EFFECT OF ORAL SILDENAFIL ON RESIDUAL PULMONARY ARTERIAL HYPERTENSION IN PATIENTS FOLLOWING SUCCESSFUL PERCUTANEOUS BALLOON MITRAL VALVULOPLASTY (PBMV): SHORT TERM RESULTS IN 12 PATIENTS.

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Introduction:
Residual pulmonary arterial hypertension is frequently associated with continued symptoms and morbidities of right ventricular (RV) failure even after successful Percutaneous Balloon Mitral Valvuloplasty. (PBMV): Vasodilators and diuretics may further add to the agony of patients by causing systemic hypotension and hypoperfusion of other organs. Inhaled nitric oxide (NO) and oral sildenafil has been effective in ameliorating symptoms of primary pulmonary hypertension (PPH). Use of oral sildenafil in secondary pulmonary arterial hypertension (PAH) is still investigational. Few favorable reports are noted in recent literature. Our aim is to evaluate the effectiveness of oral sildenafil in patients symptomatic of residual pulmonary arterial hypertension (PAH) by decreasing (RV) after load with maintaining systemic perfusion pressure, oral sildenafil will reduce symptoms and improve effort tolerance in residual PAH patients.

Materials and Methods:
Twelve patients with rheumatic mitral stenosis who underwent successful Percutaneous Balloon Mitral Valvuloplasty (PBMV) in our hospital, but had residual moderate pulmonary hypertension and symptoms related to residual PAH were evaluated for world health organization (WHO) functional class, symptoms level, 6 minute walk test & echo parameters of PAH, Tricuspid Annular Plane Systolic Excursion (TAPSE) and all of them received oral sildenafil 25 mg per day for initial one week followed by 50 mg per day. Patients were followed up in outpatient department with all evaluations repeated at 3 monthly interval including 6 minute walk test and echo parameters. Later, follow up at 6 months was done which included entire work up same as it was done at baseline.
Results:
Out of 12 patients who received sildenafil, average time since last procedure of PBMV was 4 months. Seven patients were included in the study with sildenafil at 6 months interval following Percutaneous Balloon Mitral Valvuloplasty (PBMV) procedure. All of them had no improvement in (WHO) functional class after the invasive procedure of Percutaneous Balloon Mitral Valvuloplasty (PBMV). They had moderate PAH and average pulmonary artery systolic pressure (PASP) was 58 mmHg (minimum PASP 56 and maximum values of 65 mmHg.)

Four patients received sildenafil at three months in outpatient follow up after PBMV and one patient started taking the study drug at 7 months after PBMV. Seven patients were recruited while they were in WHO functional class III and five patients were in functional class IV when they started receiving the drug. After 6 months of follow up, WHO functional class improved in all patients with 75% of patients achieving functional class II (N=9) and 25% of patient reached in New York Heart Association (NYHA) class I (N=3). The improvement in functional class was statically significant (P=0.002) at 6 months period.

Tricuspid valve Annular Plane Systolic Excursion (TAPSE) was evaluated at baseline and on each follow up. Mean value of TAPSE at baseline was 8.75 mm and it increased to 13.42 mm (46 %) at 6 months follow up (P=0.000).

At baseline, patients were made to walk on a straight surface (without slope) for 6 minutes at a stretch. The distance covered in 6 min Walk test was evaluated at each follow up also. Mean distance of 6 min. Walk test was 229.58 meters at baseline which steadily increased to 319.17 meters at 3 months and 395.17 meters at 6 months (P=0.05).

Graphs:
**Discussion:**

Moderate to severe mitral stenosis is associated with pulmonary arterial hypertension in the majority of patients (70%). The pathophysiology of PAH in MS has dynamic and fixed components where long standing mitral valve disease induces structural changes in the pulmonary vascular bed mediated by potent vasoconstrictor endothelin-1 (ET-1). Levels of ET-1 are three times higher in severe MS compared with healthy control subjects. Baseline ET-1 concentration has been documented as independent marker that predicts fall in pulmonary capillary wedge pressure (PCWP) at 6 months following PBMV.

Patients with PH secondary to mitral valve disease were not included in clinical trials approved for PAH pharmacologic vasodilator therapies. Few case reports have been published about their usage in perioperative periods of mitral valve surgery. Agents evaluated are inhaled prostacyclin, inhaled nitric oxide intravenous nitroprusside etc.

Effectiveness use of oral pulmonary vasodilator sildenafil following successful mitral valve surgery with persistent severe PAH has been noted. This novel therapy for PAH is safe and beneficial in residual PAH following PBMV but needs to be validated further in scientifically designed studies.

We aim at reporting initial evaluation of pulmonary vasodilator drug Sildenafil in symptomatic patients with residual moderate PAH following successful PBMV procedure. In the current study sildenafil oral dose 25 mg per day was introduced in significant PAH patients who had successful PBMV and WHO functional class was III and IV. The dose was up-titrated to 50 mg per day after 7 days and there were no side effects or discontinuation of drug and patients were followed up for 6 months following initiation of sildenafil therapy.

Following mitral valve surgery, significant reduction in PASP and pulmonary vascular resistance index (PVRI) is documented in various studies of sildenafil as compared to placebo. Trachte et al (2005) and shim et al (2006) have successfully demonstrated beneficial effects of sildenafil on residual PAH.
as compared to placebo in patients undergoing mitral valve surgery. This has contributed to rapid weaning from inhaled or intravenous pulmonary vasodilators. Such patients required shorter duration of postoperative ventilatory support. It probably averted the predictable rebound PAH that frequently accompanies weaning from inhaled NO after cardiac surgery. Because sildenafil preferentially inhibits PDE5 which is abundant in lung tissues, it selectively dilates pulmonary vascular beds. We use 50 mg per day dose however it has been demonstrated that peak hemodynamic responses of sildenafil on pulmonary vascular bed are seen in doses as low as 25 mg per day.

In patients with idiopathic primary pulmonary hypertension (PPH) it has been documented that syncope, hemoptysis, decreasing exercise capacity and overt signs of RV failure carry a poorer prognosis. Echocardiographic indices that predict prognostic value are pericardial effusion, indexed right atrium area, LV eccentricity index and tricuspid annular plane systolic excursion (TAPSE). Estimated pulmonary artery systolic pressure (PASP) derived from tricuspid regurgitant jet velocity is not prognostic.

For objective assessment of exercise capacity, the 6 minute walking test is commonly used in patients with PAH. This test is simple, inexpensive, well standardized and easily reproducible. Walking distances ≤ 332 meters indicate impaired prognosis in PPH. With respect to treatment effects, good effort tolerance ≥ 380 meters following 3 months of IV pulmonary vasodilators correlated well with improved survival in PPH.

Ghofrani HA et al reported beneficial effects of sildenafil in PPH patients and also in secondary pulmonary hypertension with favorable reports on exercise capacity, symptoms and hemodynamics (SUPER-1 study).

We report significant improvement in PASP, TAPSE values and clinical improvements were also seen in WHO functional class as well as distance travelled in 6 minute walk test. All patients exhibited severe symptomatic status in class III and IV at the time of initiation of the study drug and they showed significant benefit and clinical improvement at 6 monthly follow up. It is noteworthy to state that previous PBMV procedure in the recent past was not effective in demonstrating such an improvement.

Most studies till date have examined efficacy of sildenafil in idiopathic pulmonary arterial hypertension. In secondary pulmonary hypertension, studies have been observational or only case reports, although, they reported benefits with regards to pulmonary and RV hemodynamics.

Our study is also observational, small sample size and needs further evaluation on prospective, randomized study in this subset of residual PAH after successful PBMV. Moreover, whether these improvements in functional capacity, PASP, TAPSE and significant improvement in 6min walk distance are really a response to sildenafil or it is a delayed fall in PASP, slow sustained clinical improvements seen after successful PBMV, the question remains still unanswered. Slow resolution of PAH with delayed improvement may have occurred in some cases. More studies with longer duration of follow up and proper randomization are needed to prove this hypothesis.
Conclusion:
Sildenafil is a drug having several properties as strong pulmonary vasodilator compound. Successful PBMV is expected to resolve PAH in majority of patients. However, few patients continue to exhibit severe symptoms and residual PAH, despite good valve area (>1.5 cm$^2$) following PBMV. Such symptomatic patients may exhibit significant improvement after receiving oral sildenafil in follow up period.

Some patients may have chronic obstructive pulmonary disease (COPD) and pulmonary parenchymal disease also. The residual PAH may be attributable to such pulmonary parenchymal disease. Hence, residual PAH after PBMV has some additional contributing causes. Role of oral sildenafil in such cases needs further documentation before its routine use in such cases.

References:


