ORIGINAL ARTICLE

COMPARISON OF THE EFFICACY OF SILDENAFIL ALONE VERSUS SILDENAFIL PLUS BOSENTAN IN NEWBORNS WITH PERSISTENT PULMONARY HYPERTENSION

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Background: Persistent pulmonary hypertension is a serious disease among new-borns. Inhaled nitric oxide is first line of therapy along with extracorporeal membrane oxygenation. Pulmonary vasodilators such as sildenafil, bosentan and milrinone are also used to treat persistent pulmonary hypertension especially in resource limited centres where inhaled nitric oxide is not available. The objective of this study was to compare the effect of sildenafil alone and sildenafil with bosentan on severity of tricuspid regurgitation and duration of hospitalization in new-borns with persistent pulmonary hypertension. **Methods:** This was single blinded clinical trial conducted at The Children's Hospital & the Institute of Child Health, Multan, Pakistan, from July 2016 to December 2016. New-borns with pulmonary hypertension were admitted and divided into two groups. Group A was treated with sildenafil (2mg per kg per dose three times a day) and group B with both sildenafil (2 mg per kg per dose three times a day) and bosentan (1 mg per kg per dose twice a day). **Results:** There were 50 new-borns in each group. The mean age, sex distribution and baseline TR measurement (mmHg) at the time of admission was similar in both the groups. Measurement of TR (mmHg) after 72 hours admission was significantly less in Group B as compared to group A (11±4.62 versus 23±4.78), *p*-value<0.0001. The mean duration of hospital stays (days) was 10.12±5.20 in group A and 7.56±3.77 in group B (*p*-value <0.0001). There was no mortality in any group and no case of hypotension in both groups. **Conclusion:** The combined use of sildenafil and bosentan is more effective than sildenafil alone for control of pulmonary hypertension in resource limited centres.

Keywords: Persistent pulmonary hypertension; Sildenafil; Bosentan; Echocardiography

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INTRODUCTION

Persistent pulmonary hypertension of new-born (PPHN) is "a disease characterized by failure to achieve or sustain the normal decrease in pulmonary vascular resistance".[1] Shah PS *et al* reported "an incidence of 1.9 per 1000 live births (0.4–6.8/1000 live births) and associated death rate of 4–33%".[2]

Placenta is the organ of gaseous exchange in foetal life that requires pulmonary hypertension as a physiologic phenomenon for its normal functioning. Pulmonary vascular resistance is raised in comparison with systemic or postnatal pulmonary pressures of the foetus. This state of foetus allows shunting of umbilical blood that is oxygenated to left atrium through the foramen ovale, from where it bypasses the lungs by way of ductus arteriosus to descending aorta, only 5–10% of biventricular output flows into the lungs.[3] Many pathways play their part in maintaining high pulmonary vascular tone before birth. Normal fetus has pulmonary vasoconstrictors like endothelin-1, leukotrienes, Rho kinase and low oxygen tension. Low basal production of vasodilators such as prostacycline and nitric oxide[4] also promote vasoconstriction.

The failure of cardiopulmonary transition in new-born results in PPHN. It is characterized by one of these pathologic pathways:

1. Structurally normal but abnormally constricted vasculature due to lung parenchymal diseases such as in meconium aspiration syndrome (MAS), respiratory distress syndrome (RDS) or pneumonia (maladaptation)
2. Lung with normal parenchyma but remodelled pulmonary vasculature (Excessive muscularization)
3. Hypoplastic vasculature such as in congenital diaphragmatic hernia.[5]

Pulmonary hypertension leads to labile hypoxemia that responds poorly to oxygen, differential cyanosis and respiratory distress. PPHN is a disease of term neonates or near-term neonates but preterm neonates can also have this disease.[6,7]

Treatment options for PPHN include inhaled nitric oxide, sildenafil[8–12], prostacycline and extracorporeal membrane oxygenation (ECMO).

Despite advances in treatment of PPHN, mortality associated with this disease is still high and those who survive have serious long-term problems such as poor neurodevelopmental outcome, chronic lung disease and seizures.

Advanced ventilatory support like ECMO and inhaled NO is not available in resource limited centres. Data on the effectiveness of oral medications like sildenafil and bosentan alone or in combination is scarce. The objective of this study was to compare the effect of oral sildenafil alone with combined effect of sildenafil and bosentan in neonates with PPHN.

The study was based on the assumption that combined use of sildenafil and bosentan in neonates with persistent pulmonary hypertension will result in a more rapid fall in pulmonary artery pressure (measured as reduction of tricuspid regurgitation at 72 hours after admission) and shorten the duration of hospital stay as compared to sildenafil alone.

MATERIAL AND METHODS

This single blinded clinical trial was conducted at Neonatal Intensive Care Unit of The Children's Hospital & The Institute of Child Health Multan (CH & ICH), Pakistan, over a period of 6 months from July to December 2016. The study was conducted after approval by the Institutional Medical Ethics Committee and written informed consent was taken from parents.

The new-born admitted at CH & ICH, age less than 10 days of birth, >34 weeks of gestation, presenting with respiratory distress and marked hypoxemia (PaO2 <50 mm of Hg) on their arterial blood gas (ABG) underwent screening echocardiographic examination within 24 hours of admission. The echocardiography was done by a consultant paediatric cardiologist. PPHN was diagnosed on the basis of following two criteria.

a. Right- to- left or bidirectional hemodynamic shunting at the ductus arteriosus or at patent foramen ovale.

b. Tricuspid regurgitation (TR) jet pressure of >40 mm of Hg

Pulmonary artery pressure (PAP) can be measured by adding tricuspid regurgitation (TR) jet pressure with right atrial (RA) pressure [PAP=TR+RA]. The right atrial (RA) pressure is generally 5–10 mm of Hg in new-borns. Once diagnosis of PPHN is made, the new-born was sub grouped into "mild, moderate and severe PPHN on basis of TR measurement between 40 to 50, 50 to 70 and > 70 mm of Hg respectively." Babies with congenital heart disease except atrial septal defect and small ventriculo-septal defect, babies with active seizures, pneumothorax and with other congenital anomalies were excluded from study. Sample size is calculated using the formula:[14,15]

$$n = [(Z_{\alpha/2} + Z_{\beta})^2 \times \{2(ó)^2\}]/ (\mu1 - \mu2)^2$$

where, n = sample size required in each group,

μ1 = mean change in TR from baseline to 72 hrs in Drug A =15

μ2 = mean change in TR from baseline to 72 hrs in Active drug (combination)= 20

μ1-μ2 = clinically significant difference =5

ó = standard deviation=7.5

The demographic characteristics name, age, sex, and the echocardiographic findings at start of treatment were noted on proforma specifically designed for the study. The babies were randomized by sealed envelope method into two groups, A and B. Group A was assigned sildenafil (2 mg per kg per dose three times a day) and group B with both sildenafil (2 mg per kg per dose three times a day) and bosentan (1 mg per kg per dose twice a day). The principal investigator was aware of the treatment assigned to the participants but the cardiologist was blinded to treatment given. Echocardiography was repeated after 72 hours and findings were recorded. The babies were discharged when clinically stable and started taking feed orally. They were observed for main side effect of drugs, i.e., for hypotension. The outcome variables measured were the reduction of TR and duration of hospitalization. SPSS version 19 was used for the data analysis. Chi square test was used for qualitative data while student t test was used for quantitative data. The *p* value less than 0.05 was taken as significant.

RESULTS

During this study period one hundred newborns who were admitted with persistent pulmonary hypertension. There were 55 (55%) males and the mean age (days) ±SD at the time of admission was 3.56±1.52 of the studied new-born. They were randomly divided into 2 groups; group A was treated with oral sildenafil and group B with oral sildenafil plus bosentan. The sex distribution and mean±SD of new-borns age (days) at the time of admission of both the groups showed no statistically significant difference as shown in table-1. The mean± SD of baseline TR (mmHg) at the time of admission of both the groups showed no statistically significant difference while TR (mmHg) after 72 hours admission was significantly less in Group B as compared to group A as shown in table-1.

The outcome variables measured are shown in table-2. The mean duration of hospital stay was significantly less in group B (*p* value <0.0001) while the mean TR (mmHg) reduction after 72 hours of admission was significantly more in Group B (*p*-

value <0.0001). There were 48 (96%) cases who showed more than 15 mm Hg reduction in TR in group B as compared to 9 (18%) in group A (*p*-value <0.001). There were 43 (86%) children who were discharged <10 days of their hospital stay as compared to 31 (62%) in Group A (*p*-value 0.006). There was no mortality in any group and no case of hypotension was observed in any group.

Table-1: Comparison of baseline variables of both groups

Characteristics	Group A n= 50	Group B n= 50	*p*-value
Sex			
Male	25	30	0.315
Females	25	20	
Age at the time of admission(days) (Mean±SD)	3.38 ±1.47	3.74 ±1.56	0.2381
Baseline TR (mmHg) at the time of admission (Mean±SD)	64.70± 9.92	65.52±9.79	0.6783

Table-2: Comparison of outcome variables in the study group

Outcome Variable (Mean±SD)	Group A n= 50	Group B n=50	*p*-value
TR (mmHg) 72 hours after admission	53.30±9.35	41.66±9.47	<0.0001
TR (mmHg) reduction 72 hours after admission	11.40±4.62	23.66±4.78	<0.0001
Duration of hospital stay (days)	10.12±5.20	7.56 ± 3.77	<0.0001

DISCUSSION

Persistence of pulmonary hypertension was first described by Gersony and colleagues in 1969.[7] Supportive care for babies with persistent pulmonary hypertension include maintaining optimal temperature, nutritional support, avoidance of stress and gentle handling, sedation and analgesia as needed.[8] Mild PPHN without respiratory distress needs supportive care, supplemental oxygen and vigilant monitoring because condition may worsen abruptly and additional therapy including pulmonary vasodilators, non-invasive ventilation and mechanical ventilation may be needed .

For moderate to severe PPHN inhaled nitric oxide is a potent and selective pulmonary vasodilator without a significant decrease in systemic blood pressure. Konduri *et al*[10] found that severe hypoxic respiratory failure can be averted by early initiation of inhaled nitric oxide. In developing countries like Pakistan inhaled nitric oxide is not available nor is the advanced ventilatory support like ECMO available. In our hospital babies with PPHN are managed with oxygen and oral pulmonary vasodilators like sildenafil and bosentan. This study was done to evaluate the added effect of bosentan in babies with PPHN being given sildenafil for treatment.

Our study was done to compare the effect of sildenafil alone and sildenafil along with bosentan in new-borns with persistent pulmonary hypertension. Our results show that combined use of both drugs results in reduced hospital stay and improved clinical outcome reflected by reduction in Tricuspid Regurgitation (TR) within 72 hours of starting specific treatment. There were no significant side effects of drugs observed.

Engelbrecht[16] from South Africa described their experience with the use of Sildenafil in two non-ventilated neonates with moderate to severe PPHN. In both cases the addition of Sildenafil to the treatment regimen resulted in: A significant increase in haemoglobin oxygen saturation as measured by pulse oximetry; ability to wean off oxygen; and avoidance of mechanical ventilation.

Herrera *et al*[17] compared conventional management of new-born infants with PPHN with and without the addition of Sildenafil (Sildenafil 13 cases, placebo 11 cases) and showed significant improvement in OI (Oxygenation Index) in the treatment group. In addition, the PaO_2 at 72 hours was better, mean airway pressure and number of ventilation days was lower in the Sildenafil group.

In order to evaluate the effect of Sildenafil on oxygenation in newborns with PPHN, Baquero *et al*.[11] conducted a pilot randomized blinded study in infants with severe PPHN and oxygenation index (OI) >25 who received oral Sildenafil (7 infants) or placebo (6 infants). This study also showed improved survival in sildenafil group.

A Cochrane meta-analysis done in 2007 included two eligible trials from resource limited settings. A total of 37 new-borns were enrolled in both trials. It showed significant improvement in oxygenation in sildenafil receiving group.[2] A recent randomized controlled trial of bosentan in PPHN did not show any additional effect on top of INO in term new-borns with persistent pulmonary hypertension.[18] There were no studies done to see the combined effect of sildenafil and bosentan in resource limited centres so our study is the first to see their combined effect.

However, endothelin receptor antagonists in our study showed improvement in outcome when given along with sildenafil. Our results support earlier case reports that showed improvement in hypoxemia of new-borns with persistent pulmonary hypertension[19] when treated with bosentan. Our results also support the results of randomized control trial done by Mohamed et al that showed the improvement in oxygenation by using bosentan as compared to placebo.[12]

CONCLUSION

Persistent pulmonary hypertension remains a significant cause of neonatal morbidity and mortality, no single pulmonary vasodilator agent has a dramatic effect. Combined use of pulmonary vasodilators, sildenafil and bosentan, is more effective than use of single agent in resource limited centres where inhaled NO is not available. Further research is needed to improve the outcome of neonates with persistent pulmonary hypertension.

AUTHORS' CONTRIBUTION

NF: Conceived design and did statistical analysis and writing of manuscript. SA, AIQ, AR & AN: Data Collection and editing. IQ: Review and final approval of manuscript.

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