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Comparison of the Effectiveness of Bosentan and Sildenafil in the Management of Persistent Pulmonary Arterial Hypertension in Neonates

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ABSTRACT

Background: In newborns, persistent pulmonary hypertension (PPHN) poses a serious hazard to life. The principal treatment, inhaled nitric oxide, is believed to be unavailable in developing nations, where mortality is predicted to be between 10% and 20% higher. **Objectives:** This study aimed to assess the effectiveness, safety, and potential adverse reactions of bosentan and sildenafil when used in newborns with PPHN.

Patients and Methods: Between July 2021 and August 2022, a double-blind clinical experiment was carried out at Damietta General Hospital's Neonatal Intensive Care Unit. In newborns with PPHN, the effectiveness, safety, and potential adverse reactions of bosentan and sildenafil were assessed. Comparisons were done between the two groups' echocardiographic results, length of oxygen reliance, need for invasive ventilator assistance, duration of medication, and short-term results such as: blood pressure, white blood cell, and haemoglobin counts. **Results:** Bosentan has comparable PAP-lowering and cardiac output-improving effects to sildenafil. Bosentan had a considerably shorter treatment period than sildenafil (P = 0.003). During 15 and 17 days, the oxygen need time was comparable between the two groups (P = 0.175). Both groups required invasive breathing support, which was equivalent (P = 0.867). The third echocardiographic research results, including pulmonic inadequacies (P = 0.183), tricuspid regurgitations (P = 0.357), and ejection fractions (P = 0.159), were comparable in the bosentan and sildenafil groups, despite pulmonary artery pressure (PAP) and the intensity of tricuspid valve inadequacy being higher before therapies. **Conclusion:** Neonatal PPHN is successfully treated with bosentan, which decreased it more quickly. Comparing to sildenafil, it is more effective at lowering PAP and lessens the degree of tricuspid valve dysfunction in a shorter period of time.

Keywords: Bosentan, Neonates, Persistent pulmonary hypertension, Pulmonary artery pressure, Sildenafil.

INTRODUCTION

Although persistent pulmonary hypertension (PPHN) was already recognised for more than thirty years, its cause and course of treatment are still unknown. There are few research that examined the etiology, risk factors, consequences, and treatment options of PPHN [(1)]. In contrast, the usage of novel medications is restricted to experimental data or adults PPHN patients. The disease's physiopathology is caused by the pulmonary artery's inability to respond to increasing oxygenation, acute hypoxia, and persistent foetal hypoxia, all of which may be linked to thicker pulmonary artery smooth muscles [(2, 3)]. As a consequence of the pulmonary artery smooth muscles contraction, it may also cause partial or total failure of the lungs to dilate and ventilate properly, which results in a reduction in lumen diameter, an increase in pulmonary artery resistances, and an elevation in pulmonary artery pressure (PAP) [(4)].

Persistent PPHN frequently has an idiopathic cause. Most term and post-term newborns experience it [(5)]. The condition affects 1.9 out of every 1000 live babies. Early respiratory distress upon birth, that is accompanied by tachypnea, grunting, cyanosis, and lower arterial oxygen levels, is one of the disease's signs [(6)]. Even with 100% oxygenation, these signs are not restored; nevertheless, hyperventilation may normalise the arterial level of oxygen saturation. Depending on echocardiographic findings, the condition can be definitively diagnosed [(7, 8)]. The condition has a 10%–20% death rate in newborns from underdeveloped nations, but this incidence is higher in neonates without access to critical medications. The primary medication for treating this illness that produces pulmonary vascular vasodilation by elevating CGMP (Cyclic GMP) of pulmonary smooth muscles tissue is breathing nitric oxides [(9)]. Additional typical medications for PPHN include inotropes including intravenous dopamine, dobutamine, epinephrine, as well as norepinephrine. Dopamine raises the systemic blood pressure and seems to have adrenergic consequences [(10)]. Dobutamine enhances cardiac contractility while decreasing left ventricular capacity. Norepinephrine and epinephrine raise peripheral blood pressure and heart outputs, respectively [(11, 12)]. Other class of medications for treating PPHN includes phosphodiesterase inhibitors like milrinone and sildenafil. Milrinone promotes pulmonary artery vasodilatation, which in turn lowers pulmonary artery pressures by raising CGMP (Cyclic GMP). It also enhances cardiac function by reducing afterload [(13)]. It does, therefore, raise systemic blood pressure at greater dosages. By raising intracellular CGMP, the oral drug sildenafil produces vasodilation of the pulmonary artery, which lowers PAP and widens blood vessels. This increases blood circulation to particular areas of the body, which might lead to difficulties [(14, 15)]. Endothelin A and B receptors are antagonised by bosentan. It is helpful in treating pulmonary arterial hypertension, according to current data, but its impact on the pulmonary arteries is limited and specific, avoiding major systemic effects. Bosentan studies have been limited in some nations since inhaling nitric oxides is readily available. None of those trials have

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documented any severe systemic side effects brought on by bosentan [16]. Consequently, using a medication that solely influences the pulmonary arteries and has little or no effect on arterial system presents the biggest barrier for the therapy of PPHN in nations without accessibility to inhaling nitric oxide. In light of this reason, the objective of the current clinical trial study was to assess sildenafil with bosentan's effectiveness, reliability, and adverse effects.

PATIENTS AND METHODS

Performance, reliability, and potential adverse effects of sildenafil and bosentan were compared in this double-blind clinical trial on newborns with PPHN who were hospitalised to The Neonatal Intensive Care Unit at Damietta General Hospital (Ministry of Health, Damietta, Egypt) from July 2021 to August 2022.

All babies with respiratory illnesses, decreased arterial oxygen levels, and cyanosis underwent echocardiography (USA SonoSite 2010 model) prior to the participant's choice. This research included participants with PAP of ≥ 25 mmHg and tricuspid valves insufficiency of ≥ 30 mmHg, with or without right to left shunt.

Exclusion criteria: Neonates with other cyanotic heart conditions, conditions associated with cyanosis, and PPHN brought on by pneumonia or meconium aspiration.

Inclusion criteria: All PPHN neonates without any secondary causes, and there was no distinction between the two groups in terms of the origin of PPHN.

Using Excel spreadsheet, neonates were randomly assigned into group A (bosentan) and group B (sildenafil). Participants in group A were supplied with 1 mg/kg/dose bosentan (tablet 125 mg, Cipla Ltd.), whereas those in group B were given 0.4 mg/kg/dose sildenafil (tablet 50 mg, Cipla Ltd.), through gavage, every twelve hours [17-20]. The results of pulmonary artery pressure, the degree of tricuspid valves inadequacy, and cardiac output were compared among the two groups following repeat echocardiogram on days 6 and 12. Hypoxia, hyperventilation, hypercarbia, acidosis, and alkalosis were all forbidden during therapy, and inotropes were administered as recommended by neonatal cardiologist. Once the PAP was below 25 mmHg, the arterial oxygen saturation rate was above 95%, and the degree of tricuspid valve inadequacy was above 30 mmHg, the medication was halted.

Pre- and post-treatments as well as arterial oxygen saturation were checked. Responses to intervention state in which arterial oxygen level was greater than 95%, PAP was lower than 25 mmHg, and the degree of tricuspid valves insufficiency was lower than 30 mmHg were used to gauge the effectiveness of the medications. Additionally, there should not be any indication that the treatment is ineffective in lowering PAP or that any side effects necessitate stopping the medication. Because of its ineffectiveness, neonatal screening should not exceed 95% arterial oxygen level, and on days 6 and 12, PAP should not exceed 25 mmHg and the degree of tricuspid valve inadequacy should not exceed 30 mmHg. In between two categories, the length of oxygen consumption, the requirement for vigorous therapy, and the length of medicine were evaluated. Neonatal patients were monitored daily for adverse reactions such as hypertension, gastrointestinal tolerance, lung bleeding, and oedema until the completion of the treatment to assess the safety and acceptability of the drugs.

Ethical approval:

An informed written consent was obtained from each neonate' parents to participate in the current study. The Egyptian Ethical Committee of Medical Sciences approved this research. This work has been carried out in accordance with the Code of Ethics of the World Medical Association (Declaration of Helsinki) for studies involving humans.

Statistical analysis

Stata 11 (Stata Corp., College Station, TX, USA) was used for the statistical analysis, and the level of significance was adjusted at $P \leq 0.05$. The Kolmogorov-Smirnov test was used to assess the normalisation of the data sets. Crosstabs and Chi square analyses were used to contrast the percentages and frequencies for every element between the two sets of quantitative data, which were examined using descriptive testing and given as mean ± standard deviation. The average of parametric data before and after training in each category was compared using a paired t test. $P \leq 0.05$ was regarded as statistically significant in this investigation.

RESULTS

150 neonates who had PPHN had been validated by echocardiographic examination were included in the trial. An average PAP of 25 mmHg and a degree of valve tricuspid inadequacy of 30 mmHg with or without right to left shunts were used to validate the diagnoses of the condition. Subsequently, patients were randomly split into two groups, one received bosentan treatment and the other received sildenafil treatment. Thirty neonates were eliminated from the trial because of family unhappiness, and ten neonates were excluded from the research owing to syndromes. In total, 110 neonates were included in this research, 50 of whom received bosentan and 60 of whom received sildenafil. In regards of gestational age, Apgar score, weight, gravidity, gestation type, sex, parental medications, and maternal and newborn risk factors, in both groups were comparable. Similarly, bosentan markedly decreased pulmonary arterial pressure while enhancing cardiac output. Bosentan's duration of treatment was noticeably shorter than sildenafil's ($P = 0.003$) (Table 1). The oxygen therapies lasted between 15 and 17 days in both groups, which was comparable ($P = 0.175$). Additionally, there was no statistically significant difference in the demand for aggressive supports between the two groups ($P = 0.867$) (Table 1).

Table (1): Contrast of clinical features between the studied groups

Items	Bosentan group (n=50)	Sildenafil group (n=60)	P-value
Birth weight (g)*	2285.00±143.11	2129/00±143.41	0.370
Apgar score at 5 min*	8.42±0.12	8.37±0.19	0.423
Gestational age (weeks)*	31.42±0.85	33.41±0.47	0.484
Gravidity*	2.42±0.26	2.23±0.13	0.326
Mode of delivery			
NVD**	10 (20)	8 (13.33)	0.463
Caesarean section**	40 (80)	52 (86.67)	
Gender			
Female**	12 (24)	16 (26.67))	0.711
Male**	38 (76)	44 (73.33)	
Maternal risk factors			
Preeclampsia**	0	5 (8.33)	0.459
HIV**	0	2 (3.33)	
Abortion**	3 (6)	2 (3.33)	
Hypertension**	7 (14)	0	
Addiction**	5 (10)	4 (6.67)	
No risk factor**	19 (38)	29 (48.33)	
Hypothyroidism**	8 (16)	10 (16.67)	
Neonatal risk factors			
Cardiac arresting**	5 (10)	9 (15)	0.087
Meconium**	10 (20)	6 (10)	
Breeches**	10 (20)	0	
Twins**	7 (14)	10 (16.67)	
No risk factors**	18 (36)	35 (58.33)	
Drugs			
levothyroxine**	5 (10)	0	0.242
Propranolol**	4 (8)	3 (5)	
Omeprazole**	4 (8)	3 (5)	
Insulins**	6 (12)	13 (21.67)	
Corticosteroids**	10 (20)	10 (16.67)	
No drugs**	21 (42)	31 (51.67)	
Ventilations			
Mechanical ventilations**	35 (70)	44 (73.33)	0.867
Non-invasive ventilations**	15 (30)	16 (26.67)	
Additional medications			
Milrinone**	36 (72)	52 (86.67)	0.039
Dopamine**	14 (28)	8 (13.33)	
Age at the end of treatments (days)*	6.83±1.24	7.27±1.75	0.003
Age at starting drugs (days)*	1.96±0.54	1.87±0.02	0.367
Period of O_2 therapy (days)*	17.02±0.19	15.85±0.56	0.175

*Mean ± SD, **n (%). SD=Standard deviation

The results of the third echocardiography in bosentan-treated neonates were equivalent to those in the sildenafil cohort, implying that bosentan was much more efficacious than sildenafil despite the greater PAP and intensity of tricuspid valves insufficiency in newborn neonates prior to therapy (P-value for pulmonic inadequacy, tricuspid regurgitations, and ejection fractions in the third echocardiography was P = 0. 159, P = 0.357, and P = 0.183, respectively, Table 2).

Table (2): Comparison of echocardiography results of between the study groups

Items	Bosentan group (n=50)	Sildenafil group (n=60)	Average difference	P-value	95% confidence interval
PI*					
First echo	39.36±9.31	34.76±7.65	4.49±2.31	0.069	−0.388; 9.36
Second echo	25.22±6.14	22.72±3.75	4.49±1.48	0.006	1.24; 7.62
Third echo	20.18±1.64	19.66±0.53	1.16±0.79	0.183	−0.64; 3.27
TR*					
First echo	46.37±8.36	39.33±5.89	4.72±2.19	0.039	0.23; 9.35
Second echo	31.22±6.22	26.64±3.68	4.47±1.47	0.005	1.26; 7.67
Third echo	25.77±2.18	24.74±0.089	0.98±1.04	0.357	−1.25; 3.25
EF*					
First echo	53.22±5.76	43.64±12.15	−3.75±1.67	0.020	−7.37; −0.27
Second echo	52.55±10.15	56.14±5.11	−5.69±2.21	0.021	−10.39; −0.98
Third echo	58.64±2.20	58.26±2.31	14.98±9.77	0.159	−7.13; 37.13

*Mean ± SD. SD=Standard deviation, TR=Tricuspid regurgitation, PI=Pulmonic insufficiency, EF=Ejection fraction.

Prior (P = 0.197 and P = 0.857, respectively), throughout (P = 0.866 and P = 0.812, respectively), and after therapy (P = 0.127 and P = 0.513), systolic and diastolic blood pressures variations were not statistically differing between the two groups.

The difference between and within groups in the average of the systolic blood pressure pre- and post-treatment was not significant (P = 0.317, f = 1.36). Additionally, there was no statistically relevant difference in the mean of pre- and post-treatment diastolic blood pressure between groups (P = 0.784, f = 0.71).

Absorption of milrinone and dopamine was comparable in both groups (68% vs. 65%). There was no significantly substantial distinction in WBC counts according to pre (P = 0.413), throughout (P = 0.361), or post (P = 0.382) therapy among the groups, and the average white blood cells counts in the bosentan and sildenafil groups both dropped. There wasn't a statistically significant differences in the average haemoglobin amount pre- to (P = 0.237), throughout (P = 0.367), and post-therapy (P = 0.457), and the average haemoglobin level was identical between the two groups.

Table (3): Comparison between the Bosentan and Sildenafil groups according to pre, through and post therapy outcome

Variables	P-value within the two groups
WBC pre	0.413
WBC throughout	0.361
WBC after	0.382
Average haemoglobin pre	0.237
Average haemoglobin throughout	0.367
Average haemoglobin post-therapy	0.457

DISCUSSION

Within that study, bosentan and sildenafil's treatment efficacy, tolerability, and potential adverse effects in newborns with PPHN were evaluated for the first time. The study comprised newborns with PPHN who were hospitalized to the neonatal intensive care unit at Damietta General Hospital in Damietta, Egypt. The current research showed that bosentan, which works similarly to sildenafil, can lower pulmonary arterial pressure and increase cardiac outputs. Further notably, we discovered that newborns receiving bosentan had shorter treatment times than those receiving sildenafil. The length of oxygen consumption during therapy in both study groups was comparable and spanned between 15 and 17 days. The current results are in agreement with those of **Steinborn *et al.*** [21]. They found no statistically significant differences in the duration of oxygen consumption between the participants who received bosentan and those receiving a placebo. Additionally, we found that both groups needed some degree of forceful assistance, which is in line with the results of **Steinborn *et al.*** [21] In contrast, **Mohamed and Ismail** [17] found a statistically significant differences between the bosentan and placebo groups in the requirement for active supports. The present investigation evaluated the requirement for intensive supports between the sildenafil and bosentan groups, while **Mohamed and Ismail** [17] compared the effects of bosentan and a placebo on this situation. This could be the cause of the discrepancy between the findings of our study and those of the other investigators.

In this trial, more over half of the neonates in each group (54.22% in the bosentan group and 58% in the sildenafil group) were premature. In earlier research, such as the **Steinborn** [22] survey, the majority of preterm newborns with pulmonary arterial hypertension had bronchopulmonary dysplasia (BPD). To reduce the potential impact of age on treatment outcomes, we

purposefully chose age-matched neonates for both groups in the current trial.

In this investigation, sildenafil and bosentan both increased pulmonary arterial pressure and tricuspid valves inadequacy after therapy, despite the greater PAP and degree of tricuspid valves incompetence in newborns in patients receiving bosentan before treatments. Bosentan is beneficial in treating PPHN and tricuspid valve dysfunction in newborns, according to this report.

Additionally, we discovered that milrinone and dopamine usage in the sildenafil group was comparable (72% vs. 13.33%). The current results are in line with those of earlier research by **Mohamed and Ismail** [(17)] and **Maneenil *et al.***,[(8)] which declared that both the bosentan and placebo groups used inotropes equally. Contrary to this, **Steinborn *et al.*** [(21)] found that while the quantity of inotrope usage in the bosentan group was considerably greater than the placebo group, the average of systemic hypotension during the first 24 and 48 hrs post-therapy was not statistically different between bosentan and placebo groups. Hypotension, gastrointestinal intolerance, pulmonary bleeding, and oedema were not seen in either group in this study.

Bosentan was taken for a brief period throughout the current study to enhance clinical signs and cardiac functions, as well as the short-term consequences of medication use were assessed, in contrast to the work of **Mohamed and Ismail** [(17)], where after the end of the treatment, patients were monitored for up to 6 months. Long-term therapy effects were assessed, including death from BPD, neurological problems, developmental abnormalities, and alterations in liver-specific enzymes. Neither of these side effects were more pronounced in the bosentan group compared to the placebo group.

McLaughlin *et al.* [(23)] reported that bosentan was prescribed as a first line of treatment for PPHN newborns, and it was found that these patients had greater survival rates than anticipated. This was determined by looking at PPHN patient overall survival within 2 years. Bosentan was proven to be very successful in the present study's therapy of babies with persistent pulmonary arterial hypertension where it decreased pulmonary hypertension in a shorter period of time. In comparison with sildenafil, bosentan reduced PAP, the degree of tricuspid valves dysfunction, and cardiac output more rapidly and efficiently. Additionally, neither group required forceful respiratory assistance nor had equivalent oxygen demands, and neither group experienced any short-term side effects including systemic hypotension, leukopenia, or anaemia.

CONCLUSION

Yet, the usage of milrinone and dopamine in the study groups contributed to the study's weaknesses. Utilization of these combinations medications could be one of the survey's weaknesses, despite prior research on the effectiveness of combining therapies in the treatment of PPHN. Neonates in the bosentan group received dopamine, while those in the sildenafil group received milrinone. It would be preferable if participants in both groups were given similar inotrope prescriptions. It would have been beneficial to contrast participants in each research group with a placebo group in order to compare the efficacy of the medications. Another drawback of this research was the lack of availability of inhaled nitric oxide, which is the greatest therapy option for PPHN and is employed in numerous different therapies in conjunction with other drugs. Consequently, it is advised that future clinical trial investigations on term or nearly term newborns have long-term follow-up. Additionally, the test groups' inotrope types must to be comparable. Additional group receiving inhaled nitric oxide or a placebo must be included in the research for better evaluation and comparison. Further research can take the risk of mortality and long-term output into account.

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