± 20.2	0.707
Postoperative mechanical ventilation time (h)	51.6 ± 14.7	75.4 ± 16.8	0.034
Postoperative intensive care unit time (d)	3.2 ± 2.3	5.4 ± 3.5	0.040
Postoperative hospital stay (d)	13.2 ± 4.9	18.8 ± 6.3	0.031
Postoperative pulmonary hypertension (mmHg) (measured by TTE)	42.5 ± 8.3	60.2 ± 9.2	0.028
Postoperative tricuspid regurgitation			
Mild	8	8	0.808
Moderate	19	17	
Severe	1	2	

TTE: transthoracic echocardiography

treprostinil in the postpartum period may be a safe and effective approach for these very ill parturients with severe PAH.[27] Considering that all the patients in this group were suffering from severe valvular disease, the further increase in drug dosage could easily have led to the decline in arterial blood pressure. We tried to find an optimal dosage that would balance the positive and negative effects of the drug, although there were individual differences among the patients.

In this study, we found a significant reduction in the mPAP in patients in the treprostinil group, which indicated that treprostinil could reduce PAH caused by severe left heart valvular disease during the process of prosthetic valve replacement, which was conducive to the recovery of cardiac function and a good prognosis. Furthermore, the continued use of treprostinil improved the early prognosis of patients with severe left heart valvular disease based on the observed reductions in the mechanical ventilation time, ICU stay, and hospital stay. We found that the incidence of adverse events in the two groups of patients was not significantly different when the dosage recommended in the treprostinil instructions was used as the starting dosage. Therefore, we provisionally suggest that treprostinil is safe for the perioperative treatment of patients with severe left heart valvular disease with PAH undergoing prosthetic valve replacement.

This study was a retrospective analysis with selection bias and not a randomized, controlled, prospective study; however, the results supported our hypothesis to some extent. In the next step, we hope to conduct prospective randomized controlled studies with larger samples to further verify the conclusions. Second, we only analyzed the early application of treprostinil after left heart valvular disease-related PAH, and its long-term efficacy and safety in such patients remain to be verified. In addition, due to limited clinical data, in this study, treprostinil was only administered via an intravenous pump, and the prognosis and safety of other administration methods, such as the atomized inhalation of treprostinil, in such patients still need further study.

Conclusion

The administration of treprostinil to patients with severe left heart valvular disease combined with severe PAH undergoing prosthetic valve replacement is safe and effective, and it may improve the early prognosis of such patients.

Authors' Contributions

S-tH, NX, and HC designed the study, performed the statistical analysis, participated in the operation, and drafted the manuscript. K-pS and QC collected the clinical data. All authors read and approved the final manuscript.

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Dislosure Statement

The authors declare that they have no competing interests.

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