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Original Article

Effects of oral sildenafil after palliative procedures to increase pulmonary blood flow in cyanotic heart diseases

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Abstract

Background

Continuing efforts have been exerted to improve the outcome of palliative procedures for cyanotic congenital heart diseases. Sildenafil is known for the management of erectile dysfunction and pulmonary hypertension, but the cardiac benefits of this drug showed its impacts in the hemodynamic profile of cardiac patients.

Aim

To evaluate the effect of oral sildenafil on man-made shunts and vascular connection of cyanotic heart diseases.

Patients and methods

This comparative study was conducted from 2013 to 2017 on patients who had congenital cyanotic heart disease and who underwent acquired palliative procedure to increase the pulmonary blood flow. Procedures included: modified Blalock and Taussig shunts (MBTS), bidirectional cavopulmonary connections (BDCPC) or Glenn, and Fontan procedures. The pulse oximetry readings were obtained at three different stages and the results were compared with data obtained from similar procedures under the standard management regimen.

Results

Twenty-seven patients were enrolled in the case group (group 1) who received oral sildenafil compared with the control group (group 2) of patients who received the standard management which included 31 patients. The oxygen saturations showed significant difference between group 1 and group 2 in patients who had MBTS and BDCPC, while the difference was not significant in the group of patients who had Fontan procedure.

Conclusion

Sildenafil showed significant improvement in oxygen saturation in patients with complex cyanotic heart disease who have undergone palliative surgery to increase pulmonary blood flow as MBTS and BDCPC in contrast to the patients who get Fontan procedure.

Keywords: Fontan, Glenn, modified Blalock and Taussig shunt, sildenafil

Introduction

Sildenafil is a phosphodiesterase (PDE) inhibitor drug, which has a strong selective vasodilator effect on the pulmonary vasculature. It is widely used to decrease pulmonary vascular resistance (PVR) and to increase pulmonary blood flow in infants and children with congenital heart disease (CHDs) [1].

Sildenafil is a potent and selective inhibitor of cyclic guanosine monophosphate-specific PDE-5, the predominant isozyme that metabolizes cyclic guanosine monophosphate in the corpus cavernosum of the penis, which is the second messenger of nitric oxide and a principal mediator of smooth muscle relaxation and vasodilatation in the penis. Apart from smooth muscle cells of the penile corpora cavernosa, PDE-5 is expressed in various other tissues, such as the arterial vasculature, including pulmonary and coronary arteries, veins, skeletal muscles, visceral and tracheobronchial

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muscles, and platelets. Sildenafil is rapidly absorbed after oral administration, with peak plasma concentrations of within 30–120 min of oral dosing [2]. Sildenafil and its active metabolite are both highly bound to plasma proteins (96%) and their terminal half-lives are 4 h each [3]. PDE inhibitors potentially affect the other isoforms of PDE (e.g. isoform 6 in the retina and isoform 3 on platelets), hence; the side effects of these drugs can be observed [4].

Single ventricle (SV) heart disease is the most common type of severe form of CHDs [5]. It involves a spectrum of congenital cardiac anomalies describing underdevelopment of one ventricle. It is considered fatal without intervention. Despite improvement of outcomes, within the first year of life, the mortality rate is more than 30% or cardiac transplantation is required, and the10-year survival is 39%–50% [5,6]. The use of PDE-5 inhibitor in SV patients is mainly to promote relaxation of pulmonary vascular smooth muscle, improving pulmonary blood flow, and cardiac output [7].

Cyanotic CHDs with decreased pulmonary flow are frequently treated by the modified Blalock–Taussig shunt (MBTS). Systemic-to-pulmonary shunt is considered the best line of treatment in complex CHDs with restricted pulmonary blood flow [8,9]. Mortality rate after the MBTS is still elevated in spite of advances in the diagnostic tools, surgical procedures, and intensive care management [10,11]. Maintaining systemic and pulmonary circulation balance (avoiding overshunting and undershunting) has a strong impact on morbidity, ICU stay, and mortality [12].

In patients who have undertaken neonatal cardiac surgery, endothelium-dependent pulmonary vascular relaxation may be impaired after cardiopulmonary bypass (CPB) and in the postoperative course, that may complicate with transient pulmonary hypertension [13]. Inhaled nitric oxide has been demonstrated to provide safe selective pulmonary vasodilation after cardiac operations [14,15].

Thus, in this study, we aimed to benefit from the pulmonary vasodilator effect of sildenafil on oxygen saturation after palliative procedures in cyanotic patients to increase the pulmonary blood flow. This was achieved through measuring oxygen saturation in patients who received oral sildenafil compared with those of the control group who received the standard management.

Patients and methods

This study was a prospective, nonrandomized study started in 2013 till 2017 on congenital cyanotic heart disease patients who had submitted to a surgical procedure to increase the pulmonary blood flow. Those procedures were either MBTS, superior bidirectional cavopulmonary connections (BDCPC), or Fontan procedure. The group of patients who had MBTS were operated either off pump or with assisted CPB, while the patients obtained BDCPC and Fontan procedures were operated on assisted CPB.

The study entails oral sildenafil administration following a 0.5 mg/kg test dose oral sildenafil which was administered 6 hourly, with increments of 0.5 mg/kg/dose, and a target maintenance dose of 2 mg/kg 6 hourly [16].

Those patients had baseline oxygen saturation obtained before sildenafil administration and serial oxygen saturation in the stepdown unit the one before discharge to home was recorded (after 1 week from sildenafil administration). The data of this group which is the case group (group 1) were compared with other group of patients who had the similar procedure within the last 10 years. The operative records and the discharge summary of the control group (group 2) were evaluated for comparative variables. The medical research and ethics committee at the National Heart Institute approved the study. Written informed consent was obtained for all study participants.

Exclusion criteria:

(1) Presentation of shunt underflow or obstruction in patients who had MBTS.
(2) Obstruction across the Glenn or the Fontan pathway.
(3) Pulmonary venous obstruction.
(4) Left ventricular outflow tract obstruction.
(5) Significant blood dyscrasia.
(6) History of drug reaction.

Anesthetic managements

All patients in this study were subjected to routine preoperative clinical examination and laboratory investigations including complete blood count, coagulation profile, liver and renal function tests, and baseline arterial blood gases were performed. Radiological examination in the form of echocardiography, chest x-ray and multislice computed tomography were done.

All patients in the receiving area were premeditated with 5 mg/kg ketamine and 0.01 atropine sulfate intramuscular 15 min before anesthesia. Noninvasive blood pressure, ECG, and peripheral oxygen saturation were monitored and documented. Supplemental oxygen was given via a face mask. A peripheral intravenous cannula was inserted and, if possible, a radial artery catheter was inserted to monitor the arterial blood pressure and blood gas sampling and oxygen saturation.

Anesthesia was induced by 5 ml/kg thiopental, 2 μg/kg fentanyl intravenous, and 0.5 mg/kg atracurium as a muscle relaxant to facilitate endotracheal intubation. After intubation, the patients were connected to the anesthesia machine and mechanically ventilated with 40% oxygen in air and the end-tidal CO_2 were monitored and maintained between 30 and 35 mmHg. Maintenance of anesthesia was achieved by 2% sevoflurane in 40% oxygen in air, infusion of atracurium at a rate of 5–10 μg/kg/min, and fentanyl 0.05 μg/kg/min. After end of the procedures, the patients were transferred to the pediatric ICU for fast-track extubation.

Baseline transthoracic echocardiogram was performed after induction of anesthesia. For echocardiograms, two sonographers performed all studies using a standard

cardiac ultrasound system Phillips HD11XE ultrasound systems (Phillips, Andover, Massachusetts, USA), and in the last year of the study a new machine was available (Phillips EPIQ7C) using higher frequency probes (5–12 MHz).

Epicardial images were obtained by an operator who is wearing a sterile gown and gloves within the operative field as described in the guidelines [17]. Images were obtained in the parasternal long, parasternal short, apical, and suprasternal views. Measurements were performed to assess: two-dimensional systolic ventricular function (fraction of area change for systemic right ventricles, single-plane modified Simpson's rule ejection fraction for systemic left ventricles), speckle tracking systolic function (strain, strain rate), and global myocardial performance. Two physicians associated with the study independently performed all interpretations of the echocardiographic data.

Statistical analysis

Statistical analysis of the obtained data was performed in SPSS for Windows, Version 17 (Statistical Package for the Social Sciences, IBM Corp, Armonk, New York, USA),; variables were checked for distribution of normality, using: (a) normal plots, (b) Kolmogorov–Smirnov tests, and (c) Shapiro–Wilks tests. The data were presented as numbers and percentages for the qualitative data. Means, SDs, and ranges for the quantitative data with parametric distribution and median with interquartile ranges for the quantitative data with nonparametric distribution. χ^2 test was used for the comparison between two groups with qualitative data and Fisher's exact test was used instead of the χ^2 test when the expected count in any call was found to be less than 5.

Independent *t* test was used for the comparison between two groups with quantitative data and parametric distribution, while the Mann–Whitneys test was used for the comparison between two groups with quantitative data and nonparametric distribution. The confidence interval was set to 95% and the margin of error accepted was set to 5%. So, the *P* value was considered significant when less than 0.05.

Results

This study included 58 pediatric patients on different age groups who was diagnosed primarily as cyanotic heart disease and required a procedure to increase pulmonary blood flow.

Three procedures were identified in this study: MBTS, BDCPC or Glenn and Fontan procedure.

This study evaluates the short-term effect of oral sildenafil on cyanotic patients who were submitted to a procedure to increase the pulmonary blood flow. In all, 27 patients were enrolled in this group of patients who received oral sildenafil and compared with the other group of patients with the standard management which included 31 patients.

The demographic data of both groups were not normally distributed as tested by the Kolmogorov–Smirnov test and Shapiro–Wilk tests. So, Mann–Whitney test was done for descriptive statistics.

There was no significant difference between both groups regarding age, weight, height, and body surface area. There was no significant difference between both groups regarding sex distribution. Both demographic data and sex distribution are illustrated in Tables 1 and 2.

There were two types of ventricular morphology in both groups either patients with SV pathway or two-ventricle pathway and there were no significant differences between both groups regarding ventricular morphology. The distribution of both morphologies are illustrated in Table 3 and is presented in Figs. 1 and 2. Regarding the operative procedures, there were three operations done on both groups either MBTS, BDCPC and Fontan procedure, or there were no significant differences between both groups regarding the types of operation. These data are summarized in Table 4 and are presented in Fig. 1.

Postoperative outcome

Both the groups under the study had been evaluated statistically regarding predischarge oxygen saturation which revealed

Table 1: Demographic data of the studied groups

Groups	Months	kg	cm	M2
1				
n				
Valid	27	27	27	27
Missing	0	0	0	0
Median	10.0	7.5	67.0	0.38
Range	91.0	18.2	59.0	0.57
Minimum	7.0	6.0	61.0	0.32
Maximum	98.0	24.2	120.0	0.89
2				
n				
Valid	31	31	31	31
Missing	0	0	0	0
Median	9	7.000	66.0	0.36
Range	90.0	18.0	60.0	0.58
Minimum	4.0	5.0	60.0	0.29
Maximum	94.0	23.0	120.0	0.87
MWU test				
P	0.075	0.065	0.128	0.055

MWU, Mann–Whitney *U* test.

Table 2: Sex distribution between groups

Sex×Group cross-tabulation			
Count			
Sex	Groups		Total
	1	2	
Male	17	21	38
Female	10	10	20
Total	27	31	58
Pearson's χ^2	0.145	*P*	0.702

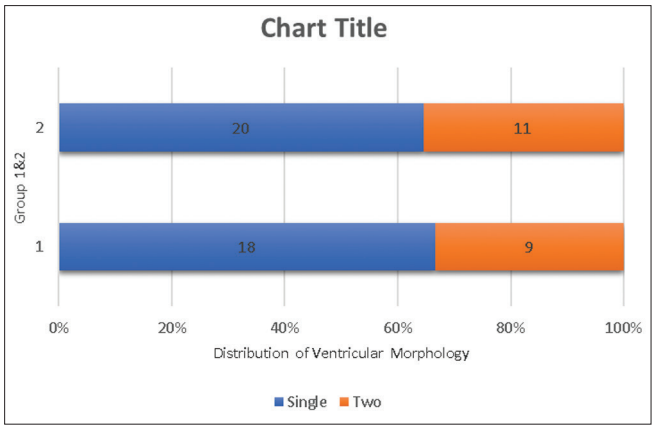

Figure 1: Bar chart for ventricular morphology in both groups.

that they are not normally distributed a nonparametric test was done, so we used the Mann–Whitney tests; the median saturation in group 1 was 84 (82–95) versus group 2 who was 82 (79–95). *P* value was 0.005 as per the Mann–Whitneys test. These data are illustrated in Tables 5 and 6.

As the postoperative outcome for all patients had a significant impact on the conclusion of our study, we had subcategorized both group 1 and group 2 based on the type of operation. Exploration of the data of each operation showed normally distributed patients on each group as per the Kolmogorov–Smirnov test. In the group of patients who had MBTS, the mean oxygen saturation of group 1 before transfer from ICU was 81.15 ± 1.625 and in group 2 was 81.36 ± 1.737; *P* value: 0.756, while in the same group of patients who had MBTS the predischarge mean oxygen saturation in group 1 was 83.15 ± 1.068 versus group 2 who was 81.57 ± 1.453; *P* value: 0.003 as illustrated in Table 7.

In the group of patients who had BDCPC, the mean oxygen saturation of group 1 before transfer from ICU was 81.90 ± 1.449 and in group 2 was 82.17 ± 1.586; *P* value: 0.687, while in the same group of patients who had BDCPC the predischarge means oxygen saturation in group 1 was 84.40 ± 0.843 versus group 2 who was 82.58 ± 1.505; *P* value: 0.002 as illustrated in Table 8.

In the group of patients who had Fontan, the mean oxygen saturation of group 1 before transfer from ICU was 91.25 ± 0.957 and in group 2 was 93.00 ± 1.581; *P* value: 0.094, while in the same group of patients who had Fontan shunt the predischarge mean oxygen saturation in group 1 was 94.50 ± 0.577 versus group 2 who was 93.40 ± 1.140; *P* value: 0.124 as illustrated in Table 9.

Discussion

In fact, there are two separate circulations in patients who have MBTS; the main one is the systemic circulation directed from the systemic ventricle, while the secondary one is the pulmonary circulation directed from the proximal end of the MBTS [12,18,19].

The BDCPC shunt, also known as the bidirectional Glenn shunt, has become an important staging procedure for the Fontan-type operation. Preoperative ventricular function and preoperative pulmonary artery pressure are the essential elements of a successful Fontan circulation. Previous studies have demonstrated that the absence of a pulsatile pulmonary flow induces endothelial dysfunction with impaired pulmonary vasodilation. On the contrary, capillary recruitment is promoted by pulsatile perfusion, thereby increasing the cross-sectional

Table 3: Types of ventricular morphology in both groups

	Count		
Ventricular morphology	**Groups**		**Total**
	1	**2**	
Single	18	20	38
Two	9	11	20
Total	27	31	58
Pearson's χ^2	0.030	*P*	0.864

Table 4: Types of operations on the studied groups

	Count		
Operation	**Groups**		**Total**
	1	**2**	
MBT	13	14	27
BDCPC	10	12	22
Fontan	4	5	9
Total	27	31	58
Pearson's χ^2			
0.054	Asymptomatic significance (two-sided)		0.973

BDCPC, bidirectional cavopulmonary connection; MBT, modified Blalock and Taussig.

Table 5: Oxygen saturation at discharge

Statistics	
Sa_Disch	
e_sildenafil	
n	
Valid	27
Missing	0
Median	84.00
Skewness	1.815
SE of skewness	0.448
Range	13
Minimum	82
Maximum	95
No_sildenafil	
n	
Valid	31
Missing	0
Median	82.00
Skewness	1.574
SE of skewness	0.421
Range	16
Minimum	79
Maximum	95

Table 6: Statistical analysis of oxygen discharge saturation of both groups

n	Null hypothesis	Test	Significance	Decision
1	The distribution of Sa_Discharge is the same across categories of groups	Independent samples Mann-Whitney *U* test	0.005	Reject the null hypothesis
2	The distribution of Sa_Discharge is the same across categories of groups	Independent samples Kolmogorov-Smirnov Test	0.026	Reject the null hypothesis
3	The distribution of Sa_Discharge is the same across categories of groups	Independent samples Kruskal-Wallis test	0.005	Reject the null hypothesis

Asymptomatic significances are displayed. The significance level is 0.05.

Table 7: Group modified Blalock and Taussig shunt statistics

Operation=MBT group statistics					
	Group	*n*	Mean	SD	Significance (two-tailed)
Sa_ICU	e_sildenafil	13	81.15	1.625	0.756
	No_sildenafil	14	81.36	1.737	
Sa_Disch	e_sildenafil	13	83.15	1.068	0.003
	No_sldenafil	14	81.57	1.453	

MBT, modified Blalock and Taussig. *t* test for equality of means.

Table 8: Group bidirectional cavopulmonary connection shunt statistics

Operation=BDCPC Group Statistics					
	Group	*n*	Mean	SD	Significance (two-tailed)
Sa_ICU	e_sildenafil	10	81.90	1.449	0.687
	No_sildenafil	12	82.17	1.586	
Sa_Disch	e_sildenafil	10	84.40	.843	0.002
	No_sildenafil	12	82.58	1.505	

BDCPC, bidirectional cavopulmonary connection. *t* test for equality of means.

Table 9: Group Fontan shunt statistics

Operation=Fontan group statistics					
	Group	*n*	Mean	SD	Significance (two-tailed)
Sa_ICU	e_sildenafil	4	91.25	0.957	0.094
	No_sildenafil	5	93.00	1.581	
Sa_Disch	e_sildenafil	4	94.50	0.577	0.124
	No_sildenafil	5	93.40	1.140	

t test for equality of means.

area of the vascular bed, lowering resistance, and increasing the gas exchange surface area [20–24].

As all patients with decreased pulmonary blood flow have hypoxia; so, they will have potential element for hypoxia induced pulmonary hypertension. Thus, any pulmonary vasodilator will increase the chance for enhancing the pulmonary blood flow if an adequate source is present [24,25].

The MBTS are continuously frustrating pediatric cardiac surgeons across the world, which led to scarcity in the available

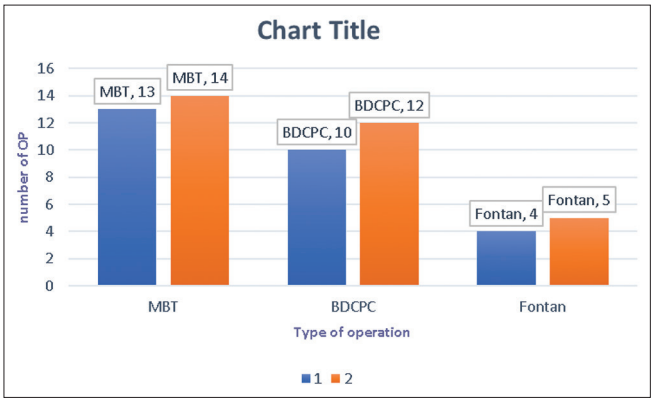

Figure 2: Column charts for different procedures in both groups.

literatures discussing the role of pulmonary vasodilators in those patients [19,26].

A study by Tweddell and colleagues had evaluated the effect of phenoxybenzamine (POB) on the pulmonary blood flow in the shunt fraction after the Norwood procedure. The authors infused POB into the CPB intraoperatively and maintained a continuous infusion at a rate of 0.25 mg/kg every 24 h for up to 48 h in the immediate postoperative period. They concluded that the addition of POB to the standard inotropic and vasodilator regimen improved early postoperative systemic oxygen delivery [27]. The pulmonary vasodilator effect fundamentally changed the relationship between blood pressure, systemic oxygen delivery, and the Qp/Qs. The use of pulmonary vasodilator was associated with improved systemic oxygen delivery and stabilization of the Qp/Qs. Those findings are equivalent to our results in the subgroup of patients who had MBTSs and received oral sildenafil.

More recently, Mori *et al.* [22] reported that sildenafil reduced PVR in patients with SV physiology. This indicated that pulmonary vasodilation has a potential therapeutic effect in selected patients with elevated PVR and SV physiology. These findings could explain the current results as we demonstrated a significant increase in oxygen saturation in group 1 compared with the control group.

The increase in oxygen saturation in our study may also be attributed to the extra benefits from sildenafil intake like its antiplatelet function, improvement in myocardial performance and others.

In the subgroup of patients who had Fontan procedure, the rise in oxygen saturation was not statistically significant, which is consistent with the findings of Goldberg and colleagues who studied the efficacy of sildenafil in the clinical performance of Fontan patients.

Unlike our study, Hirono *et al*. [20], who investigated the efficacy of Bosentan in patients with SV physiology, noticed a significant increase in pulse oximetry reading after Bosentan. The reason may be due to their inclusion criteria of staged SV who were deferred from Fontan completion because of high PVR. This was not the case in our study as the high-risk Fontan is not our preferred strategy in managing SV.

Conclusion

There have been accumulated evidence about the beneficial effect of selective pulmonary vasodilators, as sildenafil, on cardiac patients. One of these effects is the decrease in PVR which improves the pulmonary blood flow in the selected group of patients. In patients who received MBTS and BDCPC certain requirements should be fulfilled to obtain the benefit of sildenafil. However, in patients who underwent Fontan procedure, the benefit of sildenafil was not significant.

Limitation

The small number of our subgroup of patients may mask some of the approved clinical data on Fontan patients. Moreover, we may need to estimate the impact of selective pulmonary vasodilator on myocardial function and the physical performance of those patients. The subgroup of patients who have two-ventricle morphology and SV morphology may differ in physical performance, but they present the same findings of improved pulse oximetry.

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Conflicts of interest

There are no conflicts of interest.

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