Continuous Versus Intermittent Intravenous Sildenafil in Critically Ill Infants with Pulmonary Hypertension

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Abstract

Abstract Continuous intravenous (IV) sildenafil may avoid the acute systemic vasodilatory effects of bolus dosing in infants with pulmonary hypertension (PH). We aimed to examine the tolerability of different methods of IV sildenafil administration. Methods: We retrospectively evaluated subjects less than 12 months old with PH, who had been started on IV sildenafil. Vital signs, oxygen requirement, and vasoactive-inotropic score (VIS) before and after sildenafil initiation were noted, as was the need for discontinuation due to side effects. Results: Forty-three subjects were identified (23 continuous, 20 intermittent dosing). There were no statistically significant differences between groups in gender or gestational age, but higher baseline inspired oxygen (FiO2) and VIS in the continuous group suggested a higher baseline severity of illness (p=0.012). After sildenafil initiation, there were no significant differences in the change in blood pressure, oxygen saturation, FiO2, or VIS between groups, and no difference in the number of subjects requiring discontinuation due to side effects (4 in the continuous group, 1 intermittent, p=0.35). Eight subjects (34.8%) in the continuous group and 3 (15%) in the intermittent group died (p=0.024). Conclusions: In this small cohort of infants with PH treated with continuous or intermittent IV sildenafil, there were no statistically significant differences between groups in the change in vital signs, VIS, and oxygen requirement, or the need for discontinuation of therapy due to side effects. A higher mortality rate in the continuous infusion group may be explained by higher baseline illness severity.

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Forty-three subjects were identified (23 continuous, 20 intermittent dosing). There were no statistically significant differences between groups in gender or gestational age, but higher baseline inspired oxygen (FiO2) and VIS in the continuous group suggested a higher baseline severity of illness (p =0.012). After sildenafil initiation, there were no significant differences in the change in blood pressure, oxygen saturation, FiO2, or VIS between groups, and no difference in the number of subjects requiring discontinuation due to side effects (4 in the continuous group, 1 intermittent, p =0.35). Eight subjects (34.8%) in the continuous group and 3 (15%) in the intermittent group died (p =0.024).

Conclusions:

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Introduction

Pulmonary hypertension (PH) is defined as an abnormally high pulmonary artery pressure and pulmonary vascular resistance, often secondary to cardiac or pulmonary disease[1]. The gold standard for diagnosis of PH is a mean pulmonary arterial pressure of [?]25 mmHg by right heart catheterization[2]. The clinical spectrum of presentation varies from a transient neonatal condition to a disabling disease of infancy and childhood[3]. Three of the most common causes of PH in infants are classified by the World Health Organization as (1) pulmonary arterial hypertension including persistent PH of the newborn, (2) PH associated with left heart disease, and (3) PH associated with lung disease and/or hypoxemia including developmental lung disease, congenital diaphragmatic hernia, or bronchopulmonary dysplasia[4]. The incidence of severe persistent pulmonary hypertension in newborns is estimated at 0.2% of live-born term infants[4].

Treatment of PH involves selective pulmonary vasodilation, with multiple therapeutic options including phosphodiesterase type 5 (PDE-5) inhibitors[3]. Among these, the PDE-5 inhibitor sildenafil is commonly used to treat PH in newborns and infants[5]. Sildenafil is unique in that it may be delivered orally or intravenously (IV). It has a larger volume of distribution in neonates than adults, resulting in a longer terminal half-life[5]. IV delivery is sometimes chosen for critically-ill neonates in whom there are concerns of poor absorption of enteral medications[5].

Intermittent bolus IV sildenafil has demonstrated efficacy in various studies[6], however systemic hypotension has been reported as an adverse effect of IV bolus delivery[7]. Studies investigating the occurrence of hypotension in IV versus oral delivery have failed to demonstrate a statistically significant difference in safety outcomes[8].

A continuous IV sildenafil infusion may be a feasible alternative to enteral or intermittent dosing, and this method of delivery has been suggested as a possible way of avoiding the acute systemic vasodilatory effects of bolus dosing. To date, there is a dearth of data on the continuous use of IV sildenafil, and no studies comparing continuous to intermittent IV dosing in pediatric PH.

The primary aim of this retrospective study was to describe and examine the tolerability of the different methods of IV sildenafil administration in critically-ill infants with PH, including the incidence of hypotension, the need for increased inspired oxygen or vasoactive support, and the need for treatment discontinuation due to side effects.

Materials and Methods

Design and Patients

This was a single-center retrospective observational study. Subjects less than 12 months of age admitted to the neonatal or pediatric intensive care unit, who received intravenous sildenafil for PH between 01/01/2011 and 12/30/2016, were included. Data on patients receiving continuous IV sildenafil were compared with subjects receiving intermittent IV sildenafil dosing.

Baseline clinical characteristics just prior to initiation of IV sildenafil including oxygen saturation (SpO2), fraction of inspired oxygen (FiO2), systolic blood pressure (SBP), diastolic blood pressure (DBP), mean arterial pressure (MAP), and vasoactive-inotropic score (VIS). VIS as described by Belletti et al can be used to objectively quantify the degree of hemodynamic support and several studies have demonstrated a correlation between high VIS and poor outcome[9]. These data were also obtained at a time point 2 to 8 hours after the initiation of continuous IV sildenafil infusion, or 30 minutes to 2 hours after the first full IV bolus sildenafil dose (for group 2). The time frame of data collection for the IV bolus sildenafil group was chosen based on the time to maximum observed plasma drug concentration of the main metabolite of sildenafil (35 minutes after bolus IV dosing, as described by Vachiery et al[10]). As bolus dosing was administered three times per day, the chosen time frame of data collection for the continuous IV sildenafil group was that in which the patient received up to one third of the daily dose by infusion. During these specified periods after sildenafil initiation, the lowest FiO2, SBP, DBP, and MAP, and the highest FiO2 and VIS were recorded. The need for sildenafil discontinuation due to side effects at any point in the 7 days following initiation was noted.

The primary endpoint was the need for IV sildenafil discontinuation due to side effects. Secondary endpoints included mortality, and the change in FiO2, SBP, DBP, and VIS after sildenafil initiation. Mortality was defined as death at any time after the start of sildenafil until the last date of data collection (December 2019), irrespective of the time of stopping sildenafil.

Statistical Analysis

Descriptive statistics are reported for each variable stratified by sildenafil group. Continuous variables were reported as medians and interquartile ranges (IQR: 25th percentile to 75th percentile). Categorical variables were reported as frequencies and percentages.

Tests for association between groups were conducted using Wilcoxon rank sum tests for continuous variables, and chi-square or Fisher's exact tests for categorical variables, as appropriate. Wilcoxon rank sum tests were used for all continuous variables because several of the variables did not meet the distribution assumptions required to perform t-tests, and for those variables that met assumptions, results were qualitatively the same between those obtained using a t-test and those obtained using a Wilcoxon rank sum test.

In order to examine the relationship between mortality and sildenafil group, a Cox proportional hazard model was used. Because we expect the cause of mortality to be multifactorial, univariable Cox proportional hazards models were used to examine the relationship of time from initiation of sildenafil to time of death or last follow-up with gestational age, and the baseline measures of PH degree, right ventricular function, SBP, DBP, and VIS. We were restricted to univariable models because of the limited sample size and the small

number of events. Subjects were followed for the maximum time on record, such as to the date of death or latest follow-up visit.

A p -value < 0.05 was considered statistically significant. All analyses were conducted using SAS version 9.4 (SAS Institute Inc., Cary, NC).

Results

Baseline Demographic and Clinical Characteristics

Forty-three subjects were included in the study; 53% (n=23) received a continuous IV sildenafil infusion, and 47% (n=20) received intermittent IV bolus dosing (table 1). Males comprised 48% (n=11) of subjects in the continuous group and 75% (n=15) of patients in the intermittent group (p =0.069). Median gestational age was 38.7 weeks (IQR: 36 - 40) in the continuous group, and 37.8 weeks (IQR: 26 - 39),p =0.13. Classes of PH included lung disease/hypoxia (specifically, prematurity-related chronic lung disease), pulmonary arterial hypertension (specifically, persistent PH of the newborn), and PH due to left heart disease. Although not statistically significant, the dominant diagnosis in the continuous infusion group was persistent PH of the newborn, and in the intermittent group was PH associated with lung disease (p=0.07). In the continuous infusion group 13 of 23 (56%) had persistent PH of the newborn, 1 of 23 (4%) had PH due to left heart disease, and 9 of 23 (39%) had PH associated with lung disease. In the intermittent group 5 of 20 (25%) had persistent PH of the newborn, 1 of 20 (5%) had PH due to left heart disease, and 14 of 20 (70%) had PH associated with lung disease. Twelve (52%) subjects in the continuous group and 6 (30%) subjects in the intermittent group were being supported with extracorporeal membrane oxygenation prior to initiation of Sildenafil (p =0.14).

The median continuous IV dose was 1.6 mg/kg/day (range 1.3-1.6), and the intermittent IV dose was 0.5 mg/kg/dose every 8 hours. There were no significant differences in gender, gestational age, or type of PH between continuous and intermittent groups.

Table 2 demonstrates baseline clinical parameters prior to sildenafil initiation. Median baseline VIS was higher in the continuous group compared to the intermittent group (10 (IQR: 3 to 20) vs. 4 (IQR: 0 to 6.5), p =0.012). Baseline FiO2 was higher as well in subjects who received continuous IV sildenafil (93% (IQR: 55% to 100%) vs. 46% (36% to 78%), p =0.012). SBP, DBP, and MAP pre-sildenafil were similar between continuous and intermittent groups.

Changes in Clinical Parameters After Sildenafil Administration, and Need for Discontinuation of Therapy Changes in clinical parameters after initiation of IV sildenafil are displayed in table 3. The changes in MAP, SBP, DBP, SpO2, FiO2, and VIS from before IV sildenafil to the specified time point after administration were not significantly different between groups. Sildenafil was documented as discontinued due to side effects in a total of 5 subjects, including 4 (17.4%) in the continuous group (hypotension=3, ventilation/perfusion mismatch=1) and 1 (5.0%) in the intermittent group (hypotension). This difference in the need for discontinuation was not statistically significant.

Mortality

Eleven subjects (25.6%) died, including 8 (34.8%) of the continuous group and 3 (15%) of the intermittent group. Of the 11 patients who died, six died while receiving sildenafil at a mean of 11.6 days from initiation. The estimated hazard ratio for mortality in patients who received continuous vs. intermittent sildenafil was 4.9 (HR = 4.9, 95% CI: 1.231 to 19.540, p =0.024), possibly reflecting the baseline higher severity of illness in those patients who received continuous sildenafil. The 95% confidence interval indicates that the rate could be as much as a 19-fold or as little as a 1.2-fold increase in the rate of dying. In addition, significant associations were observed between mortality and systolic BP, diastolic BP, and VIS. The estimated hazard ratio for a 1 mmHg increase in systolic BP is 0.956. Patients with a 1 mmHg higher systolic BP died at a rate 4.4% lower than patients with lower systolic BP (HR=0.956, 95% CI: 0.915 to 0.999, p $<$ 0.043). The estimated hazard ratio for a 1 mmHg increase in diastolic BP is 0.919. Patients with a 1 mmHg higher diastolic BP died at a rate 8.1% lower than patients with lower diastolic BP (HR=0.919, 95% CI: 0.853 to

0.989, $p < 0.025$). The estimated hazard ratio for a 1 unit increase in VIS is 1.05. Patients with a 1 unit increase in VIS died at a rate 5% higher than patients with lower VIS (HR = 1.049, 95% CI: 1.019 to 1.079, $p < 0.001$). No statistically significant differences were observed in mortality rates by gestational age, ECMO (yes/no), PH degree (dichotomized), or RV function.

Discussion

The incidence of severe persistent PH of the newborn is 2/1000 live births[11]. Among infants born prematurely, the risk of PH is estimated to be more than three times higher than in full term births[12]. Infants with PH of many different etiologies are often treated with the PDE-5 inhibitor sildenafil, which has been shown in various studies to improve oxygenation[14]. Although well tolerated for most patients, the side effect of systemic hypotension remains a significant concern in many neonates with unfavorable hemodynamics[8,13]. Critically ill neonates who experience systemic hypotension with bolus IV sildenafil often have limited drug choices for PH treatment.

IV sildenafil may have a role in the management of critically-ill infants with PH, in whom there are concerns of poor absorption of enteral medications. A continuous IV infusion may also be considered in patients who have demonstrated intolerance of the acute systemic vasodilatory effects of intermittent bolus dosing. A continuous infusion may permit consistent, steady dosing rather than the natural pharmacokinetic rise and decline of bolus doses.

The present study is one of the few in the literature that evaluates the use of continuous IV sildenafil to treat critically ill infants with PH. To our knowledge, there are no studies comparing intermittent bolus IV dosing to continuous IV sildenafil infusion in this population. Our findings demonstrate no statistically significant difference in the tolerability of these dosing forms based on the lack of significant change in multiple clinical parameters, in the escalation of vasoactive medications, or the need for discontinuation of sildenafil due to side effects. The notable (although not statistically significant) differences in PH etiology and ECMO requirement between groups, and the higher baseline severity of illness (higher VIS and FiO2) in subjects who received continuous IV sildenafil may explain the higher mortality rate in this group.

Limitations of the present study include its small sample size, which allows only for the detection of large differences between IV groups, and for the performance of univariable analyses, and results in a lack of precision as evidenced by the large confidence intervals. In addition, the higher baseline severity of illness in the group that received continuous IV sildenafil could have confounded our results.

Conclusion:

In conclusion, in this small cohort of critically-ill infants with PH, there were no statistically significant differences in the tolerability of continuous IV sildenafil infusion compared to intermittent IV bolus dosing, based on vital signs before and after initiation, vasoactive infusion requirements, or the need for discontinuation of sildenafil due to side effects. Larger, prospective studies are needed to definitively evaluate the safety and efficacy of the different methods of administration of IV sildenafil.

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