



Effect of Tadalafil on Heart Function in Children with Severe Pulmonary Regurgitation Following Surgical Repair of Tetralogy of Fallot: A Prospective Study

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Received 2024 April 2; Revised 2024 June 30; Accepted 2024 July 11.

Abstract

Background: Tetralogy of Fallot (TOF) is the most prevalent cyanotic congenital heart defect. Pulmonary regurgitation (PR) is a common sequela following most surgical repairs for TOF. Tadalafil might reduce pulmonary vascular resistance after Tetralogy of Fallot total correction (TOFTC).

Objectives: This study evaluated the efficacy of tadalafil in reducing PR volume and improving heart function among TOFTC children with severe PR, using transthoracic echocardiography, particularly focusing on changes in N-terminal pro-b-type natriuretic peptide (NT-proBNP).

Methods: The present study was conducted on TOFTC patients consecutively between September 2019 and August 2020 at Shiraz University of Medical Sciences, Shiraz, Iran. M-mode and two-dimensional (2D) Doppler echocardiography were performed, and NT-proBNP levels were measured in 20 patients before and one month after tadalafil administration. SPSS version 23.0 was utilized to analyze all results.

Results: The patients' ages ranged from 25 to 128 months. The mean age and weight of the patients were 67.9 ± 34.5 months and 21.1 ± 6.9 kg, respectively. Tadalafil administration did not significantly improve Doppler and tissue Doppler parameters; however, it increased the pulmonary valve pressure gradient and velocity-time integral. Additionally, tadalafil had no significant effect on improving NT-proBNP levels. The Spearman correlation test did not show any significant correlation between the pulmonary valve pressure gradient and velocity-time integral with age, weight, and NT-proBNP.

Conclusions: Tadalafil increased the pulmonary valve pressure gradient and velocity-time integral in TOFTC patients with severe PR; however, it did not affect NT-proBNP levels or tissue Doppler parameters.

Keywords: Congenital Heart Disease, Tetralogy of Fallot, NT-proBNP, Transthoracic Echocardiography

1. Background

Tetralogy of Fallot (TOF) is regarded as the most prevalent cyanotic congenital heart defect (1). Since the introduction of TOF repair surgery in 1945 (2), early mortality has improved; however, long-term follow-ups of survivors with Tetralogy of Fallot total correction (TOFTC) have shown late complications such as exercise intolerance, right heart function impairment due to

pulmonary valve regurgitation (PR), arrhythmias, and sudden death (3-5). Therefore, it is recommended to continually follow up with patients following TOFTC using electrocardiography and echocardiography (1, 6).

Many long-term complications of TOFTC are correlated with the hemodynamic impacts of PR and are related to chronic right ventricular volume overload (7). These patients may remain asymptomatic for many

years, with complications directly related to PR severity (8).

Tadalafil is a selective inhibitor of phosphodiesterase type 5 recognized as a treatment to decrease pulmonary arterial pressure in both children and adults (9, 10). Tadalafil is well tolerated, and the side effects are usually transient and of mild to moderate severity (11). Few recent studies have shown that tadalafil might improve exercise performance, functional class, and pulmonary endothelial function, providing patients with prolonged periods of well-being and postponing the need for pulmonary valve replacement in TOFTC patients (12).

Some studies have shown the beneficial effect of sildenafil administration in improving myocardial activity in heart failure in adults. We hypothesized that tadalafil may reduce pulmonary artery pressure and improve myocardial function.

2. Objectives

The current study aimed to investigate the impact of tadalafil on heart function and the severity of PR in TOFTC children using transthoracic echocardiography, with a particular focus on changes in N-terminal pro-B-type natriuretic peptide (NT-proBNP).

3. Methods

The present study was approved by the Ethics Committee of Shiraz University of Medical Sciences, Shiraz, Iran (code No.: [IR.SUMS.MED.REC.1399.062](#)), in accordance with the Helsinki Declaration and its later amendments.

3.1. Study Population

This prospective study was conducted on consecutive patients with TOFTC and severe PR referred to Namazi Hospital, affiliated with Shiraz University of Medical Sciences, Shiraz, Iran, between September 2019 and August 2020.

The reconstructive surgery method for these patients was a transannular patch. Patients with TOFTC and severe PR, not receiving drugs effective in pulmonary endothelial function (e.g., lipid-lowering agents, diuretics, and nitrates) and without systemic diseases met the study inclusion criteria. If the patients had aortopulmonary collateral arteries, they were closed with devices (13). The exclusion criteria included patients undergoing interim interventions or changes in clinical condition between the two echocardiography times and those with more than mild tricuspid

regurgitation. Additionally, patients with renal or hepatic impairment, dysrhythmias or a pacemaker, tadalafil administration in the previous 3 months, or further congenital heart lesions were excluded. Considering that tadalafil has no effect on reducing pulmonary artery stenosis and that this stenosis can cause problems in the study results, patients with pulmonary artery stenosis were also excluded.

Following the recording of patients' files, an echocardiogram was obtained, and all data, including demographic and clinical features such as underlying anatomy and surgical repair details, were collected.

The patients were administered a single dose of tadalafil tablet at 1 mg per kg (maximum 40 mg) daily orally for 4 weeks. The NT-proBNP test and echocardiographic parameters were determined before and 4 weeks after the patients took tadalafil. The findings of echocardiography after 4 weeks were considered the effect of tadalafil.

3.2. Echocardiographic Measurements

All transthoracic echocardiographies were performed using an ultrasound system (Vivid S6, GE Company, USA) by a pediatric cardiologist. Echocardiographic characteristics were acquired based on the American Society of Echocardiography standard levels. Each parameter was measured twice on average for analysis. To reduce the effect of inter-observer variability on the echocardiographic findings, each data point was measured three times, and the average was used in the study.

Fractional shortening, ejection fraction, and tricuspid annular plane systolic excursion were obtained. Doppler indices of peak PR velocity, total diastolic time, and pulmonary velocity-time integral were measured for the evaluation of the pulmonary forward flow and PR flow indices. The PR Index was calculated by dividing the PR duration by the diastolic duration of constant pulse-wave spectral Doppler signals in the primary pulmonary artery. This index demonstrated PR severity; that is, if the velocity profile was higher, regurgitation was less (14). Pulmonary regurgitation time measurement was performed from its onset in early diastole to the end of the regurgitant Doppler signal. Additionally, diastolic duration was calculated from the end of forward pulmonary flow to the initiation of the next forward pulmonary flow wave.

The early diastolic inflow blood velocity (E wave) and late diastolic inflow velocity (A wave) at the tip of mitral and tricuspid valve leaflets in the apical 4-chamber view were measured using pulse wave Doppler. Moreover,

tissue Doppler of the mitral and tricuspid valves and the septum was determined (15,16).

While MRI is the method of choice for evaluating the condition and function of the right ventricle as well as PR severity, echocardiography was used in this study due to the need to anesthetize the patients and economic considerations.

3.3. Electrocardiography

The electrocardiographs of the patients were taken, and the most relevant data, such as QRS duration and R wave amplitude in the V1 lead, were obtained before and after tadalafil administration.

3.4. N-terminal Pro-b-type Natriuretic Peptide Measurement

After blood collection, 5 cc of the samples were centrifuged and kept at -20°C. Sampling was done on two occasions, one month apart, before and after taking tadalafil. A commercially available ELISA Kit E90485Hu (USCN Life Science Inc., China) was used. The normal ranges for NT-proBNP in children aged 1 - 2 years, 2 - 6 years, and 6 - 16 years were 400, 300, and 160 pg/mL, respectively (17).

3.5. Statistical Analysis

SPSS version 23.0 (SPSS, Chicago, IL, USA) was utilized to statistically analyze the data. Mean and standard deviation were employed to express the data. Numbers and percentages were appropriately used to present the continuous and categorical variables. The Mann-Whitney test was utilized to compare continuous characteristics before and after taking tadalafil. The relationship between age, weight, and NT-proBNP with echocardiographic variables was evaluated using the Spearman correlation test. A p-value < 0.05 was considered statistically significant.

4. Results

The study population consisted of 28 patients, with the parents of eight patients refusing to cooperate with the study authors.

Table 1 shows the demographic data of the 20 studied patients. The participants' ages ranged from 25 to 128 months. The mean age was 67.9 ± 34.5 months, with a median of 87 months, and the mean age of TOF surgical correction was 11.2 ± 26.72 months. In this study, 11 (55%) patients were male and 9 (45%) were female.

The echocardiographic parameters of each case before and 4 weeks after tadalafil administration are

shown in Table 2. The pulmonary valve pressure gradient and velocity-time integral were significantly higher after tadalafil administration. However, tadalafil had no significant effect on other parameters such as the PR index, NT-proBNP, tricuspid annular plane systolic excursion, fractional shortening, and ejection fraction.

Table 3 shows the tissue Doppler parameters of the lateral mitral and tricuspid valves and the septum before and 4 weeks after tadalafil administration, with no significant changes observed after tadalafil administration.

The correlation of age, weight, and NT-proBNP with changes in pulmonary valve pressure gradient, velocity-time integral, and e' and a' of the mitral and tricuspid valves and septum were assessed using the Spearman correlation test (Table 4). Although the pulmonary valve pressure gradient and velocity-time integral significantly changed after tadalafil administration among the echocardiographic factors, none of these changes were correlated with age, weight, or NT-proBNP ($P > 0.05$).

Additionally, the QRS duration and R wave amplitude of the patients in lead V1 electrogram were obtained before and 4 weeks after tadalafil administration, revealing no significant differences (Table 5).

5. Discussion

The objective of this investigation was to assess the effectiveness of tadalafil in reducing PR volume and improving cardiac function in TOFTC children, with a special focus on changes in NT-proBNP. The obtained results showed that tadalafil administration significantly improved some echocardiographic parameters, such as pulmonary valve pressure gradient and velocity-time integral. However, it did not improve tissue Doppler parameters, NT-proBNP, or electrocardiographic data, contrary to our initial hypothesis that tadalafil would have a positive effect on these latter three items.

Phosphodiesterase type 5 is not present in the normal right ventricle; however, it is up-regulated in hypertrophied myocardium. Phosphodiesterase type 5 inhibitors (e.g., sildenafil and tadalafil) can increase contractility in experimental models of right ventricular hypertrophy but not in normal myocardium (18). Compared to sildenafil, tadalafil has a more prolonged half-life (18 hours) and can be taken as a single dose per day. Different studies have shown the effectiveness of tadalafil in improving pulmonary artery hypertension and potentially right ventricular function

Table 1. Patients' Demographic Data (n = 20)^a

Variables	Values
Gender	
Male	11 (55)
Female	9 (45)
Age (m)	
25% percentile	35.01
50% percentile	65.02
75% percentile	102.51
Total age	67.9 ± 34.5
Weight (kg)	21.15 ± 6.92

^a Values are expressed as Mean ± SD or No. (%).

Table 2. Echocardiographic Parameters and the N-terminal Pro-b-type Natriuretic Peptide Level Before and 4 Weeks After Tadalafil Administration Using Mann-Whitney Test^a

Characteristics	Before Tadalafil	After Tadalafil	P-Value
TAPSE (mm)	15.25 ± 3.14	15.8 ± 3.3	0.28
Peak TR PG (mm Hg)	28.3 ± 7.0	28.0 ± 6.4	0.49
TV VTI (cm)	74.7 ± 10.4	76.1 ± 5.7	0.51
Peak PV PG (mm Hg)	23.2 ± 6.7	25.5 ± 8.5	0.04
PV VTI (cm)	56.3 ± 12.7	61.0 ± 10.2	0.00
PR index	0.7 ± 0.05	0.7 ± 0.04	0.42
NT-proBNP (pg/mL)	62.3	58.7	0.72
EF%	68.5 ± 4.3	66.6 ± 6.8	0.22
FS%	36.9 ± 3.4	35.3 ± 4.7	0.14

Abbreviations: EF, ejection fraction; FS, fractional shortening; NT-proBNP, N-terminal pro b-type natriuretic peptide; PR, pulmonary regurgitation; PG, pulmonary regurgitation pressure gradient; PV, pulmonary valve; PV PG, pulmonary valve pressure gradient; TAPSE, tricuspid annular plane systolic excursion; TR PG, tricuspid regurgitant pressure gradient; TV, tricuspid valve; VTI, velocity-time integral.

^a Values are expressed as mean ± SD.

Table 3. Tissue Doppler Parameters of the Mitral and Tricuspid Valves and the Septum Before and After Tadalafil Administration Using Mann-Whitney Test^a

Characteristics	Before Tadalafil	After Tadalafil	P-Value
MV lat e ⁻ (cm/s)	8.56 ± 0.06	0.81 ± 0.07	0.81
MV lat a ⁻ (cm/s)	7.34 ± 0.06	0.72 ± 0.05	0.26
MV lat e ⁻ /a ⁻ ratio	1.13 ± 0.08	1.17 ± 0.15	0.58
Sept e ⁻ (cm/s)	10.33 ± 2.34	10.93 ± 2.18	0.10
Sept a ⁻ (cm/s)	5.39 ± 1.35	5.63 ± 1.26	0.09
Sept e ⁻ /a ⁻ ratio	1.94 ± 3.12	1.95 ± 4.78	0.21
TV e ⁻ (cm/s)	13.31 ± 2.27	12.94 ± 2.79	0.21
TV a ⁻ (cm/s)	6.09 ± 1.28	5.75 ± 0.81	0.23
TV e ⁻ /a ⁻ ratio	2.21 ± 3.12	2.26 ± 3.45	1.02

Abbreviations: a⁻, peak late diastolic tissue velocity; e⁻, peak early diastolic tissue; Lat, lateral; MV, mitral valve; Sept, septum; s⁻, peak systolic tissue velocity; TV, tricuspid valve.

^a Values are expressed as mean ± SD.

in these patients (19-21). A previous study (12) demonstrated that tadalafil administration following TOFTC surgery positively affected exercise performance,

the New York Heart Association functional class, and endothelial function among patients with more than mild PR.

Table 4. Correlation of Echocardiographic Parameters with Age, Weight, and N-terminal Pro B-type Natriuretic Peptide

Echocardiographic Variables	Pearson Correlation	P-Value
Age (m)		
PV PG (mm Hg)	-0.25	0.36
PV VTI (cm)	-0.17	0.46
Sept e' (cm/s)	0.11	0.64
Sept a' (cm/s)	-0.23	0.25
MV e' (cm/s)	0.21	0.47
MV a' (cm/s)	-0.44	0.06
TV e' (cm/s)	0.26	0.09
TV a' (cm/s)	-0.46	0.12
Weight (kg)		
PV PG (mm Hg)	-0.09	0.70
PV VTI (cm)	-0.11	0.65
Sept e' (cm/s)	0.22	0.34
Sept a' (cm/s)	-0.30	0.19
MV e' (cm/s)	0.32	0.08
MV a' (cm/s)	-0.25	0.48
TV e' (cm/s)	0.31	0.54
TV a' (cm/s)	-0.38	0.07
NT-proBNP (pg/mL)		
PV PG (mm Hg)	-0.51	0.17
PV VTI (cm)	-0.03	0.93
Sept e' (cm/s)	0.16	0.65
Sept a' (cm/s)	0.54	0.11
MV e' (cm/s)	0.24	0.16
MV a' (cm/s)	0.46	0.87
TV e' (cm/s)	0.20	0.56
TV a' (cm/s)	0.67	0.08

Abbreviations: a', peak late diastolic tissue velocity; e', peak early diastolic tissue; MV, mitral valve; NT-ProBNP, N-terminal pro b-type natriuretic peptide; PV, pulmonary valve; PV PG, pulmonary valve pressure gradient; Sept, septum; TV, tricuspid valve.

Table 5. QRS Duration and R Wave Amplitude in Lead V1 Electrocardiogram Before and 4 Weeks After Tadalafil

Electrocardiographs Data	Before Tadalafil	After Tadalafil	P-Value
QRS duration (ms)	118.53	116.12	0.17
R wave (mv)	0.45	0.43	2.68

Abbreviations: ms, millisecond; mv, millivolt.

One study on NT-proBNP levels after surgical correction of TOF reported that its level did not correlate with right ventricular ejection fraction, but it did correlate with right ventricular dilation and PR severity in response to myocardial stretch. Another study reported that medications that reduce the severity of PR in these patients can decrease NT-proBNP.

Our study showed that tadalafil increases pulmonary valve pressure gradient and pulmonary valve velocity-

time integral, suggesting that it can reduce pulmonary vascular resistance or improve right ventricular function in these patients. However, there was no significant correlation between NT-proBNP and pulmonary valve pressure gradient or heart function. This may be because our study was conducted among patients with severe PR, and tadalafil administration could not decrease PR volume. The lack of decrease in NT-proBNP may be due to the persistence of severe PR despite a reduction in pulmonary vascular resistance,

which prevented a decrease in NT-proBNP levels despite improvement in right ventricular function.

An increase in velocity-time integral was speculated to be due to decreases in pulmonary vascular resistance and right ventricular afterload. This also suggests an increase in right ventricular stroke volume, potentially representing an improvement in cardiac output. Some researchers have reported that the administration of anti-pulmonary hypertension medications can improve exercise capacity in these patients.

The decrease in pulmonary vascular resistance may indicate an improvement in right ventricular function and a reduction in NT-proBNP levels in future follow-ups. According to the findings of the mentioned studies, the outcome of long-term administration of pulmonary antihypertensive medications should be determined in long-term research and may improve the hemodynamics of the right ventricle.

Cardiac arrhythmia is a common finding in a large proportion of patients after TOFTC (22). An increase in pulmonary artery pressure gradient similar to more than moderate PR is predictive of ventricular arrhythmia. Tadalafil was able to increase the pulmonary valve pressure gradient, which could be indirect evidence of a decrease in pulmonary artery pressure as expected. This reduction after tadalafil administration might lead to a reduction in the arrhythmia rate over a long time.

5.1. Conclusions

Tadalafil may increase pulmonary valve pressure gradient and velocity-time integral in patients with TOFTC, which could be indirect evidence of a reduction in pulmonary artery resistance or improved right ventricular function. However, tadalafil did not improve other echocardiographic parameters or decrease NT-proBNP because it could not decrease the severity of PR. These findings might indicate improved right ventricular function, although larger studies are needed to better elucidate its exact role in patients with TOFTC. Additionally, it is necessary to examine the impact of tadalafil in long-term studies with a larger sample size to determine its effect on NT-proBNP levels.

Acknowledgements

The authors extend their gratitude for the non-financial support of Shiraz University of Medical Sciences, Shiraz, Iran.

Footnotes

Authors' Contribution: M. E., design and writing the manuscript; P. M., echocardiography; N. M., corresponding author and data collection; N. O., laboratory investigation; H. A., echocardiography; K. K., manuscript revision; H. M., critical revision; A. N., data collection. All authors have read and approved the manuscript.

Conflict of Interests Statement: The authors did not receive any direct or indirect financial payment for the research, are not the owners of any related company, and are not consultants of these companies.

Data Availability: The obtained data are accessible in this paper and its Supporting Information files.

Ethical Approval: Ethical approval of the Ethic Committee of Shiraz University of Medical Sciences was received with the code number [IR.SUMS.MED.REC.1399.062](#), according to Helsinki declaration and its later amendments.

Funding/Support: This study received no funding.

Informed Consent: There were no personal data in this study, and publication consent was obtained.

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