Perioperative Sildenafil Therapy in Pediatric Congenital Cardiac Disease Patients
A Meta-Analysis

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Summary
Sildenafil is a pulmonary artery hypertension (PH)-targeted drug that finds an increased indiscriminate use in children with PH secondary to congenital heart disease (CHD).

We performed a meta-analysis to evaluate the effects of sildenafil on pediatric patients with PH secondary to CHD during perioperative period.

PubMed, EMBASE, the Cochrane Library, and the Google Scholar were searched up to May 2016 for randomized controlled trials (RCTs) assessing the perioperative treatment of sildenafil in pediatric patients with PH secondary to CHD. Major clinical outcomes were mortality before discharge, length of ICU stay, and length of hospitalization. The outcomes were analyzed as continuous and dichotomized variables by using fixed or random effect model, and we computed the pooled RR and MD with 95% confidence interval.

Five RCTs involving 238 pediatric patients with PH experienced CHD operation were included. Sildenafil was used in all trials. We observed no differences in mortality before discharge (RR 0.35; 95% CI 0.06-2.10; χ² = 1.31, I² = 0.24, P = 0.25) and length of hospitalization (MD −0.50; 95% CI −1.60 to 0.60; χ² = 5.29, I² = 62%, P = 0.38). There was a decrease in the length of ICU stay (MD −18.18; 95% CI −24.68 to −11.67; χ² = 12.61, I² = 84%, P < 0.00001), which had a high heterogeneity. The findings were robust after the sensitivity analyses.

The perioperative treatment of sildenafil for CHD pediatric patients is a potential method to reduce the length of ICU stay. We observed no differences with the use of it in the mortality before discharge and the length of hospitalization.

(Key words: Congenital heart disease, Pulmonary hypertension)

Pulmonary hypertension (PH) is characterized by a progressive increase in pulmonary artery pressure and pulmonary vascular resistance, which leads to right ventricular failure and thereupon an inevitable death. In children, congenital heart disease (CHD) is responsible for PH in pediatric patients up to almost 50% of cases. It is one of the most frequent causes of PH in children with congenital cardiac and vascular disease. In infants and children, large congenital heart defects are usually associated with PH which is likely caused by an abundant left-to-right shunt that causes increased pulmonary perfusion and pulmonary vein obstruction. This disease needs cardiopulmonary bypass surgery, after which temporary pulmonary endothelial dysfunction and suppression of endogenous NO production would occur, resulting in an increased risk of heart failure. What is more, the preoperative dynamic PH may be aggravated by an even worse postoperative PH. Historically, there have been a few rigorous clinical protocols of PH therapies in pediatric patients. In addition to the major surgery, a supportive therapy is considered to play an indispensable role in the treatment of CHD patients with PH. Inhalation of nitric oxide (iNO) is widely suggested for the perioperative management of PH in CHD children which is considered to be definitely effective. However, its long-term efficacy with respect to mortality has not been confirmed in the study of Bizzarro et al. in 2005. Bizzarro, et al. observed no differences in the outcomes by using iNO for postoperative management of PH in infant and children with CHD.

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PDE-5 inhibitor treatment in children has been embroiled in the conflict nowadays. Sildenafil is an inhibitor of PDE-5 that is widely used to treat pulmonary hypertension in children by promoting vasodilatation in the pulmonary vascular bed. Thus, inhibition of PDE-5 results in an increased level of cyclic guanosine monophosphate (cGMP) and relaxation of vascular smooth muscles. Several open-label studies such as STARTS-1 and STARTS-2 trials indicated that sildenafil improved pulmonary hemodynamics, oxygen saturations, and exercise capacity. Meanwhile, the US Food and Drug Administration has recommended against using sildenafil in the pediatric patients because it was reported in the study that more than 37 children died, 28 of whom had PH. The pharmacodynamics of perioperative management of sildenafil in children with PH associated with CHD is still a controversy and has not been studied well. What is more, the guideline of CHD related to pulmonary hypertension proposed that the efficacy of PDE-5 inhibitors such as sildenafil in the treatment of CHD associated with PH is not confirmed and needs further study. Herein, we performed a meta-analysis of randomized controlled trials on the clinical outcomes in CHD pediatric patients during perioperative period versus control.

Methods

We performed an online search for papers using PubMed, EMBASE, the Cochrane Library, Google Scholar, and ISI Web of Knowledge up to the May 2016. Initial searches included keywords such as “congenital heart disease,” “sildenafil,” “pulmonary hypertension,” “pediatric,” and “randomized controlled trial”. Searches were based on English language only.

The included criteria were as follows: a prospective randomized controlled trial; the study population comprised newborns, infants, and children (with age of post-natal to 18 years) with CHD requiring surgery associated with primary or secondary (postoperative) pulmonary hypertension; studies of any period during the administration treatment and before, during, or after surgeries; any route of administration (oral or intravenous), and any dose of administration were included; interventions including sildenafil versus placebo or no treatment or another pulmonary vasodilator were included. The PH diagnosis was based on clinical findings with or without echocardiographic confirmation.

Types of outcome measures include: mortality after operation before discharge and length of ICU stay (hours) and hospitalization (days). The continuous variables were expressed as the mean ± standard deviation. The outcomes were analyzed as continuous and dichotomized variables by using fixed or random effect model, and we computed the pooled RR and MD with 95% confidence interval (CI). Inter-study heterogeneity was analyzed by using standard $\chi^2$-tests. $I^2$ values of < 25% were considered as low heterogeneity, 25-50% as moderate heterogeneity, and those of > 75% as high heterogeneity. All analyses were performed with the Review Manager 5.3 software for Windows. Two-tailed $P$-values < 0.05 were considered statistically significant.

Results

Search results: The search strategy revealed totally 226 references. About 166 studies remained after removing duplicate references. After reviewing the topics and abstracts in terms of the inclusion and exclusion criteria, 15 studies remained after filtration. Among the 15 studies, 10 studies were further excluded, the reasons revealed in Figure 1. Finally, five RCTs were included in this article all of which were full manuscripts acquired from journal articles.

Baseline patient characteristics: Baseline characteristics
of the patients in the included studies are summarized in the Table. The five studies totally included 238 CHD pediatric patients complicated with PH. All five RCTs enrolled CHD patients with mortality before discharge, and three RCTs focused on CHD patients with the time of hospitalization and three RCTs focused on ICU stay. The number of potential confounding factors included in the multivariate-adjusted model varied.

**Pulmonary artery pressure:** Pulmonary artery pressure (PAP) reduction is the main clinical index responsible for the effectiveness of sildenafil. Three RCTs (Peiravian, et al., 2007; Alain, et al., 2011; Ashraf, et al., 2013) focused on the change in PAP directly. Three RCTs (Farah, et al., 2007, 2013; Vipul, et al., 2015) compared the change in PA/Ao by using sildenafil. Only one study (Vipul, et al., in 2015) made a simple comparison with respect to systolic PA/Ao between the two groups.

In the study of Peiravian, et al., postoperative PAP (28.61 ± 7.80 versus 39.40 ± 10.80 mmHg) was significantly lower in sildenafil group (P = 0.001), and there was no significant increase in PAP following discontinuation of the drug (26.30 ± 6.66 versus 28.49 ± 10.93 mmHg, P = 0.366). In the study of Alain, et al., systolic PAP was reduced with sildenafil (46 ± 11 to 35 ± 6 mmHg, P = 0.027 versus placebo). In the study of Ashraf, et al., mPAP decreased significantly (75.4 ± 7.8 to 59.4 ± 7.4 mmHg, P < 0.0001) after sildenafil administration in the sildenafil group preoperatively, and postoperatively mPAP was also lower (50.4 ± 6.8 to 44.2 ± 10.3 mmHg, P < 0.0001) since cardiopulmonary bypass before discharge.

Peiravian, et al., found that PA/Ao pressure (0.28 ± 0.08 versus 0.41 ± 0.11) was significantly lower in the sildenafil group (P = 0.001). Peiravian, et al., showed that PA/Ao in sildenafil group decreased from 0.74 ± 0.15 to 0.33 ± 0.07 significantly, while milrinone was even more effective on PA/Ao (P = 0.003). Vipul, et al., found that PA/Ao was 0.54 and 0.54, respectively, in Group sildenafil and Group control. After surgery, PA/Ao reduced to 0.3 versus 0.4 in the Group sildenafil and Group control, respectively, which clearly displayed thereby the superiority of Group sildenafil.

**Data analysis:** Five prospective randomized controlled trials of perioperative sildenafil therapy versus control enrolling pediatric patients with CHD undergoing cardiac operation were identified. Totally, our meta-analysis included data on 238 pediatric patients randomized to sildenafil or control group. It is demonstrated from pooled analysis that there was no statistical difference in the mortality during the perioperative management before dis-
charge (RR 0.35; 95% CI 0.06-2.10; $\chi^2 = 1.31, I^2 = 0.24, P = 0.25$; Figure 2) and the length of hospitalization (MD $-0.5$; 95% CI $-1.60$ to $0.60$; $\chi^2 = 5.29, I^2 = 62\%, P = 0.38$; Figure 3) between the two groups. The above two findings were found to be robust after the sensitivity analyses. Nevertheless, although the time on the length of ICU stay (MD $-18.18$; 95% CI $-24.68$ to $-11.67$; $\chi^2 = 12.61, I^2 = 84\%, P < 0.0001$; Figure 4A) showed an obvious difference between the two groups, the outcome displayed high heterogeneity. With a thorough analysis of the three included articles, we found that the study by Peiravian, et al. in 2013 showed that intravenous milrinone as the control group was superior to oral sildenafil, although both of them successfully decreased the risk of pulmonary hypertension crisis in perioperative CHD children with pulmonary hypertension. This conclusion was just opposite in the direction against the other two articles of Peiravian, et al. in 2007 and Vipul, et al. in 2015. This was considered to be the reason for the high heterogeneity for the analysis of ICU stay. However, if we exclude this article to analyze again, the conclusion is still consistent with that before while the heterogeneity turned out to be 0 (MD $-20.37$; 95% CI $-26.99$ to $-13.74$; $\chi^2 = 1.02, I^2 = 0\%, P < 0.0001$; Figure 4B).

Discussion

Sildenafil is receiving increasing interest in the treat-
ment of PH in CHD infants and children, but there has been no meta-analysis focused on the safety, tolerability, or efficacy of perioperative sildenafil treatment for CHD pediatric patients so far. Our meta-analysis showed that based on the standard surgery aimed at CHD and anti-PH therapy, additional perioperative sildenafil treatment reduced the time on the length of ICU stay but without changing the short-term mortality and length of hospitalization.

The intervention of sildenafil in this meta-analysis included three subtypes (before, during, and after operation). In the reports of Ashraf, et al. in 2013,19 sildenafil was administered preoperatively, and in the study of Alain, et al. in 2011,16 it was administered postoperatively. In the other three studies of Peiravian, et al. in 2007, 2013, and Vipul, et al. in 2015,11,14,15 sildenafil treatment was given since the operation started and maintained for at least 24 hours after the surgery. Data in these reports showed that irrespective of the use of sildenafil preoperatively or postoperatively, it can reduce postoperative PH and PA/AO pressure of different levels. Peiravian, et al. and Vipul, et al. thought of the advantage of starting sildenafil before or during the operation for better pulmonary vascular bed reactivity with subsequent better postoperative outcome. Therefore, all of the five studies were meaningful. However, a few RCTs that lead to subgroup analysis cannot be undertaken temporarily. Hence, we cannot exclude the possibility that different administration time (before or after surgery) of sildenafil may contribute to different results of clinical study found in the meta-analysis.

Our meta-analysis showed that although sildenafil cannot reduce mortality in short span of time after surgery and length of hospitalization, it may reduce the severe postoperative cardiovascular risk by shortening the length of ICU stay. Although studies have shown that sildenafil used for treating children with different CHD types shows good results, different individual objective factors, such as time selection of operation, the degree of right ventricular remodeling, and the misjudgment of surgical possibility, may cause variable mortality and lengthy hospital stay. The trend of the above two outcomes may not be displayed in only five RCTs. Samira, et al.16 in 2014 said that although the role of sildenafil in cardiovascular disorders in infants is still contradictory, the concurrent use of oral sildenafil with other anticoagulant agents can enhance the potential antiaggregatory effect of this drug to stop the bleeding and this may be one of the possible reasons that can shorten the length of ICU stay by reducing severe postoperative cardiovascular risk. The review also claimed that data for years did not show increased risk of mortality secondary to sildenafil therapy among infant population. This conclusion is consistent with the results of our analysis.

Another problem concerned the high heterogeneity existed in the length of ICU stay. In a research by Peiravian, et al. in 2013,14 intravenous milrinone was quite effective in reducing ICU stay compared with oral sildenafil. Milrinone is one of the most widely used vasodilators with definite curative effect; so, a different trend of clinical efficacy in RCTs is allowed and is equally inevitable. Most of the patients in our study had Ventricular Septal Defect (VSD), which were high risk factors for the development of PH and right cardiac dysfunction. Sildenafil is focused more on maintaining the correct heart function compared with milrinone. What is more, the difference in time-to-peak effect on pulmonary vasculature that we found in this report is probably because of the pharmacokinetic effects when using different routes (oral versus iv) of administration.17 More critically, the result of ICU stay analysis did not alter if we excluded data in Peiravian, et al. in 2013.14 From the above, we have reasons to believe that sildenafil can reduce the risk on the time of ICU stay. On the other hand, there was a statistically significant less ICU stay in the sildenafil group, which reflects an advantage of adding sildenafil, and this can be explained by easier weaning of postoperative inotropic support without any need to maintain the patient on inotropic support for a long time.

The suggested perioperative treatment algorithm for PAH for children includes inhaled nitric oxide (iNO), sildenafil, milrinone, and the short-term use of prostanooids.14,16 So far, inhaled NO is the most common treatment for residual pulmonary hypertension. However, there are some limitations of iNO-like rebound PH after discontinuation of iNO and incomplete elimination of PH crisis.17 So, sildenafil was usually added to iNO or just used alone. The study of Ataru revealed that PDE5-class drugs, especially bosentan and sildenafil, appeared to be superior in improving 6-minute walk distance test (6MWD) and WHO functional class (WHOFc) in PH.20 In the included five studies of our meta-analysis, other vasodilators, including iNO and O2 which may become potential confounding factors, were strictly controlled by researchers and that made the results of our meta-analysis more believable and meaningful. In our study, sildenafil reduced the time of ICU stay and did not increase the short-term mortality based on being used without concomitant pulmonary vasodilators. It encourages us to conduct more clinical researches on its curative effect and contrast treatment with other vasodilators.

The safety of sildenafil for children must be mentioned. Today, sildenafil is considered an encouraging treatment in PH in infants and children, although it is still a controversy with the need for further studies. In 2012, the US Food and Drug Administration (USFDA) issued a warning regarding the of use high dose of sildenafil in children with PH. As mentioned about STARTS-2 in a study above, one of the important reasons was that there was a higher incidence of deaths observed in the high-dose sildenafil group versus low- and medium-dose groups. However, the PAH in the high-dose group is much higher than the other two groups (46 versus 17 and 38 mmHg), which means the patients in this group were much more serious. Moreover, the trial did not include a placebo group, and doses of sildenafil changed during the STARTS-2 trial; the mortality signal was not consistent across weight groups or etiologies. As emphasized by the author, most of the adverse events were considered to be related to the disease under study or decreased weight. A recent study conducted by Roldan in children found that there was a statistically significant increase in adverse
drug reaction (ADR) frequency in patients receiving higher-than-recommended doses. However, it was not associated with a lower survival rate. In fact, common side effects of sildenafil treatment are usually nonlife-threatening. Upper respiratory tract infections are the most frequent. Severe adverse effects that were treatment-related and that required immediate termination of the treatment only appeared in five subjects of the double-blind, placebo-controlled sildenafil in treatment-naive children with pulmonary arterial hypertension (STARTS-1) study and consisted of stridor and ventricular arrhythmias. Furthermore, there was no serious adverse reaction or high mortality due to sildenafil in the five RCT studies of this meta-analysis. FDA’s statements are more uncertain about the treatment of sildenafil on children, and it is also the impetus for clinician-scientists to ensure a successful strategy for pediatric drug development.

In addition to the inherent methodological limitations of most meta-analyses, our meta-analysis has several additional limitations to consider. First of all, only 238 patients were involved in the five RCTs. Theoretically, stratification analysis of patients of different ages is more reliable and scientific, and these five articles did cover children of different ages, and their pulmonary arterial hypertension had a gap in time span. However, these clinical studies themselves have not been able to group children of different ages, which means that it is difficult to extract valid data for hierarchical analysis. Therefore, although no differences existed in the two groups on mortality and length of hospitalization, there is the potential for bias that compromise the results of the review and make it impossible to draw any fixed conclusions at present. Second, the follow-up duration was not long enough. Longer observation times should be focused on definitive endpoints in future studies to investigate long-term mortality and rebound of postoperative hypertension. Third, this meta-analysis only included the data of three clinical outcomes. Theoretically, more clinical indicators should be analyzed in the current meta-analysis, such as PAP, BP, OI, cardiac output, and so on. Whereas due to the limitation of the five reports, we failed to extract the complete data for analysis. Thirdly, since all five trials used different sildenafil concentrations, involved diverse CHD, various ages, different administration of therapy, and different dosing period (before, during, or after the surgery), the potential bias can be imagined. The rapid growth of infants and children, long life expectancy of children that makes it difficult to define study endpoints, small patient population allowed to participate in RCT research, and ethical controversy in children’s clinical research all make limitations require a long-term solution and make it hard to come to a definite conclusion about curative effects of sildenafil at the present time.

In conclusion, this meta-analysis is the first to analyze perioperative treatment of PDE5 inhibitor sildenafil specifically for CHD infants and children with PH. Sildenafil does not reduce the mortality before discharge and does not shorten the length of hospitalization, meanwhile it does reduce the time of ICU stay compared with control. Large-scale RCTs involving different risky pediatric patients should be carried out for further clinical research, and more relevant clinical data from RCTs of high methodological quality are necessary to evaluate the effect of sildenafil for children.

Disclosures

Conflicts of interest: None.

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