The Efficacy of Sildenafil in Children with Uni-Ventricle Congenital Heart Disease Post Bidirectional Cavopulmonary Shunt: An Evidence-Based Case Report

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Abstract

BACKGROUND: Univentricular congenital heart disease (CHD) is an anatomical heart defect where one of the ventricles does not develop. Management of univentricular defects is performed gradually; bidirectional cavopulmonary shunt (BCPS) is one of the surgical approaches conducted before the definite treatment in the Fontan procedure. Therefore, the average rate of pulmonary artery pressure and vascular resistance is critical factors in determining good post-surgical outcomes. However, studies exploring the evidence that sildenafil administration can reduce pulmonary pressure in patients with univentricular defects are currently limited.

AIM: This evidence-based case report aims to investigate whether sildenafil administration toward post-BCPS patients reduces mean pulmonary artery pressure (mPAP) and pulmonary vascular resistance (PVR) before undergoing the Fontan procedure.

METHODS: Available evidence was screened through four databases in PubMed, Cochrane, Embase, and ProQuest on October 9, 2022. The keywords used were (((((single Ventricle) OR univentricular heart) AND BCPS) AND Fontan) AND sildenafil) AND hemodynamic. A result of three cohorts and one clinical trial was identified and critically appraised.

RESULTS: Analytical testing of the two studies by Park I and Jeremiasen et al. shows that sildenafil significantly reduces mPAP from 18.5 ± 5.5 mmHg to 14.3 ± 3.0 mmHg (p = 0.023) and from 19 mmHg (SD = 3) to 14 mmHg (SD = 2) (p < 0.01). The studies from Hill KD and Mori et al. illustrate that sildenafil significantly reduces the PVR index by as much as 24% (p < 0.01) and from 3.2 ± 0.5 wood unit to 1.6 ± 0.6 wood unit (p < 0.0001).

CONCLUSION: The administration of sildenafil decreases pulmonary artery pressure and vascular resistance in post-BCPS pediatric patients, allowing patients to undergo the Fontan procedure.

Introduction

Congenital heart disease (CHD) is one of the world’s most common congenital defects, with a million births yearly. About 20% of CHD is caused by genetic defects associated with teratogen substances, while 80% is due to unknown etiology [1, 2]. The epidemiology showed that the prevalence of CHD from 1970–2017 was 8224 for every thousand birth [1], [2]. One of the most frequent causes of CHD is CHD with uni-ventricle. It is a condition with one undeveloped ventricle in the heart or no wall between two ventricle chambers [2, 3]. Uni-ventricle CHD causes 6000–8000 children with circulation failure to be admitted to hospitals with a mortality rate of up to 20–50% in America. Due to the high mortality rate, a comprehensive explanation of the mechanism and complications of uni-ventricle CHD is still limited [2, 3].

On uni-ventricle CHD, oxygenated and de-oxygenated blood mixed at the ventricle chamber goes toward blood circulation. Oxygen saturation in systemic circulation can reach only 75–85% [2, 3]. The severity of uni-ventricle CHD depends on other anatomical anomalies to compensate for pulmonary and systemic circulation [2, 3]. The treatment of this disease remains challenging for clinicians. The main goal of therapy is to return the primary function of the ventricle in systemic circulation and connecting veins and pulmonary arteries.

Due to high resistance in the pulmonary artery, treatment for uni-ventricle CHD cannot be performed during the early years of life. It can only be done subsequently, with the end procedure called the Fontan procedure [2]. The Fontan procedure was first introduced in 1971 by Frances Fontan and Eugene Baudet that operated uni-ventricle for physiology. The Fontan operation has three steps, with the first two steps called bidirectional cavopulmonary shunt (BCPS) operation. This operation was done before the Fontan procedure to decrease the mortality rate. A high pulmonary artery and venous resistance are the most common mortality risk factors for both BCPS and The Fontan procedure [2].
To increase the survival rate, a patient needs to fulfill Choussat’s “Ten Commandments” before undergoing the Fontan operation, which includes high pulmonary artery pressure and pulmonary vein resistance [4], [5], [6].

A pulmonary vasodilator in children has been introduced to patients with pulmonary hypertension in CHD. However, there was slight evidence regarding pulmonary vasodilators on uni-ventricle CHD [5], [6]. One of the pulmonary vasodilators is sildenafil (phosphodiesterase 5-inhibitor). Sildenafil works to inhibit PDE-5 increases cycline guanosine monophosphate rate and vasodilates pulmonary vascularization.

The Pharmacokinetics of sildenafil in children has not been evaluated thoroughly. In adults, sildenafil gets absorbed after being given peroral and reaches a maximum serum concentration of 0.5–2 h after administration. Sildenafil gets first-pass metabolism in the liver with oral bioavailability is 40% [5], [6]. There is no substantial evidence to show whether sildenafil can decrease hemodynamic parameters that can increase the success rate of The Fontan procedure. An evidence-based case report was conducted to analyze the use of sildenafil in post BCPS patients to decrease the mean pulmonary artery pressure or vascular resistance before and after the Fontan procedure.

**Clinical scenario**

A 3-year-old female patient came to our clinic with a post-BCPS procedure. The patient was diagnosed with Pulmonary Atresia-Intact Ventricular Septum (PA-IVS), hypoplastic RV, and hypoplastic TV, and routinely visited the National Cardiovascular Centre Harapan Kita Hospital for treatment and control. The patient had a history of undergoing a BT-shunt procedure at 1 month old and failed BT-shunt, alongside an administration of a BT-shunt stent at 2 years old. The patient’s oxygen saturation at the time was 86%. Through echocardiography, an adequate superior vena cava anastomosis with the right pulmonary artery was evaluated; thrombus and backflow were absent. Ramipril and sildenafil were prescribed. Catheterization 1-year post-BCPS was planned as the primary evaluation method before the Fontan surgery at 4 years old.

**Clinical question**

In patients with uni-ventricle CHD who undergo BCPS, does treatment with pulmonary vasodilator give better hemodynamic outcome than without pulmonary vasodilator?

**Methods**

On October 9, 2022, literature searching was searched on four databases, including Pubmed, Embase, Cochrane, and ProQuest. We designed a search filter using relevant synonyms for the domain: “single ventricle,” “univentricular heart,” “bidirectional cavopulmonary shunt,” “Glenn,” “sildenafil,” and “hemodynamic.” Our search yielded 12 records in PubMed, two in Embase, 13 in Cochrane, and 49 in ProQuest (Table 1).

<table>
<thead>
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<th>Database</th>
<th>Search strategy</th>
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<td>Embase</td>
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We found four eligible studies from PubMed and two studies from Cochrane (Figure 1). Inclusion criteria were patients undergoing BCPS who have not done the Fontan procedure, a study with the hemodynamic outcome (mean pulmonary artery pressure [mPAP] and PVR), systematic review, meta-analysis, RCT, clinical trial, and cohort (Table 2). Exclusion criteria included patients with pulmonary vein obstruction, arrhythmias, and mitral valve abnormalities. Four articles were critically appraised, one article was excluded because there was no full-text article, and another article was excluded because the study was done in a different population (Table 3).

**Results**

In a study by Park et al., 18 subjects were treated with sildenafil before undergoing the Fontan procedure and 16 subjects after the Fontan procedure. The median age in this study was 4 years (Age range from 4 months to 30 years). The sildenafil dose was 0.5 mg/kg/day, and the average maintenance dose was 1.4 mg/kg/day. Patients treated with sildenafil also had diuretics, ACE-inhibitor, ARB, beta-blocker, and anti-coagulant therapy as indicated. Sildenafil therapy showed a significant decrease mPAP from 19.5 ± 5.5 mmHg to 14.3 ± 3.0 mmHg (p = 0.023). PVR was not decreased significantly after sildenafil therapy (p = 0.2). No side effects were reported from sildenafil therapy in this study population.

Hill et al. have an open-label prospective cohort study with 12 uni-ventricle CHD children who underwent BCPS. The median age of patients was 1.9 years (ranging from 9 months to 4 years). Patients were examined with transthoracic echocardiography and catheterization before being treated with sildenafil. Intravenous sildenafil was administered with starting dose of 0.125 mg/kg–0.45 mg/kg for 20 minutes. After the treatment, hemodynamics assessment with transthoracic echocardiography and catheterization was performed. Sildenafil therapy was associated with lowering 24% the PVR index (PVR) by (p < 0.01). No side effects were reported from sildenafil therapy in this study population.
Jeremiasen et al. divided into three groups: A, B, and C. Group B was included because its criteria matched this study (patients underwent BCPS surgery). The mean age of patients who started sildenafil therapy in Group B was 4.4 years (from 0.9 to 8.5 years). All the patients in Group B were treated with sildenafil in the early phase. However, at the end of the study, additional bosentan therapy was added to four patients. MPAP hemodynamics mean pressure was obtained in six patients from Group B. There was significantly reduced MPAP from 19 mmHg (SD = 3) to 14 mmHg (SD = 2) (p < 0.01). Three patients stopped the medication because the patients were allowed to perform surgery without vasodilator indication. No significant side effects of sildenafil were reported in this study.

Mori et al. also split into three groups (Groups 1, 2, and 3). Group 2 population were all of the patients who performed BCPS surgery. In this group, the mean age of patients was 39 ± 82 (median 14) months, and sildenafil therapy started from the mean age of 44 ± 84 (median 9.8) months after BCPS surgery. Sildenafil therapy significantly decreased PVRI in Group 2 from 3.2 ± 0.5 unit wood to 1.6 ± 0.5 unit wood (p < 0.001). There was also significantly reduced MPAP from 12.5 ± 3.0 mm Hg to 10.6 ± 2.2 mm Hg (p < 0.05) in Group 2. All the patients in Group 2 performed Fontan surgery without any mortality events. Side effects from sildenafil were observed in one patient within Group 3 but not in Group 2.

Discussion

High pulmonary arterial pressure and vasculature resistance are predictors of post-palliative procedure mortalities in uni-ventricular heart defects, with a figure reaching 30%. Thus, the usage of vasodilator therapy is reasonable [5], [7]. Jeremiasen et al. showed that low pulmonary vascular resistance in uni-ventricular heart defects affects patient survival, quality of life, and functional capacities from a 1.3 (0.3–2.6) years follow-up study. Sildenafil treatment significantly reduces the mean pulmonary artery resistance from 19 mmHg to 14 mmHg [5]. This finding was reinforced by the Mori et al. study, where there was a decrease of mPAP

### Table 2: Characteristics studies

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<tr>
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Representativeness
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Selection of the
exposure
Ascertainment
of exposure
Demonstration that
outcome of interest
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start of study
Comparability of
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on the basis of the
design or analysis
controlled for
confounders
Assessment of
outcome
to occur
Was follow-up long
enough for outcomes
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Adequacy of
follow-up of cohorts

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from 15.9 ± 4.4 to 12.8 ± 3.0 mmHg (p < 0.01), and the study by Park I with a decrease of mPAP from 19.5 ± 5.5 mmHg to 14.3 ± 3.0 mmHg (p = 0.023) [6], [8].

Mori et al. study observed that the administration of sildenafil before Fontan surgery results in PVR reduction from 3.2 ± 0.5 wood unit to 1.6 ± 0.6 wood unit (p < 0.0001), which improves the outcome of the procedure [6]. Similarly, the research by Hill KD also produces a significant decrease in the PVR index after sildenafil administration by as much as 24% (p < 0.01). Jeremiasen et al. study also concluded an increase reaching 80–85% in mean oxygen saturation 12 months after vasodilator initiation, which could be in consideration as an indirect parameter of pulmonary vascular resistance reduction [9]. In contrast, Park et al. results stated that sildenafil does not significantly affect PVR [8]. The difference in results is possibly generated due to the study population difference. Park I study included pediatric and adult patients (with an age span of 4–30 years old), whereas Mori et al. and Hill et al. only included pediatric patients [6], [8], [9]. A systematic review by Varela et al. shows that sildenafil could repair the functional capacity and hemodynamic parameters in adult patients with pulmonary hypertension due to CHD. However, there is still a lack of studies observing the efficacy and dose-response effect of sildenafil on adult patients compared to pediatric patients [10].

As a strong, comprehensive pulmonary vasodilator, understanding the safety of sildenafil usage is essential. Jeremiasen et al. and Mori et al. discussed the side effects of sildenafil with a follow-up period of 4.7 (0–12.8) years. They found that they were minimal and tolerable in their study population [5], [6]. Nemoto et al. similarly concluded that sildenafil was safe and effective even for post-cardiac surgery pediatric patients [11]. Furthermore, Cohen et al. observed that sildenafil administration to children with pulmonary hypertension was effective and safe [12]. In conclusion, there is strong evidence that substantiates the safety of sildenafil administration. From the studies mentioned, the results indicated that sildenafil decreased the parameter for pulmonary hemodynamic in uni-ventricular heart defects. The need for future studies exploring the long-term prognosis of patients post-BCPS administered by sildenafil is acknowledged. However, the limitations of this study should also be noted. First, there are different patient baseline characteristics, especially with their pulmonary hemodynamics and other comorbidities, which are hypothesized to affect the results. In addition, randomization was not performed in all the studies, resulting in a possibly biased result. The short follow-up duration was also an issue that requires addressing in future studies. Finally, no control group was formed for comparison to the sildenafil group in all of the studies.

**Conclusion**

Sildenafil therapy decreases pulmonary artery pressure and vascular resistance in children with uni-ventricle CHD post BCPS to fulfill the criteria for the Fontan procedure. Minimal side effects are also reported for sildenafil usage in children. A future RCT still needs to be conducted to gather a higher level of evidence.

**References**


