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Comparative Efficacy of Low Dose vs High Dose Sildenafil in Treatment of Pulmonary Hypertension in Neonates

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ABSTRACT

Background: Persistent Pulmonary Hypertension of the Newborn (PPHN) is a life-threatening condition caused by increased pulmonary vascular resistance, leading to right-to-left shunting of blood and severe hypoxemia. **Objective:** To compare the efficacy of low dose sildenafil with that of high dose in treatment of PPHN. **Methods**: This experimental study was conducted at the Neonatology Department of the Children's Hospital and University of Child Health Sciences, Lahore. 60 neonates diagnosed with PPHN within the first week of life were enrolled. Patients were administered sildenafil orally, starting at 0.5 mg/kg every six hours. The dose was gradually titrated to 2 mg/kg based on oxygen saturation and clinical stability. Key outcomes included improvements in oxygen saturation, echocardiographic measures, and the incidence of adverse effects. **Results**: Sildenafil treatment significantly improved oxygen saturation in neonates with pulmonary hypertension. The Wilcoxon Signed-Rank Test showed a statistically significant increase in oxygen saturation after treatment. A Mann-Whitney U Test comparing low-dose (0.5 mg/kg) and high-dose (2 mg/kg) groups revealed no significant difference in post-treatment oxygen saturation ($p = 1.000$). The Spearman's Rank Correlation test confirmed no correlation between sildenafil dose and oxygen saturation before ($\rho = 0.000$, $p = 1.000$) or after treatment ($\rho = 0.000$, $p = 1.000$). Additionally, a Chi-Square test found no significant relationship between sildenafil dose and side effects such as hypotension, hypokalemia, anemia, or bradycardia, with all p-values greater than 0.05. **Conclusion**: Sildenafil effectively increases oxygen saturation in neonates with pulmonary hypertension. Results indicate that increasing sildenafil dose does not provide additional benefits in oxygen saturation or in reducing side effects, supporting the use of lower doses in clinical practice.

INTRODUCTION

Persistent pulmonary hypertension of the newborn (PPHN) is a commonly seen disease in neonate. PPHN is defined as increased vascular resistance (PVR) leading to right to left shunting of blood.[1] The incidence of PPHN ranges from 0.4 to 2 per 1000 live births, and mortality rate is 11%, worldwide. [2] The mean pulmonary arterial pressure (mPAP) in babies with PPHN is more than 25mmHg. Normally it takes two months to achieve mPAP less than 25mmHg by pulmonary vascular transition, allowing increasing pulmonary blood flow after birth.[3] Risk factors for PPHN are related to lung diseases (meconium aspiration, respiratory distress syndrome or pneumonia), heart diseases (TAPV or TGA), miscellaneous (birth asphyxia, sepsis).[1] This condition presents with respiratory distress, cyanosis, tachycardia, loud second heart sound and difference >5% between preductal and postductal oxygen saturation.[4] PPHN is exclusively a diagnosis of exclusion, with echocardiography being the gold standard for diagnosis.[4] A newborn is said to have pulmonary hypertension when at least two of the following four criteria are present : 1- Systolic pulmonary arterial pressure more than 2/3 of systolic systemic pressure (echo), 2- RV dilatation /septal displacement , RV dysfunction, +/-left ventricular dysfunction, 3- Pre-post ductal SPO2 difference more than10%. 4)01 more than 20.[3]

Many drugs are currently in use for treatment of pulmonary hypertension. One of them is sildenafil. It affects the vessels and cause increase in nitric oxide (NO). Increased nitric oxide (NO) will increase cGMP, and this ultimately will cause vasodilation. Sildenafil thus has shown to be effective and important oral drug for PPHN.[5] It improves oxygenation index, decreases pulmonary arterial pressure and has no significant side effect.[6] Some of the side effects are hypotension, hypokalemia, anemia, drug withdrawal syndrome, and bradycardia.[7] Sildenafil along with other vasodilator agents (milrinone, benprost)

are alternatives treatment and provide effective rescue therapy. [8] Sildenafil is available in oral form and intravenous form.[9] But in Pakistan it is available in oral form only. Studies showed that Sildenafil had significant effect on lowering pulmonary hypertension in children whereas in some patients who didn't respond to Sildenafil alone, a combination with bosentan or benprost showed improvement.[10, 11] Sildenafil is administered orally with a dose of 0.5mg to 2mg/kg/dose every 6 hourly, with maximum dose of 12mg/kg/day.[12]

The importance of this study lies in its potential to improve the management of pulmonary hypertension in neonates, a condition that can lead to severe complications and even death if not effectively treated. Pulmonary hypertension is a significant cause of morbidity and mortality in neonates, and sildenafil has shown promise as a therapeutic option. By evaluating the effective dose of sildenafil, this study aims to provide critical insights into its safety and efficacy in neonates, ensuring that clinicians can make informed decisions about its use. Furthermore, this study may help refine treatment protocols, optimizing dosages to maximize therapeutic benefits while minimizing risks. Identifying the most appropriate dose of sildenafil for neonates could lead to improved clinical outcomes, including better pulmonary function, reduced hospital stays, and overall enhancement in quality of life for affected infants.

METHODOLOGY

Our study is an experimental study conducted at Neonatology Department of The Children's Hospital and University of Child Health Sciences, Lahore, from August 2023 to August 2024. 60 patients diagnosed with PPHN in the first week of life were included in our study. The inclusion criteria for this study are as follows: newborns who are born at or after 34 weeks of gestational age will be included. Additionally, neonates diagnosed with pulmonary hypertension, as confirmed by echocardiography and meeting the specified diagnostic criteria, will also be the part of the study population.

On the other hand, the exclusion criteria are: neonates with cardiac anomalies that are expected to require corrective surgery within the first few months of life; those with renal anomalies, particularly in cases where there is an antenatal history of oligohydramnios; neonates with severe skeletal or orthopedic deformities that may impact thoracic or lung development; those with severe central nervous system anomalies; neonates born before 34 weeks of gestational age; and infants whose parents refuse to provide consent for participation in the study. The neonates were randomized in two groups (group 1) and (group 2) using online software https://www.randomizer.org . Concealment of allocations was done by using a serially numbered opaque sealed envelope. Procedure operators and care providers were not blinded due to nature of the treatment. After randomization of patients diagnosed with PH in the first week of life, the patients allocated to one of the two study groups. One group (group A) will receive the low dose 0.5mg/kg/day sildenafil per orally/ OG, second group (group B) will receive high dose 2mg/kg/day orally/OG. The treatment of all patients was started with sildenafil low dose 0.5mg/kg orally. Dose was gradually increased and titrated to high dose 2mg/kg orally/OG depending on the saturation and respiratory rate. Minimum eight doses given with repeat echo after 8 doses. The principal outcomes include improvement in SP02 (91-95%), hemodynamic stability and echocardiographic measurements (improvement in pulmonary hypertension), as well as adverse outcomes.

Data entry and analysis was done with SPSS version 25. Quantitative variables were presented with mean±SD and qualitative variables were presented with frequency and percentage. Oxygen saturation before and after treatment with group and between groups was compared with Mann Whitney U test and Wilcox signed ranked test. P-value <0.05 was taken statistically significant. A Spearman's Rank Correlation further used to analyze the relationship between sildenafil dose and oxygen saturation levels. Chi Square test was used to compare treatment outcome between two groups.

RESULTS

Sildenafil, a phosphodiesterase type 5 (PDE5) inhibitor, has been used to increase oxygen saturation in the neonate patients having pulmonary hypertension. Wilcoxon Signed-Rank Test: this test is done to determine if there was an improvement in oxygen saturation after the administration of sildenafil, a Wilcoxon Signed-Rank Test was done. The results showed a Z-value of -6.769 and a p-value of 0.000, showing a statistically significant improvement in oxygen saturation ($p < 0.05$). This ensures that sildenafil treatment effectively increased oxygen saturation levels. The before treatment median oxygen saturation was 79%, which improved to 93% after treatment. The statistical significance of this improvement suggests that sildenafil have an important role in increasing the oxygen delivery in patients with pulmonary hypertension. A Mann-Whitney U Test was run to compare the after-treatment oxygen saturation between the two groups which are the low-dose (0.5 mg/kg) and high-dose (2 mg/kg) groups. The findings specified a Mann-Whitney U value of 450.000, Wilcoxon W value of 915.000, and a p-value of 1.000. Because of the p-value is greater than 0.05, we can say that there is no statistically significant difference between the two groups. This explains that increasing the sildenafil dose does not show any additional increase in oxygen saturation. Two groups having different dose had a median oxygen saturation of 93% after treatment, confirming the point that an increasing the dose does not necessarily get the better outcomes. The boxplot shows the comparison of after-treatment oxygen saturation levels between the low and high dose sildenafil groups (Graph 1). The almost identical distributions in the boxplot conclude that the two groups had same oxygen saturation outcomes, strengthening the findings that increasing sildenafil dose did not provide any additional benefit.

A Spearman's Rank Correlation further analyzes the relationship between sildenafil dose and oxygen saturation levels. The results show that sildenafil dose is not correlated with oxygen saturation before or after treatment ($p = 1.000$). However, oxygen saturation before and after treatment were perfectly correlated ($\rho = 1.000$, p

< 0.001), explaining that all patients showed improvement in oxygen saturation, no matter what sildenafil dose is given (Table1).

Graph 1

Boxplot of Oxygen Saturation after Group Assignment

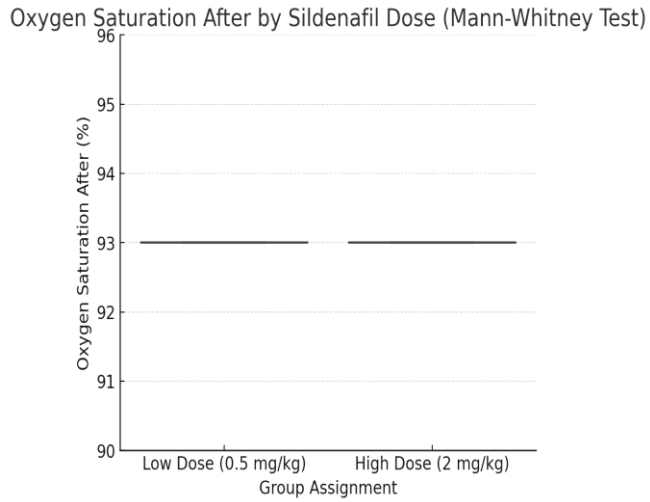


Table 1

Spearman's Rank Correlation Test Revealing the Relationship between Sildenafil Dose and Oxygen Saturation Levels

Variable Pair	Spearman's rho	p-Value	Conclusion
Sildenafil Dose vs. Oxygen Before	0.000	1.000	No Correlation
Sildenafil Dose vs. Oxygen After	0.000	1.000	No Correlation
Oxygen Before vs. Oxygen After	1.000	0.000	Perfect Correlation

To find out the Association between Group Assignment and Side Effects a Chi-Square Test was performed to assess if there is a significant relationship between sildenafil dose (low-dose vs. high-dose) and the appearance of side effects like hypotension, hypokalemia, anemia, and bradycardia. The results we get are as all p-values are more than 0.05; the results show no statistically significant relationship between sildenafil dose and the occurrence of side effects (Table 2). This means that both the low-dose and high-dose groups had an equal chance of having side effects and increasing the dose did not increase or decrease the risks of side effects.

Table 2

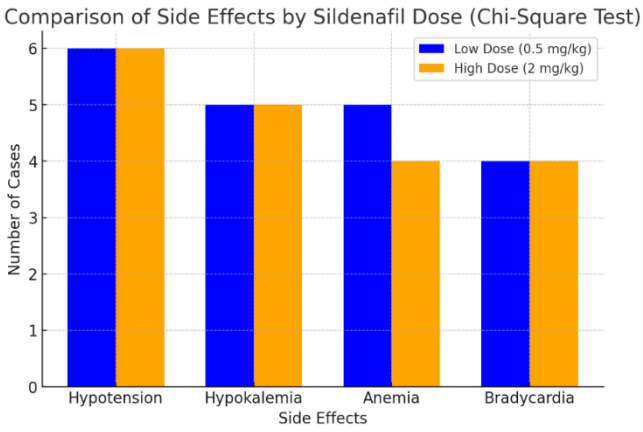
Relationship between Sildenafil Dose and the Occurrence of Side Effects

Side Effect	Pearson Chi-Square	p-Value	Conclusion
Hypotension	0.000	1.000	No Significant Association
Hypokalemia	0.000	1.000	No Significant Association
Anemia	0.131	0.718	No Significant Association
Bradycardia	0.000	1.000	No Significant Association

Chi-Square test findings, indicating that sildenafil dose are not linked to an increased risk of adverse effects. The bars show that the occurrence of hypotension, hypokalemia, anemia, and bradycardia is almost the same in both the low-dose and high-dose groups (Graph 2).

Graph 2

The Frequency of Side Effects in Two Groups



DISCUSSION

The findings from this study provide valuable insight into the effectiveness and safety of sildenafil in treating neonatal pulmonary hypertension, specifically in terms of improving oxygen saturation levels and its potential impact on side effects across varying doses. The results of the statistical analyses confirm the positive impact of sildenafil on oxygen saturation but previous study suggest that increasing the dosage does not provide any additional benefit in terms of oxygen delivery or the incidence of side effects.[9] The Wilcoxon Signed-Rank Test revealed a statistically significant improvement in oxygen saturation after sildenafil treatment, with a notable increase from a median pre-treatment value of 79% to 93% post-treatment. This finding underscores the efficacy of sildenafil in improving oxygen saturation in neonates with pulmonary hypertension. The extremely low p-value (0.000) supports the conclusion that the observed improvement in oxygen saturation was not due to random chance but is a real effect of the treatment. Sildenafil's role in enhancing oxygen delivery is therefore confirmed as significant, contributing to its utility as a therapeutic agent for neonates suffering from pulmonary hypertension.[13]

Interestingly, the results from the Mann-Whitney U Test, which compared oxygen saturation levels between low-dose (0.5 mg/kg) and high-dose (2 mg/kg) groups, showed no statistically significant difference in post-treatment oxygen saturation between the two groups (p = 1.000). Both groups had identical median oxygen saturation values of 93% after treatment, suggesting that increasing the sildenafil dose beyond the low dose does not provide additional therapeutic benefits. This lack of dose-response relationship is important because it indicates that a higher dose does not necessarily lead to better outcomes for oxygen saturation in these patients. Thus, a lower dose of sildenafil may be equally effective, which could be beneficial in minimizing the risk of potential side effects and reducing healthcare costs.[14]

The Spearman's Rank Correlation analysis further reinforced the conclusion that sildenafil dose did not correlate with changes in oxygen saturation, both before and after treatment. With a rho value of 0.000 and p-value of 1.000 for both pre- and post-treatment oxygen saturation, the results strongly suggest that sildenafil dose does not influence oxygen saturation outcomes. The

perfect correlation between oxygen saturation before and after treatment ($\rho = 1.000$, $p < 0.001$) indicates that the improvement in oxygen saturation was consistent across all patients, regardless of the dose administered. This finding further highlights that the efficacy of sildenafil in improving oxygen saturation is not dose-dependent and supports the use of lower doses to achieve the desired therapeutic effect as seen in previous studies.[15,16]

In addition to examining oxygen saturation, this study also explored the association between sildenafil dose and the occurrence of side effects. The Chi-Square test results showed no significant association between sildenafil dose and the incidence of common side effects, such as hypotension, hypokalemia, anemia, or bradycardia. With p-values greater than 0.05 for all side effects, we can conclude that both low-dose and high-dose groups experienced similar rates of side effects. This finding suggests that increasing the dose of sildenafil does not elevate the risk of adverse events, making it a safe treatment option regardless of the dose used however; higher doses of sildenafil were found to be associated with higher mortality.[17,18] One analysis showed that utilizing 80 mg and 20 mg doses, there were no appreciable changes were found in terms in mortality, clinical deterioration.[19] Graphical representations of these findings, particularly the boxplot and bar chart, provide a clear visual understanding of the results. The boxplot illustrates the similarity in post-treatment oxygen saturation between the low and high-dose groups, reinforcing the statistical conclusion that dose escalation does not improve oxygen saturation outcomes. Similarly, the bar chart highlights the comparable frequency of side effects in both groups, confirming the Chi-Square test results that sildenafil dose is not associated with increased risk of side effects. One review has included three trials, documented that usage of sildenafil was associated with lower death rate when compared to placebo. Studies that contrasted sildenafil with other drugs or used it in conjunction with other therapies, however, did not demonstrate statistically significant reduction in mortality. Oxygen levels were improved more by sildenafil than by a placebo. Safety concerns were not raised by any of the studies. Still, only small number of infants was included in this research, and many of them were carried out in environments where access to alternative treatments was restricted.[20] In comparison to lower doses 0.3mg/k- 1.0mg/kg, dose of 1.5 mg/kg dramatically reduced pulmonary artery systolic pressure and enhanced oxygenation indices in neonates, according to meta-analysis with no observed difference in side effects was noted.[21] Numerous studies that looked at sildenafil and neonates found no serious side effects, indicating that it is safe to use in this age group.

This study has certain limitations that need to be addressed. Small sample size, single centered study will affect the results implications on wide range of population. Furthermore, we have not studied patients according to PAH severity. Further research will be needed to cover these aspects.

CONCLUSION

This study highlights the effectiveness of sildenafil in improving oxygen saturation in neonates with pulmonary hypertension. However, the results also suggest that increasing the sildenafil dose does not offer any additional benefits in terms of oxygen saturation or the incidence of side effects. Based on these findings, clinicians may consider using lower doses of sildenafil, as they are equally effective in improving oxygen saturation and are associated with a similar safety profile compared to higher doses. Further research with larger sample sizes and long-term follow-up may help to better understand the optimal dosing strategy and any potential long-term effects of sildenafil treatment in neonates.

Author Contribution

Dr Hafiz Zeekash Ur Rehman Malik: Conception and designing of the study
Muhammad Shahzad: Data analysis and interpretation
Javaria Younus: Drafting of the article
Dr Mayda Riaz: Critical appraisal of findings with literature search
Professor Dr Farah Haron: Critical revision for important intellectual content
Dr Bushra Tariq: Write up of manuscript

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