

The effect of tadalafil on functional capacity and echocardiographic parameters in patients with repaired Tetralogy of Fallot

Mohammad Reza Sabri⁽¹⁾, Mohammad Shoja⁽²⁾, Mohsen Shoja⁽³⁾, Mohsen Hosseinzadeh⁽²⁾

Original Article

Abstract

BACKGROUND: Tetralogy of Fallot (TOF) is one of the most common cyanotic congenital heart diseases (CHD) in children. Various surgical procedures including palliative shunts and TOF total correction (TFTC) were done with some complications, of which, the most common is pulmonary valve regurgitation (PR). Tadalafil is a phosphodiesterase 5 inhibitor which reduces pulmonary vascular resistance, and improves right ventricular function and vascular endothelium, and may have some beneficial effects after TFTC.

METHODS: We studied 18 patients with TOF and PR, with some impaired right ventricular function after TFTC. Tadalafil tablets at a dose of 1 mg per kg (maximum 40 mg) per day as a single dose was administered orally for 8 weeks. In all patients, before and after taking tadalafil, functional class assessment, electrocardiography (ECG) changes, some echocardiographic and endothelial function parameters [flow-mediated dilation (FMD) and intima-media thickness (IMT) of carotid artery], and exercise test were determined.

RESULTS: The patient's mean age was 10.11 ± 4.03 years, and the mean age of operation was 2.52 ± 1.12 years. The effect of tadalafil on different echocardiographic parameters and also on tricuspid valve regurgitation (TR) and PR severity and gradient was not significant. Moreover, it had no effects on QRS duration. Tadalafil had a significant effect on improving FMD and exercise test ($P = 0.01$). The effect of tadalafil on echocardiographic parameters, carotid artery IMT, and ECG parameters was not significant ($P > 0.05$). Tadalafil was tolerated well, and the most common side effects were headache and myalgia.

CONCLUSION: This study showed that tadalafil is a safe and well-tolerated drug. It might improve exercise performance, endothelial function, and functional class, and possibly could allow patients a longer period of well-being and could possibly delay the need for pulmonary valve replacement (PVR).

Keywords: Tetralogy of Fallot, Cardiac Surgery, Tadalafil

Date of submission: 11 Jan. 2017, *Date of acceptance:* 18 May 2018

Introduction

Tetralogy of Fallot (TOF) is the most common cyanotic congenital heart disease (CHD) in children.^{1,2} Various surgical procedures are popular at different ages to treat episodes of cyanosis in these patients, and includes the creation of a palliative shunt and TOF total correction (TFTC).² One of the most common problems after TFTC surgery is pulmonary valve regurgitation (PR).^{1,2} Therefore, continuous follow-up of patients after TFTC via electrocardiography (ECG), chest radiography, echocardiography, exercise test (ET),

magnetic resonance imaging (MRI), and sometimes angiography should be performed as needed.^{1,3} There are some paraclinical parameters which are correlated with long-term prognosis in these patients, and include QRS prolongation in ECG, degree of right ventricular (RV) dilatation and systolic function, degree of PR and tricuspid valve regurgitation (TR), and arrhythmia such as premature ventricular contraction (PVC). These patients may need pulmonary valve replacement (PVR) procedure either by surgical or percutaneous approaches. Drugs which improves ventricular

1- Professor, Department of Pediatric Cardiology, Pediatric Cardiovascular Research Center, Cardiovascular Research Institute, Isfahan University of Medical Sciences, Isfahan, Iran

2- Pediatric Cardiology Fellow, Pediatric Cardiovascular Research Center, Cardiovascular Research Institute, Isfahan University of Medical Sciences, Isfahan, Iran

3- Department of Epidemiology, Esfarayen School of Medical Sciences, Esfarayen, Iran

Correspondence to: Mohammad Shoja, Email: mshoja84@yahoo.com

function, and reduce long-term PR in these patients, may have a positive effect in improving the above-mentioned complications, and delay the PVR.^{4,6}

In recent years, studies had shown the positive effect of sildenafil in the treatment of adults with heart failure.⁶ Over the past few years, several studies about the effects of sildenafil on myocardial performance index (MPI) were conducted, but no study has been done on the effects of tadalafil on MPI.⁴ Tadalafil is a selective inhibitor of phosphodiesterase 5 that is used once a day.^{7,8} It is used for treatment of pulmonary arterial hypertension (PAH) in both children and adults.^{4,9} Moreover, endothelial dysfunction can play an important role in deterioration of the clinical condition in patients with CHD, especially in patients with cyanosis.^{6,10} With the best of our knowledge, there are no studies about the effect of tadalafil after TFTC, and so we decided to study the effect of tadalafil on symptoms and physical activity, and also the degree of PR and right ventricular function in these patients.

Materials and Methods

The study was conducted in the Imam Hussein Children's Hospital of Isfahan University of Medical Sciences, Isfahan, Iran, from April 2015 to September 2016. This study in terms of ethics in research involving human subjects was approved by Isfahan University of Medical Sciences, and ethical approval of Regional Ethics Committee of Isfahan University of Medical Sciences was received with the code number 395032. All the performed procedures in this study involving human participants were in accordance with the ethical standards of the institutional and/or national research committee, and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

The study population included 18 patients who had TFTC and PR, and some impaired RV functions. All patients were initially informed about the side effects and benefits of the project and the informed consent form was signed by their parents or the patients. Two of these patients deny continuing the study due to side effects of the drug (headache and myalgia) in first day, and excluded.

Inclusion criteria's were as patients with TOF after TFTC, aged 6 to 35 years, did not use any drugs which could affect endothelial function (diuretics, lipid-lowering agents, nitrates, etc.), lack of systemic diseases, and did not use vitamins or fruits which has effect on flow-mediated dilation (FMD) (vitamin C, Kiwi, strawberry, etc.) at least

during 5 days before the paraclinical evaluation.

Exclusion criteria were as patients with residual defects remaining after TFTC surgery, such as atrial or ventricular septal defect, severe renal or hepatic dysfunction, patients with dysrhythmia or has pacemaker, the use of tadalafil in the past three months, and hypersensitivity to tadalafil.

After reviewing the patients' files, history taking, and physical exam, baseline assessment which included lab workup for renal and hepatic function and complete blood count, echocardiogram, sonographic evaluation of endothelial function (FMD), and intima-media thickness (IMT) of carotid artery, and ET was done for all patients. Tadalafil tablets at dose of 1 mg per kg (maximum 40 mg) per day in single dose were administered orally for 8 weeks. Patient's functional class was evaluated using New York Heart Association (NYHA) classification. In all patients, before and after taking the tadalafil, an ECG, brachial artery diameter at rest, the diameter of the brachial artery at the time of hyperemia, carotid artery IMT at rest, and evaluation of echocardiographic parameters such as left ventricular ejection fraction (LVEF) and fractional shortening (FS), LV myocardial performance index (LV MPI), RV size and MPI, tricuspid annular plane systolic excursion (TAPSE), fractional area change (FAC), PR, and TR were determined. ET was done according to modified Bruce protocol before and after taking tadalafil in five steps (four running and one recovery step), each step lasted 3 minutes.³ During the follow-up and medical visits, patients were asked about the side effects of tadalafil (headache, nasal congestion, flushing, myalgia, allergic reactions, and priapism).

Echocardiogram was performed with an ultrasound system (EKO 7, Samsung Medison Company, South Korea) before and after tadalafil administration by a certified pediatric cardiologist.¹⁰ Echocardiographic parameters were obtained according to the standards of the American Society of Echocardiography.¹¹ Each Doppler variable was measured several times, and the mean value was used for analysis. FS and EF were obtained using M-mode images from a parasternal long-axis view. Early diastolic inflow velocity (E-wave) and late diastolic inflow velocity (A-wave) were obtained by using pulse wave Doppler at the tips of the atrioventricular valves (AVV) leaflets in an apical 4 chamber view. MPI was calculated as (a-b)/b, where a is the distance between cessation and onset of mitral or tricuspid valve inflow, and b is the ejection fraction of the ventricular outflow.¹¹

TAPSE, PR, and TR were measured according to the pediatric echocardiography references.¹¹

TOF after repair needs careful evaluation of the RV size and function. Currently, cardiac MRI (CMR) is the gold standard for RV function evaluation. Echocardiogram is the most non-invasive method for RV assessment.³ Promphan et al.³ showed significant correlations between RV end-diastolic volume index (RVEDVI) and RVED area ($R = 0.768, P < 0.01$), RVEF with FAC ($R = 0.759, P < 0.01$), and RVEF with TAPSE ($R = 0.688, P < 0.01$). They found 100% correlation in moderate to severe PR assessment by echocardiography and CMR ($Kappa = 0.912$).³ According to their results and because of feasibility of echocardiography, we assessed our patients with echocardiogram carefully.

Endothelial function (IMT, FMD) was assessed after 6 hours fast in the morning with ultrasound images using 7-MHz linear array transducer.¹¹ In the longitudinal plane, at 2-5 cm above the antecubital fossa, the artery was evaluated, and from anterior to posterior at end-diastole incident with the R wave on the ECG, the measurements were taken. Arterial flow velocity was evaluated using a pulsed Doppler signal at 70 angles to the vessel. A baseline scan after 15 minutes initial rest period was taken in the supine position.^{9,10,12} A proper pneumatic tourniquet was used and inflated to 50 mm Hg above the systolic blood pressure of the patient for 5 minutes, then released. Reactive hyperemia was measured 60 seconds after cuff deflation by another scan. FMD was measured as percentage of increase in arterial diameter during hyperemia compared to the corresponding value at rest as $FMD = (D2 - D1)/100$, where D1 is the vessel diameter at rest, and D2 is the vessel diameter during reactive hyperemia as described.¹³ A 7-MHz high-frequency vascular linear transducer was used to image the right carotid artery for IMT. At supine position and while head turned 45 degree away from the scanner, IMT was taken. Three segments of the common carotid artery 1 cm distal to its bifurcation were measured at a distance between the lumen-intima and the media-adventitia interface on a B-mode image, and the average value was used.^{9,10,12} A single pediatric

cardiologist performed these evaluations.

Data were analyzed using SPSS software (version 18.0, SPSS Inc., Chicago, IL, USA). Normality of data was checked using Kolmogorov-Smirnov test; continuous and discrete variables were represented as mean \pm standard deviation (SD) and number (percent), respectively. Quantitative and qualitative data of the parameters before and after tadalafil were compared using paired t test. For all analyses, statistical significance was assessed at a level equal or less than 0.05.

Results

Of the 18 studied patients, 7 (31.9%) were boys and 11 (61.1) were girls. The mean age of the patients was 10.11 ± 4.03 years. Patient demographics data are shown in table 1.

Associated CHD and details of the surgical procedures are shown in table 2. Fourteen patients had only TOF and 3 had associated patent ductus arteriosus (PDA) and one had pentalogy of Fallot [TOF with atrial septal defect (ASD)]. All of them were corrected by transannular patch. Two patients had a previous Blalock-Taussig (BT) shunt operation. The mean \pm SD age of operation was 2.52 ± 1.12 years.

The frequencies of each echocardiographic parameter in this study as well as mean \pm SD values of before and after tadalafil administration are shown in table 3. The effect of tadalafil was not significant on TR, and PR severity and gradient.

Mean \pm SD of ET parameters, NYHA functional class, and ECG findings before and after tadalafil usage is shown in table 4. The results showed that tadalafil had a significant effect on improving FMD and ET, as well as improvement in NYHA functional class of patients ($P = 0.01$). Tadalafil had no significant effect on echocardiographic parameters (LVEF and LVFS, LV MPI, RV MPI, TAPSE, FAC, PR, and TR), IMT, and ECG parameters ($P > 0.05$ for all).

The most common side effects of tadalafil were headache in 7 patients (38.9%), and myalgia in 3 patients (16.7%). These side effects were transient and lasted for 3-7 days. 8 patients (44.4%) had no side effects after tadalafil use.

Table 1. Patients' demographics data (n = 18)

Demographics	Minimum	Maximum	Mean \pm SD
Age (year)	6.00	19.00	10.11 \pm 4.03
Age at TFTC (year)	1.50	6.00	2.47 \pm 1.11
Weight (kg)	13.50	60.00	31.25 \pm 14.91
Height (cm)	110.00	170.00	132.94 \pm 17.82

TFTC: Tetralogy of Fallot total correction; SD: Standard deviation

Table 2. The history of congenital heart disease (CHD), cardiac malformations, and surgical procedures in study population

Patient number	Cardiac malformation	Surgical procedures	Age of TFTC (years)	History of palliation surgery
1	TOF	TFTC (with transannular patch)	2.5	No
2	TOF, PDA, PFO	TFTC (with transannular patch and PDA ligation)	3.0	No
3	TOF	TFTC (with transannular patch)	4.0	No
4	TOF	TFTC (with transannular patch)	1.5	No
5	TOF	TFTC (with transannular patch)	2.0	No
6	TOF	TFTC (with transannular patch)	2.0	No
7	TOF	TFTC (with transannular patch)	3.0	No
8	TOF	TFTC (with transannular patch)	6.0	No
9	TOF, PDA	TFTC (with transannular patch and PDA ligation)	3.0	No
10	PFO	TFTC (with transannular patch and ASD closure)	2.0	BT shunt
11	TOF	TFTC (with transannular patch)	1.5	No
12	TOF	TFTC (with transannular patch)	2.0	No
13	TOF	TFTC (with transannular patch)	3.0	No
14	TOF	TFTC (with transannular patch)	1.5	No
15	TOF, PDA	TFTC (with transannular patch and PDA ligation)	2.0	No
16	TOF	TFTC (with transannular patch)	2.0	BT shunt
17	TOF	TFTC (with transannular patch)	3.0	No
18	TOF	TFTC (with transannular patch)	1.5	No

TOF: Tetralogy of Fallot; TFTC: Tetralogy of Fallot total correction; PDA: Patent ductus arteriosus; PFO: Pentalogy of Fallot; ASD: Atrial septal defect

Discussion

Drugs that reduce pulmonary vascular resistance and improve RV function and vascular endothelium might have positive effect on patients with cyanosis. This study appears to be the first one according to the best of our knowledge on the effectiveness of tadalafil among patients with TOF that suffered PR and RV dysfunction after TFTC. The results showed that the use of tadalafil after

TFTC surgery had a positive effect on exercise performance, NYHA functional class, and improvement in endothelial function (FMD). Improvement in well-being was observed in most patients, and they have a tendency to continue the tadalafil use. A previous study by Sabri and Beheshtian⁹ performed in children with PAH showed that tadalafil had a better effect than sildenafil on this group of children.

Table 3. Echocardiogram parameters before and after tadalafil administration following Tetralogy of Fallot total correction (TFTC)

Variable	Before tadalafil		After tadalafil		
	Mean	SD	Mean	SD	
FMD	12.88	± 2.16	11.88	± 1.64	0.04
IMT	0.19	± 0.01	0.18	± 0.01	0.96
LVEF	66.38	± 1.37	66.33	± 1.02	0.93
LV FS	35.44	± 0.51	35.38	± 0.50	0.70
LV MPI	0.36	± 0.01	0.36	± 0.01	0.33
RV MPI	0.33	± 0.01	0.32	± 0.01	0.28
TAPSE	13.03	± 1.30	13.22	± 1.11	0.52
FAC	28.61	± 5.33	28.11	± 4.94	0.08
PR gradient	25.66	± 4.05	23.27	± 4.83	0.10
TR gradient	35.88	± 8.53	35.33	± 7.27	0.90
		Frequency (%)	Frequency (%)		P
PR severity	Mild	5 (27.8)	9 (50.0)		0.10
	Moderate	13 (72.2)	9 (50.0)		
TR severity	Mild	11 (61.1)	10 (55.6)		0.65
	Moderate	7(38.9)	8(44.4)		

SD: Standard deviation; FMD: Flow-mediated dilation; IMT: Intima-media thickness; LV: Left ventricular; LVEF: Left ventricular ejection fraction; FS: Fractional shortening; MPI: Myocardial performance index; RV: Right ventricular; TAPSE: Tricuspid annular plane systolic excursion; FAC: Fractional area change

Table 4. Performance parameters before and after tadalafil administration following Tetralogy of Fallot total correction (TFTC)*

Variable		Before tadalafil Frequency (%)	After tadalafil Frequency (%)	P
Exercise test	Stage 2	1 (5.6)	0 (0.0)	0.02
	Stage 3	11 (61.1)	8 (44.4)	
	Stage 4	6 (33.3)	10 (55.6)	
Functional class	Class 1	0 (0.0)	5 (27.8)	0.01
	Class 2	16 (88.9)	12 (66.7)	
	Class 3	2 (11.1)	1 (5.6)	
		Mean ± SD	Mean ± SD	P
QRS widening (ms)		0.106 ± 0.012	0.103 ± 0.011	0.16

SD: Standard deviation

*Exercise test protocol: Modified Bruce, functional class in New York Heart Association (NYHA)

In another study that performed by Sabri et al.¹⁰ as the first report on the effectiveness of tadalafil among patients undergoing modified Fontan operation, the use of tadalafil after modified Fontan operation had a positive effect on myocardial function and performance, exercise performance, and improvement in NYHA functional class. The most common side effects in their patients were transient priapism, leg pain, headache, and back pain that lasted 2-7 days.¹⁰

In Rosano et al report,⁷ by long-term therapy with tadalafil in patients with high-risk cardiovascular disease, the endothelial function improved (improving FMD). Other researches on the effect of tadalafil and sildenafil on exercise capacity had different results.^{4,13} Some of them showed no significant improvement, and others indicated a significant effect. The long-term effect of tadalafil should be investigated with a higher number of cases for better evaluation. The most common side effects reported for tadalafil are headache, myalgia, nausea, nasal congestion, flushing, and allergic reactions.^{8,14-16}

The limitations of present study include its small sample size, lack of control or placebo group (because of limit TOF cases with this situation in this center), unavailability of CMR in most patients, and relatively short observational period. We hope these findings introduce a basic and primary data for future large-scale clinical studies in this field.

Conclusion

This study showed that tadalafil is a safe drug, well-tolerated and its side effects were disappeared after a few days and could be used after TFTC. It might improve exercise performance, endothelial function and functional class and possibly could allow patients a longer period of well-being and could possibly delay the need for PVR.

Acknowledgments

With best regards to Ms. Tahereh Baran and Ms. Zahra Rezaie for their help, this study was not funded by any company.

Conflict of Interests

Authors have no conflict of interests.

References

- Luijnenburg SE, Helbing WA, Moelker A, Kroft LJ, Groenink M, Roos-Hesselink JW, et al. 5-year serial follow-up of clinical condition and ventricular function in patients after repair of tetralogy of Fallot. *Int J Cardiol* 2013; 169(6): 439-44.
- Allen HD. Moss and Adams' heart disease in infants, children, and adolescents: Including the fetus and young adult. Alphen Aan Den Rijn, Netherlands: Wolters Kluwer; 2016. p. 969-78
- Promphan W, Wonglikhitpanya T, Katanyuwong P, Siripornpitak S. A comparative study: Right ventricular assessment in post-repaired tetralogy of Fallot patients by echocardiogram with cardiac magnetic resonance imaging. *J Med Assoc Thai* 2014; 97(Suppl 6): S232-S238.
- Affuso F, Palmieri EA, Di Conza P, Guardasole V, Fazio S. Tadalafil improves quality of life and exercise tolerance in idiopathic pulmonary arterial hypertension. *Int J Cardiol* 2006; 108(3): 429-31.
- Croxtall JD, Lyseng-Williamson KA. Tadalafil: In pulmonary arterial hypertension. *Drugs* 2010; 70(4): 479-88.
- Jackson KW, Butts RJ, Svenson AJ, McQuinn TC, Atz AM. Response to a single dose of sildenafil in single-ventricle patients: An echocardiographic evaluation. *Pediatr Cardiol* 2013; 34(7): 1739-42.
- Rosano GM, Aversa A, Vitale C, Fabbri A, Fini M, Spera G. Chronic treatment with tadalafil improves endothelial function in men with increased cardiovascular risk. *Eur Urol* 2005; 47(2): 214-20.

8. Takatsuki S, Calderbank M, Ivy DD. Initial experience with tadalafil in pediatric pulmonary arterial hypertension. *Pediatr Cardiol* 2012; 33(5): 683-8.
9. Sabri MR, Beheshtian E. Comparison of the therapeutic and side effects of tadalafil and sildenafil in children and adolescents with pulmonary arterial hypertension. *Pediatr Cardiol* 2014; 35(4): 699-704.
10. Sabri MR, Zolfi-Gol A, Ahmadi A, Haghjooy-Javanmard S. Effect of tadalafil on myocardial and endothelial function and exercise performance after modified fontan operation. *Pediatr Cardiol* 2016; 37(1): 55-61.
11. Eidem BW, O'Leary PW, Cetta F. Echocardiography in pediatric and adult congenital heart disease. Alphen Aan Den Rijn, Netherlands: Wolters Kluwer Health; 2014. p. 666-72.
12. Meyer AA, Kundt G, Steiner M, Schuff-Werner P, Kienast W. Impaired flow-mediated vasodilation, carotid artery intima-media thickening, and elevated endothelial plasma markers in obese children: The impact of cardiovascular risk factors. *Pediatrics* 2006; 117(5): 1560-7.
13. Jackson G. Hemodynamic and exercise effects of phosphodiesterase 5 inhibitors. *Am J Cardiol* 2005; 96(12B): 32M-6M.
14. Galie N, Brundage BH, Ghofrani HA, Oudiz RJ, Simonneau G, Safdar Z, et al. Tadalafil therapy for pulmonary arterial hypertension. *Circulation* 2009; 119(22): 2894-903.
15. Forgue ST, Patterson BE, Bedding AW, Payne CD, Phillips DL, Wrishko RE, et al. Tadalafil pharmacokinetics in healthy subjects. *Br J Clin Pharmacol* 2006; 61(3): 280-8.
16. Magee AG, Makhecha S, Bentley S. Risk-benefit considerations when prescribing phosphodiesterase-5 inhibitors in children. *Expert Opin Drug Saf* 2015; 14(5): 633-42.

How to cite this article: Sabri MR, Shoja M, Shoja M, Hosseinzadeh M. **The effect of tadalafil on functional capacity and echocardiographic parameters in patients with repaired Tetralogy of Fallot.** *ARYA Atheroscler* 2018; 14(4): 177-82.