



## Surgery

## EFFICACY OF ORAL TADALAFIL IN PREOPERATIVE MANAGEMENT OF ADULT OSTIUM SECUNDUM ARTERIAL SEPTAL DEFECT COMPLICATED WITH PULMONARY ARTERIAL HYPERTENSION

**Dr. Santanu Dutta\***

Department Of CTVS, IPGME& RSSKM Hospital, Kolkata \*Corresponding Author

**Sanchita Das**

Department Of CTVS, IPGME& RSSKM Hospital, Kolkata

**Sumanta Ghosh**

Department Of CTVS, IPGME& RSSKM Hospital, Kolkata

**Dr. Shilpa Basu Roy**

Department Of CTVS, IPGME& RSSKM Hospital, Kolkata

### ABSTRACT

**PURPOSE:** To evaluate the efficacy and safety of oral tadalafil in reducing pulmonary arterial hypertension (PAH) in adult ostium secundum atrial septal defect (OS-ASD) patients.

**METHODS:** Pre-operative patients with OSD complicated with PAH, age >18 years, were enrolled into two groups; Group A (oral tadalafil) and Group B (without tadalafil) for over a period of 3 months. Pulmonary artery pressure (PAP) at baseline and post three month of treatment was measured to evaluate the efficacy of tadalafil. Independent t-test and p-value were used to compare the various parameters between two groups. Safety was assessed as the incidence of adverse events (AEs) during the three month treatment period.

**RESULTS:** A statistically significant reduction in PAP from baseline was observed after completion of 3 months in patients receiving tadalafil ( $p=0.0004$ ). On the contrary, an increase in PAP was observed in Group B patients not receiving tadalafil (from  $41.86 \pm 6.42$  to  $44.86 \pm 5.33$ ). Additionally, after three months of treatment, PAP between the two treatment groups was also statistically significant ( $p=0.0006$ ). No adverse events were associated with the use of oral tadalafil.

**CONCLUSION:** Oral tadalafil reduced pulmonary artery pressure in adult OS-ASD with PAH patients.

### KEYWORDS :

#### INTRODUCTION

Atrial septal defects (ASDs) are one of the most common congenital heart defects, affecting about 1 in 100 births [1], predominating in females with a 1.5 - 3.5:1 female/male ratio [2]. Particularly, ostium secundum ASD (OS-ASD) constitutes about 75% of all ASDs [2]. Majority of patients with OS-ASD have an uncomplicated clinical course with a high probability of survival into adulthood [3]. Having said, a proportion of patient present with symptoms such as, right heart failure, left-to-right (systemic-to-pulmonary) shunt, arrhythmia, paradoxical embolism, and a variable degree of pulmonary arterial hypertension (PAH) due to the high pulmonary blood flow and/or increased pulmonary vasculature abnormality [4].

PAH may be severely disabling and rapidly progress leading to right ventricular dysfunction and death, but patient benefit from therapeutic targeting of specific pathways [5]. Up to 30% of adult- [6, 7] and 75% of pediatric-onset PAH cases [8] are associated with congenital heart disease (PAH-CHD), and paradoxically, due to improved treatments, the number of adults with PAH-CHD is rising [6, 9]. When OS-ASD patients are untreated, increased levels of PAH with ~45mmHg have been observed, whereas normal PAH ranges between 25-30 mmHg. Furthermore, PAH may persist following surgical repair of cardiac defects or recur many years after repair [10].

Although the therapeutic goal of OS-ASD management is the prompt repair of defect(s), supportive or preoperative measures are usually targeted to treat or avoid the chronic hypoxemia, low cardiac output and the PAH complications [10].

There is growing evidence in the favour of phosphodiesterase type 5 (PDE5) inhibitor in the management of idiopathic OS-ASD complicated with PAH with improvement in exercise capacity, and overall hemodynamics [11]. PDE5 inhibitors, promotes the synthesis of cyclic adenosine monophosphate leading to inhibition of cyclic guanosine monophosphate hydrolysis causing pulmonary arterial smooth muscle relaxation through enhanced opening of large calcium sensitive potassium channels [11].

Tadalafil is an oral PDE5 inhibitor that is indicated for the treatment of PAH (World Health Organization Functional Class II and III). In a previous PHIRST-1 trial, tadalafil, administered in the doses of 2.5 mg, 10 mg, 20 mg, or 40 mg once-a-day for 16 weeks, improved the mean

six minute walking distance, increased time to clinical worsening and decreased incidence of clinical worsening, compared to placebo. Significant improvements in quality of life (QoL), cardiopulmonary hemodynamics, including mean PAP were also observed [12].

The present study assessed the efficacy and safety of a 20-mg oral tadalafil once in a day in patients with OS-ASD patient undergoing corrective heart surgery.

#### MATERIALS AND METHODS

This was a single-centre prospective observation study, which was carried out at Cardio Thoracic & Vascular Surgery OPD of SSKM hospital, Kolkata from August 2017 to August 2018. Thirty patients with OS-ASD, age >18 years were selected with high PAH (>30mmhg) for the study. Efficacy was measured in terms of reduction in the PAP from baseline, which was recorded using echocardiography. The patients were divided into two groups. Patients in Group A received 20mg of tadalafil once a day for 3 months, along with the other medications. While, patients in the Group B received similar treatment as that of patients in the Group A, except tadalafil. After 3 months of treatment, the patients again undergo echocardiography to measure PAP. Safety was assessed in terms of incidence of adverse events (Aes).

#### STATISTICAL ANALYSIS

All the data were expressed as mean  $\pm$  standard deviation (SD) if normally distributed or as median (range) for nonparametric distribution. The mean values were compared between the two treatment groups using unpaired t tests, and chi-squared test for frequencies. A p value of <0.05 was considered significant. All the analysis were done using SPSS software.

#### RESULTS

Overall, the baseline characteristics of the patients were similar between the two groups (Table 1) with a mean age of 36.8 and 39.4 years, respectively.

The three months of treatment with tadalafil patients in Group A, observed a statistically significant reduction in mean PAP (two-tailed  $p=0.0042$ , Figure 1). On the contrary, an increase in mean PAP was observed in the Group B. Additionally, after 3 months of medication, PAP between the two treatment groups was also statistically significant ( $p=0.0006$ ). Also in three patients in Group A, it was observed that

there was a reduction in extubation time, post-operative ventilation and ICU stay. Furthermore, no safety signals were observed in the Group A patients.

**DISCUSSION**

PDE-5 is the predominant phosphodiesterase in the pulmonary vasculature responsible for the rapid degradation and inactivation of cGMP [13, 14], leading to production and release of nitric oxide (NO). As a result of pulmonary endothelial dysfunction in patients with OS-ASD, there is a decreased production and release of NO. A reduction in NO release leads to a decreased cGMP and thus increased PAP [15]. Tadalafil is a PDE-5 inhibitor that regulates intracellular signalling pathway of pulmonary vasculature. By inhibiting, PDE-5, Tadalafil leads to an improved vasodilation via NO pathway and thus reduction in PAP [16].

The results of the present study showed that three months treatment with once-a-daily oral tadalafil in Group A patients, had a statistically significant reduction in PAP from baseline. The reduction in PAP in Group A was also significant as compared with Group B patients not receiving tadalafil. On the contrary, Group B patients showed an increased in PAP after three months of routine care, sans tadalafil.

Group A patients receiving tadalafil, observed a reduced extubation time and postoperative ventilation and ICU stay as compared with Group B patients, who took more time to recover in postoperative care. However, only three patients in Group A could be studied for the purpose due to scarcity of the hospital bed schedule. Thus because of lower sample size the data could not be validated, which should be considered as the limitation of this study.

Adverse events like flushing, headaches, diarrhea, flu-like symptoms, dementia, back pain and nausea are quite common with PDE-5 inhibitors [17]. However, no such events were observed during the course of three month treatment period, suggesting a good safety profile of tadalafil in patients with OS-ASD.

Currently, there is a scant data that discusses reduction in PAP with tadalafil, however, safety and efficacy of other PDE-5 inhibitors like sildenafil, in terms of improved quality of life, improved exercise capacity have been published previously. Having said that, the results of the present study are consistent with a prior trial in paediatric patients, wherein tadalafil led to statistically significant reduction from baseline in PAP [18]. Additionally, although the present study was not powered for comparison with sildenafil, tadalafil could be considered as an alternative to sildenafil in terms of treatment simplification. This is because the current dose of sildenafil ranges from 12-30 mg three times a day, while tadalafil requires to be administered once-a-day only.

**CONCLUSION**

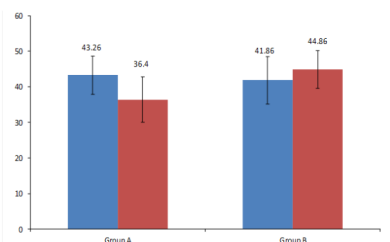
Tadalafil is a convenient and generally well tolerated 20mg once-a-day PDE-5 inhibitor for treating patients OS-ASD with PAH, undergoing corrective heart surgery and may lead to reduced extubation time, postoperative ventilation and ICU stay. The results of this study also suggest that tadalafil may be a suitable alternative to sildenafil for patients opting for treatment simplification with once-a-day tadalafil.

**TABLE AND FIGURE**

**Table 1. Baseline characteristics**

	Group A	Group B	p value
Patient, n	15	15	
Female, n	11	10	
Age, mean (±SD)	36.8 (± 10.59)	39.4 (± 11.4)	0.5229
PAH, mean (±SD)	43.26 ± 5.36	41.86 ± 6.4	0.5224

**Figure 1. Pulmonary arterial pressure comparison between the two groups**



**REFERENCES**

- Oster ME, Lee KA, Honein MA, Riehle-Colarusso T, Shin M, Correa A. Temporal trends in survival among infants with critical congenital heart defects. *Pediatrics*. 2013;131:e1502-8. doi: 10.1542/peds.2012-3435.
- Chen FL, Hsiung MC, Hsieh KS, Li YC, Chou MC. Real time three-dimensional transthoracic echocardiography for guiding Amplatzer septal occluder device deployment in patients with atrial septal defect. *Echocardiography*. 2006;23:763-70.
- Nashat H, Montanaro C, Li W, Kempny A, Wort SJ, Dimopoulos K, Gatzoulis MA, Babu-Narayan SV. Atrial septal defects and pulmonary arterial hypertension. *J Thorac Dis*. 2018;10(Suppl 24):S2953-S2965. doi: 10.21037/jtd.2018.08.92.
- Nassif M, Heuschen CB, Lu H, Bouma BJ, van Steenwijk RP, Sterk PJ, Mulder BJ, de Winter RJ. Relationship between atrial septal defects and asthma-like dyspnoea: the impact of transcatheter closure. *Neth Heart J*. 2016;24:640-646.
- Giaid A, Saleh D. Reduced expression of endothelial nitric oxide syn-thase in the lungs of patients with pulmonary hypertension. *N Engl J Med*. 1995;333:214-221.
- Li L, Jick S, Breitenstein S, Hernandez G, Michel A, Vizcaya D. Pulmonary arterial hypertension in the USA: an epidemiological study in a large insured pediatric population. *Pulm Circ*. 2017;7:126-36.
- Marelli AJ, Ionescu-Ittu R, Mackie AS, Guo L, Dendukuri N, Kaouache M. Lifetime prevalence of congenital heart disease in the general population from 2000 to 2010. *Circulation*. 2014;130:749-56.
- Galiè N, Hoeper MM, Humbert M, Torbicki A, Vachiery JL, Barbera JA, Beghetti M, Corris P, Gaine S, Gibbs JS, Gomez-Sanchez MA, Jondeau G, Klepetko W, Opitz C, Peacock A, Rubin L, Zellweger M, Simonneau G. Guidelines for the diagnosis and treatment of pulmonary hypertension. *Eur Respir J*. 2009;34:1219-63.
- Jean-LUC Vachiery, Sandrine Huez, Hunter Gillies, Gary Layton, Naoto Hayashi, Xiang Gao and Robert Naeije. Safety, tolerability and pharmacokinetics of an intravenous bolus of sildenafil in patients with pulmonary arterial hypertension.
- Fathallah M, Krasuski RA. Multifaceted Approach to Pulmonary Hypertension in Adults With Congenital Heart Disease. *Prog Cardiovasc Dis*. 2018; 61: 320-327. doi: 10.1016/j.pcad.2018.07.017.
- Giaid A, Saleh D. Reduced expression of endothelial nitric oxide syn-thase in the lungs of patients with pulmonary hypertension. *N Engl J Med*. 1995;333:214-221.
- Galiè N, Brundage BH, Ghofrani HA, Oudiz RJ, Simonneau G, Safdar Z, Shapiro S, White RJ, Chan M, Beardsworth A, Frumkin L, Barst RJ; Pulmonary Arterial Hypertension and Response to Tadalafil (PHIRST) Study Group. Tadalafil therapy for pulmonary arterial hypertension. *Circulation*. 2009; 119: 2894-903. doi: 10.1161/CIRCULATIONAHA.108.839274.
- Archer SL, Huang JM, Hampl V, Nelson DP, Shultz PJ, Weir EK. Nitric oxide and cGMP cause vasorelaxation by activation of a charybdotoxin-sensitive K channel by cGMP-dependent protein kinase. *Proc Natl Acad Sci U S A*. 1994;91:7583-7587.
- Corbin JD, Beasley A, Blount MA, Francis SH. High lung PDE5: a strong basis for treating pulmonary hypertension with PDE5 inhibitors. *Biochem Biophys Res Commun*. 2005;334:930-938.
- Beavo JA. Cyclic nucleotide phosphodiesterases: functional implications of multiple isoforms. *Physiol Rev*. 1995;75:725-748.
- Henrie AM, Nawarskas JJ, Anderson JR. Clinical utility of tadalafil in the treatment of pulmonary arterial hypertension: an evidence-based review. *Core Evid*. 2015 Nov 2;10:99-109. doi: 10.2147/CE.S58457. eCollection 2015.
- Yamazaki H, Kobayashi N, Taketsuna M, Tajima K, Suzuki N, Murakami M. Safety and effectiveness of tadalafil in pediatric patients with pulmonary arterial hypertension: a sub-group analysis based on Japan post-marketing surveillance. *Curr Med Res Opin*. 2017; 33: 2241-2249. doi: 10.1080/03007995.2017.1354832.
- Maki S, Tanaka H, Tsuji M, Furuhashi F, Magawa S, Kaneda MK, Nii M, Tanaka K, Kondo E, Tamaru S, Ogura T, Nishimura Y, Endoh M, Kimura T, Kotani T, Sekizawa A, Ikeda T. Safety Evaluation of Tadalafil Treatment for Fetuses with Early-Onset Growth Restriction (TADAFER): Results from the Phase II Trial. *J Clin Med*. 2019; 8. pii: E856. doi: 10.3390/jcm8060856.