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The Impact of Oral Sildenafil on Retinopathy of Prematurity in Very Preterm Newborns With Early-Onset Pulmonary Hypertension: A Retrospective Cohort Study

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Abstract

Background: Sildenafil, a phosphodiesterase type 5 inhibitor, is increasingly used in neonatal intensive care units (NICUs) to treat pulmonary arterial hypertension in preterm infants.

Objectives: This study aimed to evaluate whether oral sildenafil therapy in very preterm infants with early-onset pulmonary hypertension is associated with the development of retinopathy of prematurity, particularly treatment-requiring (type 1) retinopathy of prematurity.

Methods: We conducted a retrospective cohort study of preterm neonates with a gestational age ≤ 31 weeks and early-onset pulmonary hypertension who were admitted to 2 tertiary NICUs in Tehran between 2017 and 2022. Infants who received oral sildenafil comprised the exposed group, and those managed without sildenafil comprised the unexposed group. Retinopathy of prematurity screening was performed according to national guidelines. Univariable and multivariable Poisson regression models were used to estimate crude and adjusted risk ratios for treatment-requiring (type 1) retinopathy of prematurity.

Results: Of 303 screened neonates, 74 met the inclusion criteria, including 38 sildenafil-exposed infants and 36 unexposed infants. The mean (SD) gestational age was 28.5 ± 1.5 weeks. The overall incidence of retinopathy of prematurity did not differ significantly between the sildenafil-exposed and unexposed groups (68.6% vs 72.2%; P = 0.700). Treatment-requiring retinopathy of prematurity occurred in 26.5% of infants in the sildenafil-exposed group and 27.8% of infants in the unexposed group, with no significant difference between groups (P > 0.99). The incidence of stage 3 retinopathy of prematurity was also similar between groups (8.6% vs 11.1%; P = 0.800). Univariable analysis showed no association between sildenafil exposure and retinopathy of prematurity (crude risk ratio, 0.95; 95% CI, 0.70 - 1.29; P = 0.740), and this association remained nonsignificant after adjustment for relevant clinical covariates (adjusted risk ratio, 1.04; 95% CI, 0.70 - 1.55; P = 0.840).

Conclusions: Early oral sildenafil therapy was not associated with an increased risk of severe retinopathy of prematurity or treatment-requiring retinopathy of prematurity in very preterm infants. Larger prospective studies are warranted to confirm its ocular safety.

Keywords: Sildenafil, Retinopathy Of Prematurity, Premature Newborn, Pulmonary Hypertension

1. Background

Sildenafil, a phosphodiesterase type 5 (PDE5) inhibitor, has been increasingly used in neonatal intensive care units (NICUs) for preterm newborns with pulmonary arterial hypertension (PAH), bronchopulmonary dysplasia (BPD), and persistent pulmonary hypertension of the newborn (PPHN) when nitric oxide is not available (1). When the transition from fetal to neonatal circulation fails, newborns are at risk of developing PAH. The incidence of pulmonary hypertension (PH) in preterm newborns varies widely, ranging from 2% to 42% (2). PH is a complication attributed to various underlying causes, including PH associated with lung disease, most commonly BPD (PH-BPD); PH associated with congenital heart disease (PH-CHD); PH associated with congenital diaphragmatic hernia (PH-CDH); and PPHN (3). The first recommended option for managing PH is inhaled nitric oxide (iNO), but it is expensive and unavailable in many medical

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centers, particularly in low-income countries. Second-line treatments include systemic vasodilators, including PDE5 inhibitors, prostaglandins, PDE3 inhibitors such as milrinone, and endothelin-1 receptor antagonists (3-5). Inhaled nitric oxide has been approved by the Food and Drug Administration as a selective pulmonary vasodilator for treating neonatal PH. However, oral sildenafil is the most accessible drug in resource-limited countries and is prescribed off-label as a therapeutic alternative for PPHN in newborns (6). A recent systematic review published in June 2024 reported that the best choice for managing newborn PPHN is inhaled nitric oxide plus oral sildenafil. If iNO is unavailable in some centers, the best-recommended approach is oral sildenafil plus milrinone (7).

Sildenafil is known to decrease pulmonary vascular resistance by reducing the conversion of cyclic guanosine monophosphate (cGMP) to guanosine monophosphate, resulting in increased cGMP levels (8, 9). In addition, sildenafil is believed to play a key role in nitric oxide-induced pulmonary artery vasodilation, regardless of whether the endothelium is functional, and to enhance the vasodilatory response to exogenous nitric oxide (10, 11). Changes in ocular blood flow after sildenafil treatment have been the subject of substantial debate. Some studies suggest a significant increase in choroidal blood flow, whereas others do not. cGMP accumulation after sildenafil use may have proliferative effects on retinal postcapillary venules.

In addition to its effect on the PDE5 enzyme in the choroidal vasculature, sildenafil can also affect the PDE6 enzyme, which is specific to the retina and is more strongly expressed in rod and cone photoreceptors. Although sildenafil has a lower potency, about one-tenth, for inhibiting PDE6 than PDE5, concerns remain regarding potential complications of sildenafil in immature eyes (12).

Data on the ocular adverse effects of sildenafil in newborns are scarce, and no specific increase in severe retinopathy of prematurity (ROP) has been found (13). However, the increasing use of sildenafil as rescue treatment for preterm neonates with respiratory failure or pulmonary hypertension necessitates further prospective trials to confirm its safety and efficacy.

2. Objectives

This study aimed to evaluate the effect of early exposure to oral sildenafil on the development of ROP in very preterm newborns with early-onset PH.

3. Methods

3.1. Setting

This retrospective cohort study was conducted in the NICU of Shariati Hospital, a tertiary hospital, as the sildenafil-exposed group, and in the NICUs of Imam Khomeini Hospital, a tertiary hospital, as the sildenafil-unexposed group. Both hospitals are affiliated with Tehran University of Medical Sciences. All ROP screening techniques and other ophthalmologic examinations in these 2 hospitals are identical and based on the national protocol.

This study was approved by the Medical Ethics Committee at Tehran University of Medical Sciences (IR.TUMS.TIPS.REC.1399.108).

3.2. Study Design and Population

We conducted a retrospective cohort study of premature newborns with gestational age (GA) ≤31 weeks who were hospitalized in the NICUs of Shariati Hospital and Imam Khomeini Hospital between March 21, 2017, and August 22, 2022. In the neonatal department of Shariati Hospital, oral sildenafil was prescribed for neonates with pulmonary hypertension according to the institutional protocol. Therefore, newborns from this hospital were selected as the sildenafil-exposed group. Imam Khomeini Hospital treats newborns with PAH with drugs other than sildenafil; therefore, newborns from this hospital were selected as the unexposed group. Pulmonary hypertension was managed according to routine institutional care in both hospitals. Neither hospital had access to inhaled nitric oxide during the study period. Imam Khomeini Hospital used conservative management, including sedation, optimization of ventilation, maintenance of adequate oxygenation with a target saturation of 92%-95%, and inotropic support with agents such as milrinone or dobutamine when indicated. Oral sildenafil was added to standard care in Shariati Hospital according to the institutional protocol but was not used in Imam Khomeini Hospital.

The inclusion criteria were neonates with GA ≤ 31 weeks whose early-onset PH was confirmed during the first 2 weeks after birth (2). PH was defined as a tricuspid regurgitation (TR) jet gradient of more than 36 mm Hg in preterm infants (14). In this study, newborns were considered to have PH if echocardiographic reports by the pediatric cardiologist stated systemic or suprasystemic pulmonary artery hypertension, evaluated by TR jet velocity on Doppler ultrasonography. The exclusion criteria were chromosomal anomaly, congenital cyanotic heart disease, noncardiac congenital malformation, death before 28 days after

birth and before the first ROP screening, and absence of PH confirmed by our criteria.

Sildenafil was prescribed for every patient according to the NICU protocol. A 50-mg sildenafil tablet was crushed, diluted in distilled water, and administered to newborns via an oral nasogastric tube at a dose of 1 mg/kg per dose every 6 hours for at least 14 days.

The first ROP screening reports for newborns examined by an ophthalmologist at 28 days of age were retrieved from the records.

This was a retrospective cohort study using a convenience sample of eligible cases from 2 tertiary NICUs during the specified study period (2017 - 2022). Rather than using a prospective power calculation, we conducted a post hoc sample size assessment based on the available cohort. Of 303 consecutive neonates screened for early-onset pulmonary hypertension, 74 met the inclusion criteria, including gestational age ≤ 31 weeks, complete follow-up data, and ROP screening performed according to guidelines. The final sample comprised 38 sildenafil-exposed and 36 unexposed infants.

Post hoc power analysis indicated that, with this sample size and the observed outcome rates (68.6% ROP in exposed infants and 72.2% in unexposed infants), the study could detect a risk ratio of approximately 0.50 (50% risk reduction) with 80% power at $\alpha = 0.05$. Although the study was underpowered to detect the small observed effect (risk ratio, 0.95), it was adequately powered to exclude clinically important protective effects (risk ratio ≤ 0.50) or harmful effects (risk ratio ≥ 1.5) of sildenafil on ROP development.

3.3. Data Collection

Data were collected from the hospitals' databases. Data retrieved from newborns' medical records included neonatal baseline characteristics, first ROP screening reports, duration of respiratory support, noninvasive positive pressure ventilation (NIPPV), invasive mechanical ventilation, BPD, neonatal respiratory distress syndrome (RDS), necrotizing enterocolitis (NEC), sepsis, PPHN, grade III or IV intraventricular hemorrhage (IVH), number of packed cell transfusions, and surfactant volume administered intratracheally. Maternal characteristics, including gestational diabetes mellitus (GDM), preeclampsia, receipt of antenatal steroids, in vitro fertilization (IVF), and age, were also abstracted.

3.4. ROP Screening

The participating medical centers screen for ROP according to the national protocol. Under this national guideline, every preterm newborn younger than 34 weeks of gestational age or weighing less than 2 kg receives an ROP examination by an expert ophthalmologist 4 weeks after birth or at 31 weeks of postmenstrual age, whichever is later. Monitoring continues until newborns reach 50 weeks of GA or complete retinal vascularization (15). Retina specialists examine the infants at the bedside in the NICU, and the ophthalmologist determines treatment based on ROP stage, ROP zone, presence of plus disease, and the need for repeated examinations.

ROP was classified according to the International Classification of Retinopathy of Prematurity. Treatment-requiring ROP (type 1 ROP) was defined by integration of disease stage, retinal zone, and presence of plus disease, as determined by a pediatric retina specialist in accordance with international treatment criteria.

If hospitalized newborns required treatment, they were transferred by ambulance with health care staff to Farabi Hospital, the referral ophthalmology hospital of Tehran University of Medical Sciences. If patients were discharged before the first ROP examination, parents were given a card containing the patient's past medical history and the date on which they should bring the newborn for ROP examination. Stage 3 - 5 ROP was considered severe for descriptive reporting; however, treatment-requiring ROP (type 1) was the primary clinically relevant outcome in this study.

3.5. Statistical Analysis

Study data were collected using case report forms and entered into spreadsheets. The collected data were analyzed according to a prespecified statistical analysis plan based on the study objectives. Descriptive analyses included reporting numerical variables as the mean and standard deviation (SD) or median and interquartile range (IQR), depending on normality as determined by the data distribution and the Shapiro-Wilk normality test. Categorical variables were summarized as frequencies and percentages. The Pearson chi-square test or Fisher exact test was used to examine differences and associations between categorical variables. Mean values of numerical variables were compared across groups using the 2-sample independent t-test; if the assumptions for the t-test were not satisfied, median ranks were compared using the Mann-Whitney U test (Wilcoxon rank sum test). The presence of ROP as the dependent dichotomous outcome in association with sildenafil exposure was assessed using univariable Poisson regression with a log link function. Clinically

relevant confounders and covariates at baseline, including gestational age, sex, birth weight, Apgar score at 1 minute, intubation days, NIPPV days, packed cell transfusions, and amount of surfactant exposure, were included in the multivariable Poisson regression model. Risk ratios and 95% CIs were obtained by exponentiating Poisson regression coefficients using robust standard errors (HC1 sandwich estimator). All statistical tests were 2-sided, and the significance level was set at P = 0.05. Data curation, statistical analysis, and visualizations were performed using R (R Project for Statistical Computing; RRID: SCR_001905), version 4.5.1.

4. Results

Initially, data were collected for 303 newborns with GA ≤ 31 weeks who were admitted to the participating hospitals between March 21, 2017, and August 22, 2022. Of these, 229 neonates did not meet the study criteria and were excluded. Statistical analysis was ultimately performed on 74 patients. Among these infants, 38 received oral sildenafil (exposed group) and 36 did not receive oral sildenafil (unexposed group). The sildenafil-exposed and sildenafil-unexposed groups did not differ significantly in baseline birth weight, sex, or Apgar score at 1 minute, but they differed in gestational age.

Among the 74 newborns (mean gestational age, 28.5 ± 1.5 weeks), infants in the sildenafil-exposed group had higher GA than those in the unexposed group (28.9 ± 1.7 vs 28.1 ± 1.2 weeks; P = 0.017). However, the distribution of extremely preterm infants (≤28 weeks) and preterm infants (>28 weeks) did not differ significantly between the exposed and unexposed groups (P > 0.9). Newborn baseline characteristics are described in Table 1. Neonates in the sildenafil-exposed group required a longer duration of respiratory support than those in the unexposed group. The median (Q1 - Q3) duration of invasive mechanical ventilation was 10.5 (5.0 - 25.0) days in the exposed group versus 5.0 (3.0 - 12.0) days in the unexposed group (P = 0.021). Similarly, the median (Q1 - Q3) duration of NIPPV was 16.0 (10.0 - 29.0) days in the exposed group compared with 3.5 (2.0 - 7.0) days in the unexposed group (P < 0.001).

In addition, the median (Q1 - Q3) number of packed red blood cell transfusions was significantly higher in the sildenafil-exposed group than in the unexposed group (2.0 [1.0 - 3.0] vs 1.0 [1.0 - 2.0]; P = 0.027). There were no significant differences between the 2 groups in the incidence of BPD, NEC, sepsis, or grade III or IV IVH (Table 1).

Details of maternal characteristics are presented in Table 2. Maternal age, gravidity, IVF use, GDM, and receipt of antenatal steroids did not differ significantly between the sildenafil-exposed and sildenafil-unexposed groups. The incidence of preeclampsia was higher in the sildenafil-exposed group than in the unexposed group; however, this difference did not reach statistical significance (39.5% vs 19.4%; P = 0.060).

Table 3 presents the findings of ROP examinations in the sildenafil-exposed and unexposed groups. The overall incidence of ROP was 68.6% in the sildenafil-exposed group and 72.2% in the unexposed group, with no significant difference between the 2 groups (P = 0.700).

The distribution of ROP stages did not differ significantly between the sildenafil-exposed and unexposed groups (P = 0.800). No cases of stage 4 or stage 5 ROP were identified at the initial screening examination.

The distribution of ROP zones differed significantly between the 2 groups (P < 0.001). Zone 2 involvement was more frequent in the sildenafil-unexposed group (88.9% vs 34.3%), whereas zone 3 involvement was more common in the sildenafil-exposed group (60.0% vs 5.6%).

There were no significant differences between the 2 groups in the presence of plus disease or pre-plus disease (P = 0.200). Treatment-requiring ROP occurred in 27.8% of infants in the sildenafil-unexposed group and 26.5% of infants in the exposed group, with no significant difference between the groups (P > 0.99).

The association between sildenafil treatment and ROP was not statistically significant in univariable Poisson regression (crude risk ratio, 0.95; 95% CI, 0.70 - 1.29; P = 0.740). Multivariable Poisson regression adjusted for gestational age, sex, birth weight, Apgar score at 1 minute, intubation days, NIPPV days, packed cell transfusions, and amount of surfactant exposure also showed no statistically significant association (adjusted risk ratio, 1.04; 95% CI, 0.70 - 1.55; P = 0.840) (Table 4). Among the covariates, the number of packed cell transfusions was independently associated with an increased risk of ROP (adjusted risk ratio, 1.25; 95% CI, 1.02 - 1.54; P = 0.033).

5. Discussion

We present the results of a study of preterm newborns admitted to the participating hospitals and treated with oral sildenafil before their first ROP screening. The sildenafil-exposed and unexposed groups did not differ significantly in the incidence of severe ROP (stage ≥ 3). Sildenafil has been approved by the FDA for the management of PAH in adults and children aged 1 to 17 years; however, it is not approved for infants younger than 1 year. In developing countries where iNO

Table 1. Newborn Characteristics and Morbidities [a]

Variables	Overall n = 74)	Sildenafil-Unexposed (n = 36)	Sildenafil-Exposed (n = 38)	P-Value [b]
Gestational age (wk)	28.5 ± 1.5	28.1 ± 1.2	28.9 ± 1.7	0.017
Gestational age categories (wk)				> 0.99
Extremely preterm (≤ 28)	25 (33.8)	12 (33.3)	13 (34.2)	
Preterm (> 28)	49 (66.2)	24 (66.7)	25 (65.8)	
Birth weight (g)	1085 (950, 1290)	1015 (940, 1200)	1213 (950, 1370)	0.088
Gender				0.063
Female	37 (50.0)	22 (61.1)	15 (39.5)	
Male	37 (50.0)	14 (38.9)	23 (60.5)	
Apgar score at 1 min	4.0 (3.0, 6.0)	3.5 (2.5, 5.5)	4.0 (3.0, 6.0)	0.600
Intubation (d)	8.0 (3.0, 17.0)	5.0 (3.0, 12.0)	10.5 (5.0, 25.0)	0.021
NIPPV (d)	9.0 (3.0, 19.0)	3.5 (2.0, 7.0)	16.0 (10.0, 29.0)	< 0.001
PPHN	13 (17.6)	1 (2.8)	12 (31.6)	0.001
BPD	40 (54.1)	19 (52.8)	21 (55.3)	0.800
RDS	60 (81.1)	36 (100.0)	24 (63.2)	< 0.001
Sepsis	54 (73.0)	27 (75.0)	27 (71.1)	0.700
NEC	14 (18.9)	6 (16.7)	8 (21.1)	0.600
Grade III or IV IVH	7 (9.5)	4 (11.1)	3 (7.9)	0.700
Number of packed cell transfusions	2.0 (1.0, 3.0)	1.0 (1.0, 2.0)	2.0 (1.0, 3.0)	0.027
Surfactant, mL	3.8 (3.0, 6.0)	3.0 (3.0, 4.5)	4.0 (3.0, 7.0)	0.200

[a] Values are expressed as mean ± SD, No. (%) or median (Q1, Q3). Abbreviations: NIPPV, noninvasive positive pressure ventilation; PPHN, persistent pulmonary hypertension of the newborn; BPD, bronchopulmonary dysplasia; RDS, respiratory distress syndrome; NEC, necrotizing enterocolitis; IVH, intraventricular hemorrhage.

[b] Wilcoxon rank sum test, Pearson chi-square test, or Fisher exact test.

Table 2. Maternal Characteristics of Neonates [a]

Variables	Overall (n = 74)	Sildenafil-Unexposed (n = 36)	Sildenafil-Exposed (n = 38)	P Value [b]
Age (y)	31.8 ± 6.0	31.7 ± 6.0	31.9 ± 6.1	0.800
Gravidity	2.0 (1.0, 3.0)	2.0 (1.0, 3.0)	1.0 (1.0, 2.0)	0.120
IVF	11 (14.9)	4 (11.1)	7 (18.4)	0.400
GDM	20 (27.0)	13 (36.1)	7 (18.4)	0.087
Preeclampsia	22 (29.7)	7 (19.4)	15 (39.5)	0.060
Receipt of antenatal steroids	41 (55.4)	19 (52.8)	22 (57.9)	0.700

[a] Values are expressed as mean ± SD, No. (%) or median (Q1, Q3). Abbreviations: IVF, in vitro fertilization; GDM, gestational diabetes mellitus.

[b] Wilcoxon rank sum test or Pearson chi-square test.

is unavailable or unaffordable, sildenafil is used off-label as rescue therapy in the NICU for neonatal PH (3). Sildenafil may cause ocular complications in adults, such as visual blurriness, and may affect choroidal perfusion (16). Many studies have evaluated ocular findings associated with sildenafil in term and near-term neonates and have not identified specific adverse effects related to sildenafil use (17-19). However, in 2004, a case report described a very low birth weight newborn born at 26 weeks of gestation and weighing 525 g who was treated with intravenous sildenafil plus inhaled nitric oxide and developed stage 3 ROP requiring laser photocoagulation (20). To our knowledge, the adverse effects of sildenafil in very preterm infants have not been widely investigated to date (21).

Despite a significantly longer duration of respiratory support in the sildenafil-exposed group than in the unexposed group (median [Q1-Q3], 10.5 [5.0 - 25.0] vs 5.0 [3.0 - 12.0] days for invasive mechanical ventilation, P = 0.021; and 16.0 [10.0 - 29.0] vs 3.5 [2.0 - 7.0] days for NIPPV, P < 0.001), the incidence of severe ROP did not differ significantly between groups. One potential explanation is careful oxygen targeting in our NICUs, in which oxygen saturation was maintained at the lower end of

Table 3. Details of Retinopathy of Prematurity Examination Between Study Groups [a]

Variables	Overall (n = 74)	Sildenafil-Unexposed (n = 36)	Sildenafil-Exposed (n = 38)	P-Value [b]
ROP	50 (70.4)	26 (72.2)	24 (68.6)	0.700
ROP stage				0.800
0	21 (29.6)	10 (27.8)	11 (31.4)	
1	23 (32.4)	10 (27.8)	13 (37.1)	
2	20 (28.2)	12 (33.3)	8 (22.9)	
3	7 (9.9)	4 (11.1)	3 (8.6)	
ROP zone				< 0.001
1	4 (5.6)	2 (5.6)	2 (5.7)	
2	44 (62.0)	32 (88.9)	12 (34.3)	
3	23 (32.4)	2 (5.6)	21 (60.0)	
ROP plus				0.200
No	58 (84.1)	31 (88.6)	27 (79.4)	
Yes	8 (11.6)	4 (11.4)	4 (11.8)	
Pre-plus	3 (4.3)	0 (0.0)	3 (8.8)	
Treatment-requiring ROP	19 (27.1)	10 (27.8)	9 (26.5)	> 0.99

[a] Abbreviation: ROP, retinopathy of prematurity.
[b] Pearson chi-square test or Fisher exact test.

Table 4. Results of the Adjusted Multivariable Poisson Regression [a]

Variables	Adjusted Risk Ratio (95% CI)	P-Value
Sildenafil (sildenafil-exposed vs sildenafil-unexposed)	1.04 (0.70 - 1.55)	0.840
Gestational age (wk)	0.95 (0.85 - 1.07)	0.391
Sex (male vs female)	0.79 (0.55 - 1.15)	0.221
Birth weight (g)	1.00 (1.00 - 1.00)	0.612
Apgar score at 1 min	0.98 (0.90 - 1.08)	0.718
Intubation days	1.00 (0.98 - 1.01)	0.622
NIPPV (d)	0.99 (0.98 - 1.00)	0.110
Number of packed cell transfusions	1.25 (1.02 - 1.54)	0.033
Surfactant (mL)	1.00 (0.98 - 1.03)	0.816

[a] Abbreviations: NIPPV, noninvasive positive pressure ventilation; CI, confidence interval. Risk ratios were estimated by multivariable Poisson regression with robust (HC1 sandwich) variance.

the recommended range (91%-92%) rather than the suggested normal range of 91%-95%; however, this hypothesis could not be directly evaluated in the present study (22).

In our study, the incidence of overall ROP was 68.6% in the sildenafil-exposed group versus 72.2% in the unexposed group; this finding is roughly similar to that in the Fang et al. study, which investigated ROP incidence in preterm neonates younger than 30 weeks who were treated with sildenafil (64.7% vs 70.6%). We identified 3 infants with severe ROP (stage 3) in the sildenafil-exposed group. The observed frequency of severe ROP in our cohort was numerically lower than that reported by Fang et al. (23.5%; 4 of 17 patients) (1). In a retrospective case-control study, Aboudi et al. evaluated ROP in very low birth weight preterm newborns with BPD treated with sildenafil and reported a higher prevalence of severe ROP in the sildenafil group than we observed in the sildenafil-exposed group (26% [6 of 23 newborns] vs 8.6% [3 of 38 newborns]); however, the mean GA in their study was lower than that in our study (25 ± 1 weeks vs 28.5 ± 1.5 weeks) (23). One possible explanation for the lower observed frequency of severe ROP in our cohort may be the lower oxygen saturation targets used in our NICU protocol (91%-92%), although this association cannot be confirmed based on the present data, and more prospective trials are necessary.

Similar to our study, Samiee-Zafarghandy et al. investigated the effect of early exposure to sildenafil on ROP in very low birth weight newborns and found no difference in severe ROP associated with sildenafil therapy (12). In addition, Dehdashtian et al. conducted a clinical trial in Iran among 102 preterm newborns with GA under 30 weeks, which showed that the association between ROP and sildenafil was not significant; they reported stage 1 and 2 ROP in the sildenafil group (14%; 7 of 52) and placebo group (22%; 11 of 50), without any stage 3 ROP, which was lower than our results for stage 1 and 2 ROP (60% in the sildenafil group and 60.1% in the placebo group). They also reported that most ROP in the sildenafil group was in zone 3 (71.5%), whereas most ROP in the placebo group was in zone 2 (55%). Similar to our findings, 60% of the sildenafil group showed ROP in zone 3 and 88.9% of the control group showed ROP in zone 2. Despite treatment, the outcome for neonates with ROP in zone 1 is not satisfactory. We had 2 patients in each group (24).

Previous studies have reported an association between blood transfusion and ROP. In our adjusted multivariable analysis, a greater number of packed cell transfusions was independently associated with an increased risk of ROP (adjusted risk ratio, 1.25; 95% CI, 1.02 - 1.54; P = 0.033). In a 2020 systematic review, Zhu et al. reported that blood transfusion was significantly associated with ROP among preterm newborns, particularly in infants with gestational age under 32 weeks (odds ratio, 1.77; 95% CI, 1.29 - 2.43) (25). Many studies have investigated the correlation between blood transfusion and ROP, but findings are controversial; some studies agree (26-29), whereas others disagree (30). Although packed cell transfusions were identified as an independent predictor of ROP in our cohort, sildenafil exposure was not significantly associated with ROP after adjustment for potential confounders.

5.1. Study Limitations

This study has several limitations. First, due to institutional treatment protocols, the exposed and unexposed groups were drawn from 2 different hospitals. At Shariati Hospital, oral sildenafil is routinely used to manage early-onset PH, whereas Imam Khomeini Hospital follows a protocol that excludes sildenafil. This setting-based allocation may introduce residual confounding related to institutional differences in care practices.

Second, the small sample size limited the statistical power of our analysis. Because oral sildenafil use in the study setting was protocol dependent and severe ROP was a rare outcome, a formal a priori sample size calculation was not feasible, and the study relied on a convenience sample of all available eligible infants during the study period. As a result, the study may be underpowered to detect small true differences in the association between sildenafil exposure and ROP risk, and the possibility of a type II error cannot be excluded. These findings should be considered exploratory and hypothesis generating, highlighting the critical need for larger prospective studies to establish the ocular safety profile of sildenafil in very preterm infants with early-onset pulmonary hypertension.

Third, although there was a statistically significant difference in gestational age between groups, we did not perform matching or stratified analyses due to the limited sample size. Instead, gestational age was included as a covariate in the multivariable model to adjust for its potential confounding effect.

5.2. Conclusions

In this retrospective cohort study, early exposure to oral sildenafil was not associated with an increased risk of ROP, including severe or treatment-requiring ROP, in very preterm infants with early-onset PH. However, given the study's limited sample size and potential institutional confounding, these findings should be considered exploratory, and larger prospective studies are required to confirm these observations.

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Footnotes

AI Use Disclosure: The authors declare that no generative AI tools were used in the creation of this article.

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