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Use of Sildenafil in Heart Transplant Recipients With Pulmonary Hypertension May Prevent Right Heart Failure

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ABSTRACT

Purpose. We performed a short-term outcome analysis of orthotopic heart transplantation (OHT) in patients with pulmonary hypertension (PH) treated perioperatively with oral sildenafil.

Methods. PH (pulmonary vascular resistance $>$ 2.5 Wood units, and/or transpulmonary gradient $>$ 12 mmHg) was diagnosed in 6 of 25 (group A) heart transplant recipients operated in 2006. This group of patients underwent a modified medication protocol including perioperative administration of oral sildenafil: 50 mg before followed by 50 or 25 mg TID after heart transplantation. Sildenafil treatment was discontinued 10 to 14 days post OHT, after stepwise dose reduction. During the ICU stay all patients underwent circulatory monitoring of pulmonary and systemic pressures and resistance as well as transthoracic echocardiogram (TTE) evaluation.

Results. Perioperative oral sildenafil administration in PH patients undergoing OHT was associated with good short-term outcomes in the majority of transplanted patients (4/6). Sildenafil treatment reduced pulmonary resistance and pressures with a low rate of hemodynamic instability among OHT patients.

Conclusions. Pharmacologic perioperative reduction of PH improves the short-term prognosis for successful OHT. One may speculate whether sildenafil treatment transplant recipients with PH would be associated with long-term improvement of pulmonary vascular status, therefore leading to extended life-expectancy and improved outcomes.

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TRANSPLANTATION is an established treatment option for end-stage heart failure of any cause. Patients with long-standing heart failure who are referred for orthotopic heart transplantation (OHT) commonly have significant pulmonary hypertension (PH). Although incompletely understood, PH appears to be independent predictor of poor outcome in a large subset of patients. Potential mechanisms for PH development include elevated left ventricular filling pressure owing to impaired systolic function, neurohormonal activation with increased circulating levels of vasoactive substances, structural changes in the pulmonary vasculature, and pulmonary parenchymal factors, such as alveolar hypoventilation and interstitial edema. Depending on the severity and duration of heart failure, PH may be reactive and reversible, or fixed and permanent as a result of morphologic abnormalities of the pulmonary vasculature, or, more commonly, a combination of both.[1]

Isolated OHT may be contraindicated by an elevated pulmonary vascular resistance. Posttransplant PH can be treated with vasodilators, such as phosphodiesterase inhibitors, inhaled nitric oxide, and intravenous prostacycline. Nevertheless, the greatest challenge facing heart transplant clinicians in this regard lies in the determination of whether to consider patients with certain degrees of fixed PH for OHT, as well as the pre- and postoperative management of such individuals.

The challenge lies in identifying a therapeutic agent that is efficacious, selective for the pulmonary vasculature, has minimal systemic effects, and is easily administered. Although phosphodiesterase inhibitors (e.g., milirinone) have been used for the short-term treatment of perioperative PH, there is increasing interest in the utilization of newer phosphodiesterase-5 (PDE-5) inihibitors.[2–4] There are several small reports of sildenafil demonstrating beneficial effects in the treatment of pulmonary hypertension.[5,6]

The purpose of this study was to assess the short-term outcomes of perioperative oral sildenafil treatment administered to heart transplant recipients with PH.

MATERIALS AND METHODS

Among 25 patients, who were of mean age 52 ± 11 years and were 20 males, underwent OHT in 2006 has 76% has dilated or 24% ischemic cardiomiopathy (ejection fraction < 26%). Group A 6 of subjects had a mean age 53 ± 12 years and included 9 men with a ratio of dilated/ischemic disease of 69/31%. They had been diagnosed with PH (pulmonary vascular resistance > 2.5 Wood units and/or transpulmonary gradient > 12 mmHg) using a pulmonary artery (PA) catheter (Swan-Ganz catheter, cardiac output measurements by thermodilution techniques). Group B consisted of 19 patients of mean age 52 ± 10 years and 11 men who had a ratio of dilated/ischemic disease of 80/20% without any signs of PH. The average cold ischemia time was 212 ± 59 minutes namely 173 ± 36 in group A versus 194 ± 52 in group B (P = NS).

The typical operative protocol included no induction therapy, off-pump weaning supported by transesophageous echocardiogram (TEE), and dobutamine infusion. Adrenaline was added for patients with extended ischemia time (>200 minutes) or poor heart function. Sequential (atrial/ventricular) external pacing wires were routinely attached prior to weaning off cardiopulmonary bypass.

Table 1. Postoperative Hemodynamic Parameters (group A, n = 6)

Patient	PVR (Wood units)	TPG (mmHg)	Cardiac Output (L/min)	Cardiac Index (L/min/m^{-2})
1	1.73 ± 0.6	9.2 ± 2.6	5.6 ± 1.3	3.7 ± 0.7
2	2.0 ± 0.7	10.5 ± 3.3	5.5 ± 1.1	3.7 ± 0.7
3	2.4 ± 0.6	11.5 ± 2.2	4.9 ± 1.3	3.0 ± 0.8
4	1.3 ± 0.4	9.0 ± 2.7	7.1 ± 1.1	3.3 ± 0.5
5	2.0 ± 0.4	13.4 ± 2.2	6.8 ± 0.8	3.5 ± 0.4
6	1.8 ± 0.8	13.2 ± 2.7	7.8 ± 1.7	4.2 ± 0.9

Abbreviations: PVR, pulmonary vascular resistance; TPG, transpulmonary gradient.

OHT recipients with PH were weaned off pump after the constant nitric oxide (NO) inhalation (20 to 60 ppm) and milrinone IV infusion added to the standard treatment. Protocol modification included oral sildenafil treatment starting before anesthesia (50 mg) followed by TID dosage of 25 to 50 mg during ICU stay and early stages of the rehabilitation process. During the ICU stay, hemodynamic parameters were measured repeatedly (average 52 records/patient) with once-a-day TEE evaluation. Once a stable hemodynamic status was reached, we attempted to discontinue NO inhalation and milrinone infusion.

RESULTS

Perioperative oral sildenafil administration in PH patients undergoing OHT was associated with good short-term outcomes in the majority of transplanted patients (4/6). One of the patients died owing to multiorgan dysfunction and infection, and another underwent a major perioperative stroke. All patients have shown excellent postoperative stability.

Sildenafil treatment resulted in reduction of pulmonary resistance and pressures in PH patients who underwent OHT (Table 1). TEE examination revealed normal heart function in both groups with mean ejection fractions of 50 ± 8% in group A versus 59 ± 5% in group B (P = NS). The average level of tricuspid insufficiency did not exceed grade 1 in both groups, with no significant difference between them. Postoperative intra-aortic balloon pump use was insignificantly higher in the PH group (4/6 vs 4/19), which may be explained by an extraordinary sensitivity of the transplant team with regard to any hemodynamic instability.

DISCUSSION

OHT has become standard therapy for patients with severe chronic heart failure. Unfortunately, OHT, candidates by virtue of their advanced heart disease, frequently suffer from concomitant pulmonary vascular disease. Perioperative PH, a challenging clinical problem, has numerous etiologies, including hypoxia, adrenergic stimulation, and local inflammation. Bourge et al[7] examined PVR after OHT using frequent right heart catheterizations beginning 1 week postoperatively. They observed that OHT patients with reversible PVR elevation preoperatively typically showed both reactive and fixed components. In these

patients, both early and late after OHT, PVR had fallen but had not completely normalized.[7] The results our study showed that perioperative PH treatment with sildenafil may lead to normalization of PVR. The right ventricle of the transplanted heart functions in a normal hemodynamic milieu before OHT as a predominantly volume-driven pump. It therefore may respond poorly when subjected to the abrupt increase in afterload associated with OHT into a recipient with preoperative PH. Examining the effects of elevated PVR on posttransplant right ventricular function by echocardiography, Bhatia et al[8] reported tricuspid regurgitation in the majority of patients on the first postoperative day.

Many transplant groups cite a specific PVR value as an absolute contraindication for OHT. However, the exact level of pulmonary vascular resistance in heart failure patients beyond which the risk of post-OHT right ventricular failure is excessive remains unclear.[1]

Ghofrani et al[9] noted that sildenafil caused pulmonary vasorelaxation and a significant improvement in arterial oxygenation. It has also reduced the pulmonary to systemic vascular resistance ratio.

The present study showed that a proper perioperative protocol, including selection of innovative drugs, may not only prevent right heart failure but also lead to complete normalization of pulmonary vasculature status. Improvement of PH treatment reduces the risk of early and late heart failure post-transplantation.

In conclusion, In this study, we evaluated whether perioperative sildenafil treatment of heart transplant recipients with pulmonary hypertension prevented right heart failure and improved pulmonary vascular status without influencing hemodynamic stability in the early days post-transplant. Pharmacological perioperative reduction of PH with the use of oral sildenafil improved the short-term prognosis for successful OHT, providing a stable, uneventful hemodynamic condition in the postoperative period. The results of postoperative TTE examinations proved protective effect of the new medication protocol on heart contractility and tricuspid function. Multiple hemodynamic measurements have also shown the benefits and long-term effects of PDE-5 inhibition on pulmonary vasculature status.

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