

ORIGINAL ARTICLE

Role of Sildenafil in the Treatment of Persistent Pulmonary Hypertension of Newborn (PPHN) - Should it Be Withdrawn from Market of Bangladesh due to Threat of being Misuses

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Abstract

Background: Recently it has been apprehended that sildenafil, a drug which has been successfully using in the treatment of PPHN and erectile dysfunction in adult, is going to be withdrawn from the market of Bangladesh due to threat of its misuses.

Objective: The aim of this study was to see the extent of uses of sildenafil in the treatment of PPHN and importance of availability of this drugs in the market in spite of its probable misuses.

Methods: This cross sectional study was conducted in neonatal intensive care unit (NICU), special baby care unit (SCABU) and cardiac intensive care unit (CICU) of Dhaka Shishu (Children) Hospital from June, 2017 to May 2018. Neonates with PPHN were enrolled in the study. All cases were treated with oral sildenafil for PPHN along with others management according to hospital protocol. Data along with other parameters were collected and analyzed.

Results: Total 320 patients with suspected PPHN were admitted during the study period. Among them 92 (29%) cases had PPHN. Male were 49 (53%) cases and female were 43 (47%) cases. Mean age at hospital admission was 29.7 ± 13.4 hours. Based on echocardiography, 13 (14%) cases had mild, 38 (41%) cases moderate and 41 (45%) cases severe PPHN. Mean duration of sildenafil therapy was 11.9 ± 7.1 days. Improved from PPHN were 83 (90%) cases. Mortality was 10% (9).

Conclusion: In this study it was found that the incidence of PPHN is 29% among the suspected newborns. Sildenafil is successful in improving the oxygenation of PPHN and to decrease the mortality of neonates.

Key words: Sildenafil, PPHN.

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Introduction

Persistent pulmonary hypertension in newborn (PPHN) occurs in as many as 6.8 of 1000 live births. It is likely to be much more in developing countries, where little data is available.¹ Mortality is 10% to 20% with high-frequency ventilation, surfactant, inhaled nitric oxide, and extracorporeal membrane oxygenation but it is much higher when these therapies are not available.²

Nitric oxide alone does not appear to be a solution to the problem. Upto 30% infants fail to improve despite nitric oxide.³ The cost of its use is prohibitive. Also inhaled nitric oxide has the ability to displace oxygen and bind to hemoglobin forming methemoglobin, thereby further reducing the oxygen carrying capacity of blood. The availability of extracorporeal membrane oxygenation (ECMO), even in developed countries, is limited to few specialist centers and almost always involves transport of a very sick baby to the nearest available centre. ECMO as an option is almost nonexistent in developing countries.¹

The role of sildenafil in the treatment of PPHN was first reported in the lay press way back in 2002.⁴ There were a few who felt that the use was justified⁵ as there were no other options for the attending neonatologist in face of non-availability of inhaled nitric oxide and ECMO. There have been published reports of its usefulness in adult cardiac patients as well as in animal models, prior to its use in newborns.^{6,7} Since then there have been many more case reports and some small randomized studies regarding the use of sildenafil in babies with severe PPHN. The drug is now frequently being used in many centers in Bangladesh and other developing countries where the availability of high frequency ventilation, nitric oxide (iON) and ECMO is extremely limited.¹

The management strategies for PPHN must include optimization of ventilation, fluid, electrolyte and acid base balance along with the maintenance of blood pressure. Oral sildenafil can be a useful adjunct to the treatment of PPHN. It can also be used in conjunction with nitric oxide to facilitate quicker weaning off nitric oxide.⁸

Recently it is apprehended that sildenafil is going to be withdrawn from the market of Bangladesh due to threat of its misuse. But it has great role to reduce neonatal mortality and morbidity from PPHN. The aim of this study was to see the extent of use of sildenafil in the treatment of PPHN in neonates and importance of availability of this drugs in the market inspite of its probable misuses.

Materials and Methods

This cross sectional study was conducted in neonatal intensive care unit (NICU), special baby care unit (SCABU) and cardiac intensive care unit (CICU) of Dhaka Shishu (Children) Hospital from June, 2017 to May, 2018. Among the PPHN cases 20(21%) were managed in NICU, 42(46%) in CICU and 30(33%) in SCABU. All admitted patients with or without respiratory distress, presented with cyanosis that was not improved after oxygen therapy ($\text{FiO}_2 > 40\%$) and/or with murmur and/or with difference in pre-post ductal oxygen saturations of more than 15%⁹, were suspected and evaluated for PPHN by echocardiogram. Clinical features of cardiac problems were included for suspicion of PPHN as it is sometimes associated with PPHN. Then neonates including term and preterm who had hypoxemia and pulmonary hypertension confirmed by echocardiogram were taken as cases. The neonates having moderate to severe PPHN and need FiO_2 100% were selected for sildranafil therapy. Besides, the neonates with mild PPHN and having respiratory distress with oxygen requirement $> 40\%$ with comorbidity including meconium aspiration syndrome (MAS), respiratory distress syndrome (RDS), pneumonia, perinatal asphyxia and culture positive sepsis were also given sildranafil. Neonates whom pulmonary pressure fall below 25% during sildenafil therapy were considered as improvement and neonates who required $> 40\%$ oxygen having respiratory distress with comorbidity when decreased oxygen need and respiratory distress were considered as improvement. Discontinuation of sildenafil was done when mild pulmonary pressure achieved and in mild PPHN cases when distress and oxygen requirement decreased ($< 40\%$ of FiO_2). All cases were monitored in hospital and repeated echocardiogram was done to see the

pulmonary pressure. Few patients discharged with moderate PPHN without having distress and needed extra oxygen, and were followed up for discontinuation of sildenafil. All patients were managed as per hospital protocol even in case of sildenafil. Doses of sildenafil were 2mg/kg/day 3 times daily and decreasing the doses when response occurred. Data regarding number of cases getting sildenafil, improved from PPHN and mortality along with other parameters were collected and statistical analysis were done by using SPSS version-17.

Results

Total 320 patients with suspected PPHN admitted during the periods of July 2017 to June 2018 in Dhaka Shishu (Children) Hospital. Among them 92 cases (29%) cases were PPHN. Male were 49(53%) cases and female were 43(47%) cases. Mean gestational age was 37.5±1.9 wks. Term baby was 59 (64%) and Preterm was 33 (36%) cases. Mean weight was 2718.3±450.4 gms. Mean age at hospital admission was 29.7±13.4 hours (Table-I).

Sex	
Male	49(53%)
Female	43(47%)
Gestational age (mean±SD)	37.5±1.9 wks
Term	59(64%)
Preterm	33(36%)
Birth weight (mean±SD)	2718.3±450.4gms
Age at admission ((mean±SD)	29.7±13.4 hours

Associated conditions were present in 29(32%) cases. These were perinatal asphyxia (9,10%), meconium aspiration syndrome (7,8%), respiratory distress syndrome (3,3%), pneumonia (3,3%) and culture positive sepsis (7,8%) (Table II).

Associated condition	Number (%)
Meconium aspiration	7(8)
Respiratory distress syndrome,	3(3)
Perinatal asphyxia	9(10)
Pneumonia	3(3)
Culture positive sepsis	7(8)
Total	29(32)

Based on echocardiogram, 13(14%) cases had mild, 38 (41%) cases moderate and 41(45%) cases severe PPHN (Table III).

Grading (Pulmonary pressure)	Number (%)
Mild (<36-45mmHg)	13(14)
Moderate (46-60mmHg)	38(41)
Severe (>60mmHg)	41(45)

Mean duration of sildenafil therapy was 11.966±7.1 days. Among the studied neonates with PPHN 90% (83/92) were improved. Mortality was 10% (92) (Table-IV, Table-V).

Duration of therapy (days)	Mean ±SD
Total	11.9±7.1
Cases in SCABU	7.1±1.6
Cases in NICU+CICU	14.5±7.5

Outcome	Number (%)
Improved	83 (90)
Death	9 (10)

Discussion

Total 320 admitted cases were evaluated for PPHN. Among them 92 (29%) cases had PPHN. In different study it was shown that the incidence of PPHN in as many as 6.8 of 1000 live births.² Rate is high in this study as only suspected cases were analyzed, not among all sick neonates.

In this study male were 49 (53%) cases and female were 43(47%) cases. In the study of Hernando et al² the male was 57% and female was 43%. Mean gestational age was 37.5±1.9 wks in this study and it was found 38.4 ±2.6 wks by Hernando et al². In this study term baby was 59 (64%) and preterm was 33 (36%) cases. In other study 72% patients were term and 28% cases were near term (35-37 weeks).⁹ Mean birth weight was found 2718.3±450.4gms in this study and Hernando et al² found mean weight 2803±617 gms in their study. In this study mean age at hospital admission was 29.7±13.4 hours. In the study of Hernando et al² they showed that the median age of the 13 infants at the time of entry was close to 25 hours (range: 3-72 hours).

In this study associated conditions were present in 29(32%) cases. These were perinatal asphyxia (9,10%), meconium aspiration syndrome (7,8%), respiratory distress syndrome (3,3%), pneumonia (3,3%) and culture positive sepsis (7,8%). In the study of Ali et al⁹ associated conditions were respiratory distress syndrome 5(28%), meconium aspiration syndrome 5(28%) pneumonia 1(5.6%) and Hernando et al² found meconium aspiration, in 57%% cases and respiratory distress syndrome in 43% cases.

Based on echocardiogram, 13(14%) cases had mild, 38 (41%) cases moderate and 41(45%) cases severe PPHN in this study whereas in the study of Ali et al⁹ it was found that 17% patients had mild, 28% moderate and 55% severe PPHN.

In this study mean duration of sildenafil therapy was 11.966±7.1 days and it was 12.6 days in study of Ali et al⁹. In this study 83 (90%) cases were improved from PPHN and the mortality was 10% (9). Ali et al² showed in their study that mortality was 33%.

Recently it has been apprehended that sildenafil is going to be withdrawn from the market of Bangladesh due to threat of its misuses despite its

successful use in PPHN and erectile dysfunction in adult. Since sildenafil is easily available and convenient to administer, it has the potential for inappropriate use. This drug is the most commonly used 5 Phosphodiesterase (PDE5) inhibitor and the most commonly misused PDE5 inhibitor. Studies have reported the increasing misuse of unprescribed sildenafil for enhancing sexual performance among college going males, night clubbers and illicit drugs users. It is used along with other recreational agent like cocaine, amphetamine, marijuana, testosterone, steroids etc. Athletes also abuse sildenafil for enhancement of on-field performance.¹¹⁻¹⁸

All this misuses occurred in other countries specially developed countries. At present there is no definite data regarding misuse of this drugs in Bangladesh. But threat of misuse of this drug is present. Sildenafil has great role to reduce neonatal mortality and morbidity from PPHN that has also seen in this study. As at present no alternative treatment like inhaled nitric oxide and ECMO are available to treat this disease, it should be available in market to ensure the treatment of PPHN inspite of threat of its misuses.

Though the misuse of sildenafil is not so many in Bangladesh, nevertheless it is the time to take measurement against its abuse. Here is the some way of prevention of misuse of this drug. Firstly prepare tablets in small doses (5mg/10mg). Secondly dispensing should be done by only prescriptions from registered, qualified physicians. Thirdly small amounts (5 to 10 tablets at a time) should be dispensed for a particular patient. Fourthly stocks of pharmacies should be checked time to time and regulated, and finally create public awareness.

Conclusion

In this study it was found that the incidence of PPHN is 29% among the suspected newborns. Sildenafil is successful in improving the oxygenation of PPHN and to decrease the mortality of neonates. This drug is essentials in the management of PPHN and thereby to reduce neonatal mortality. At this time alternative drugs are not available to treat this disease in Bangladesh. So sildanafil should be available in the market and necessary actions should be taken to prevent its misuses as well.

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