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Research Article

### EFFECTIVENESS OF VERBAL SILDENAFIL IN INFANTS OVERWHELMING INSISTENT PULMONIC STRAIN

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**Abstract:**

*The utmost to treat neonates suffering from strain of the pulmonic kind is breath of nitric oxide counting vasodilator of the pulmonic type. Sildenafil engaged verbally is a good potential description to the problematic but it hasn't been methodically evaluated in children with PPHN. Every seven out of thousand live deliveries engrossment Tenacious pulmonic strain. The degree of expiries is extraordinary but is instantaneous to everywhere 15.0% with the use of breath of nitric oxide, surfactant and freshening of the high regularity kind. Perceptive reduction in the pulmonic vascular confrontation is realized with Sildenafil, which is a phosphodiesterase inhibitor of caring.*

**Material & Methods:** All victims who satisfied the presence criteria and stayed to section of pediatrics, Services Hospital were comprised in the study. Conversant accord was taken from parents / guardian after explanation the process, dangers and assistances of the study. Sildenafil tablet [50 mg] was creased and reconstructed with purified water and then stowed in a soft vessel in a refrigerator at 5°C. Oral sildenafil was given as per study procedure with a preliminary dosage of 0.50 mg/kg/dose and amplified by 0.50 mg/kg/dose to a supreme of 2 mg/kg/dose after evaluating every 6 h if non-responsive. OI, oxygen overloads [SpO], alveolar-arterial oxygen incline [A-aDO<sub>2</sub>], a/A ratio, and SOPI [for non-invasive publicized babies] were checked successively every 6 hours.

**Results:** Mean ± SD of incubation stage was 38.5±8.39 with C.I [37.6 to 39.7] weeks. Mean ± SD of birth weight was 3215±348 with C.I [3172.7 to 3257.8] grams. Effectiveness of oral sildenafil was noted in 208 [78.72%] patents while 56 [21.23%] was found to be non-effective [P-value<0.001\*].

**Conclusion:** It is to be decided that the effectiveness of verbal sildenafil in management of determined pulmonic straining was instigate to be real and features the need for a large, measured provisional.

**Keywords:** Persistent pulmonic Strain, Neonates, Oral Sildenafil, Effectiveness.

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**INTRODUCTION:**

Thoughtful dissatisfaction of the breathing system and hypoxemia are the features of a bodily disorder called Tenacious pulmonic strain[1, 2]. Tenacious pulmonic strain is related with high rates of humanity and illness happening in about 2 for every 1000 births around the globe[1]. Although positive growths have taken place to treat PPHN, it still remnants a deadly sickness chiefly in low revenue republics everywhere the biosphere who don't have the essential possessions[1]. Walsh-Sukys et al.[1] recognized a total humanity rate of 11.0% with the general range amongst 5% and 32%] in a collective examination led across the United States of America. Razzaq et al[3]. recognized a humanity rate of 25.0% at Lahore Children's Hospital in Pakistan and Abdel et al.[4] recognized a humanity rate of 22.0% at Al-Minya University Hospital in Egypt.

The incidence of PPHN through various results in South Africa was recognized to be around 1% with a high rate of humanity fluctuating from 25.0% to 3.0% and 48.0% at Chris Hani Baragwanath Hospital as recognized by Velaphi et al[5].

Due to its undertone with high degrees of humanity and injury in the past, Tenacious pulmonic strain of the newborn [PPHN] is measured as a very problematic newborn sickness. This sickness is initiated by the powerlessness of the neonatal to make a postpartum move from a high confrontation fetal pulmonic public to a less resilient pulmonic undertaking[4, 6].

PPHN is a newborn thoughtful disorder considered by a shared physiopathology constructions containing incessant raise of pulmonic vascular confrontation and hypoxemia because of the right-to-left supplementary pulmonic assertive of the flow of blood concluded the ductus arteriosus[7]. PPHN impacts 2-6/1,000 of live deliveries or around 1 in 10 of mutual newborns unveiled to focused upkeep of the newborn type and is completed with a 7 to 9% risk of transience counting extensive illness[4].

The corporeal consequences of PPHN influence conceive with comparative to a vast assortment of complaints counting but not incomplete to inherited diaphragmatic hernia [CDH], suffocation, pneumonia, meconium ambition and se sepsis[7].

Besides the treatment mentioned above, there are other ways to treat strain including bosentan, milrinone, magnesium sulfate, sildenafil and epoprostenol. The best to treat neonates suffering

from strain of the pulmonic type is inhalation of nitric oxide including vasodilator of the pulmonic type Sildenafil yields vasodilatation by growing cyclic guanosine monophosphate [cGMP] by the reticence of the phosphodiesterase included in the dilapidation of cGMP to guanosine monophosphate. [8]. Regardless, it must be noted that these methods of treatment are particularly proscribed in treating neonatal strain[9, 10].

In both models of the humans and animals, it has been proven that the use sildenafil is able to decrease resistance in the pulmonic vascular vein. The goal of these methods of treatment is to decrease pulmonic vascular resistance, regulate blood pressure, inverse right to left shunt, and better arterial O2 saturation.

To treat pulmonic arterial strain and to better the ability to work out and in delaying physical defragmentation in people of old age, sildenafil has been regulated by the US Food and Drug Administration [FDA][11, 12].

The treatment of newborns in Pakistan remains a dire issue due to the lack of nitric oxides availability, which is the main way for its treatment. The goal of our analysis is to categorically find the initial data with relation to the viability of administering oral sildenafil and its impact on babies' oxygenation suffering from PPHN. Therefore, this study will help establish sildenafil as treatment modality for PPHN locally. Since sildenafil is readily present in Pakistan, this study will focus on its use for treating PPHN in a local setting.

**DATA COLLECTION:**

Echocardiography [ECHO] was used to screen all newborns entering neonatal intensive care and after they fulfilled the predefined criteria, they were induced in the study following signed permissions from the family. A total of n=264 consecutively newborns having persistent pulmonic strain were recruited in the study was conducted at Department of Paediatric Medicine, Ziauddin University Hospital, Karachi, Pakistan after approval from institutional ethical review committee [ERC]. Neonates with Hyaline membrane sickness diagnosed by clinical features and X-ray findings or having any congenital heart sicknesss are excluded from the study. Those Infants of >42 weeks with mild respiratory sickness were also excluded. Those Neonates of incubation age 35-42 weeks with [PAP] on ECHO >25 mm of Hg were included in the study.

A 50 mg tablet of was turned into powder form and

reconstructed with purified water and then placed in a plastic bottle to be refrigerated at 5°C. Sildenafil was then orally administered as defined previously in the protocols of the study with the first dose of 0.5 mg/kg/dose and gradually augmented by another 0.5 mg/kg/dose to a total of 2 mg/kg/dose after evaluating each six hours if the victim was non responsive.

To evaluate the PAP, ECHO was conducted earlier and each 6 hours after the administration of sildenafil. The criteria for eligibility included all newborns born in the range of 34 to 42 weeks incubational age. OI, oxygen saturations [SpO<sub>2</sub>], alveolar-arterial oxygen gradient [A-aDO<sub>2</sub>], a/A ratio, and SOPI [for non-invasive ventilated newborns] were observed consecutively each six hours. Separate evaluations were conducted for all newborns regardless if they were noninvasive ventilated or invasive.

Sildenafil was then orally administered as defined previously in the protocols of the study with the first dose of 0.5 mg/kg/dose and gradually augmented by another 0.5 mg/kg/dose to a total of 2 mg/kg/dose after evaluating each six hours if the victim was non responsive. A 50 mg tablet was turned into powder form and reconstructed with purified water and then placed in a plastic bottle to be refrigerated at 5°C. Pulmonic strain [PPHN] considered present when the following criteria satisfied like 1] PAP > 25 mmHg, 2] PO<sub>2</sub> < 80 mmHg, 3] SPO<sub>2</sub> < 90% at 100% respectively. According to their predefined standard criteria the effectiveness were evaluated was considered effective if at least 2 out of the three indicators are present from the baseline values like 1] SaO<sub>2</sub> > 10% increase in ABG from baseline, 2] OI decreases by 10-20% from the baseline, 3] Decrease in FiO<sub>2</sub> by 5-10% from the baseline PPHN. The stratification was done according to gender, incubational age, birth weight, and Apgar score to see the effect of these modifiers on outcome using Chi-square test/Fisher exact test. P value < 0.05 was considered as significant in all analysis. All analysis were performed in SPSS-21. Frequency and percentage was computed for qualitative variables like gender, cesarean section, and efficacy. Mean ± SD was calculated for quantitative variable i.e. incubational age, birth weight, apgar score at 1 and 2

min, peak inspiratory pressure, peak end expiratory pressure, airway pressure, rate, inspired oxygen, duration of time, FiO<sub>2</sub>, PaCO<sub>2</sub>, PaO<sub>2</sub>, HCO<sub>3</sub>, A-aDO<sub>2</sub> and Oxygen Indices.

Victims name were not mentioned at any stage the data were kept confidential with primary investigator and were not be shared with anyone else. Confidentiality about the victim's particulars was ensured. All the cases/subjects were entered on the proforma by their MR number and a separate study ID number were assigned to each case and it were used during further analysis. The entire evaluation of the victims, diagnostic tests and treatment were at the discretion of treating pediatric physician. Data were stored in password protected computer with principal investigator.

### RESULTS:

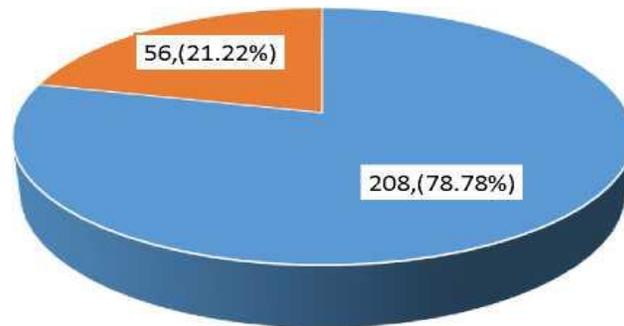
In this study, sildenafil was not effective in 21.22% newborn victims with severe PPHN, 5 newborn were transferred to another center for iNO and/or ECMO and one newborn died with sepsis. Mean birth weight of neonatal baby was 3215 ± 348 with C.I [3172.8 to 3257.1] grams in contract Apgar score at one and two minute reading was 6.48 ± 1.25 with C.I [6.3 to 6.63] & 6.56 ± 1.34 with C.I [6.396.72]. In this study 264 victims were included to the efficacy of oral sildenafil in newborns having persistent pulmonic strain and the results were analyzed as the average maternal age of the mother was 38.5 ± 8.39 with C.I [37.48 to 39.51] years. Significant improvement of oxygenation after sildenafil treatment was indicated by a significant reduction of oxygenation index [OI] and increase of PaO<sub>2</sub> ranging from 34.9 ± 9.6 to 13 ± 3.2 [p < 0.001], 42.4 ± 13.5 to 78 ± 11.5 [ < 0.01], and reduction of FiO<sub>2</sub> from 1.22 ± 0.45 to 0.3 ± 0.06. Out of 264 victims 114 [56.81%] were male and 150 [43.19%] were female. Female are more predominant in this study. Cesarean section was documented in 76 [28.78%] victims. Reduction of OI was more significant in post-hoc analysis after the 3rd and 4th doses of sildenafil i.e. from 18 to 24 hours from the start of treatment. Similarly mean peak inspiratory pressure was 33.2 ± 5.1 & peak end expiratory pressure was observed 4.2 ± 0.75 with C.I [4.10 to 4.29] respectively. Efficacy of oral sildenafil was noted in 208 [78.78%] patents while 56 [21.22%] was found to be non-effective as shown in **Chart#1**.

**Table 1: Descriptive Statistics of demographics and babies characteristics at time of entry**

Descriptive statistics	Mean±SD	95% C.I.
Rate [beats/min]	42.2±5.4	[41.5 to 42.8]
FIO2 in Days	2.7±1.6	[2.5 to 2.89]
Duration of Treatment	1.22±0.45	[1.16 to 1.27]
PaCo2	34±8.2	[33 to 34.9]
HCO3	34.2±12.48	[32.6 to 35.7]
PaOz	19.1±2.9	[18.7 to 19.4]
A-aDOz	42.5±7.48	[41.6 to 43.4]
Incubational Age in [Weeks]	38.5±8.39	[37.4 to 39.5]
Birth weight in [Gram]	3215±348	[3172.8 to 3257.1]
Apgar Score at 1 Min	6.48±1.25	[6.32 to 6.63]
Peak Inspiratory Pressure [cm H20]	6.56±1.34	[6.39 to 6.72]
Peak End Expiratory Pressure [cm H20]	4.2±0.75	[4.1 to 4.29]
Inspired Oxygen	19.2±4.2	[18.69 to 19.7]
Airway Pressure [cm H20]	1.34±0.72	[1.25 to 1.42]

**Table 2: Comparison of efficacy of sildenafil among demographics and study characteristics**

Study Characteristics	EFFICACY		P-Value
	Yes	No	
Gender Male Female	105 [39.8%] 103 [39.0%]	45 [17.0%] 11 [4.2%]	<0.001*
Incubation Age [Weeks] 35—39 >39	150 [56.8%] 58 [22.0%]	30 [11.4%] 26 [9.8%]	0.008
Birth Weight [gm] 100-300 >3000	72 [27.3%] 136 [51.5%]	40 [15.2%] 16 [6.1%]	<0.001*
Apgar Score at 2 [min] 3-5.5 >5.5	72 [27.3%] 136 [51.5%]	38 [14.4%] 18 [6.8%]	<0.001*
Apgar Score at 1 [min] 3-5 >5	60 [22.7%] 148 [56.1%]	42 [15.9%] 14 [5.3%]	<0.001*

**Chart 1: Stratification of Incubation Age Group with Efficacy [N=264]****DISCUSSION:**

Furthermore any bias in the study was reduced by using definitions that were objective for predicting and outcome variables. The strict criteria for including and excluding newborns in the study made it a strong one. The strength of the study was further enhanced by the use of successive sampling which was perfectly suited in conducting the study. No calculation of the prior sample size is required for a successful conduct of this study. The chief confines of our analysis was the use of a substandard study plan case series the analysis and power of indication of which is inadequate and ergo.

There were a cumulative effect for multiple dosing; oxygenation further improved with each dose of sildenafil. Sildenafil causes pulmonic vasodilatation by increasing the availability of cGMP. Measurement of oral sildenafil in newborns to measure the effectiveness having [PPHN] has been significantly varied range of severity. Reduction of OI was more significant in post-hoc analysis after the 3rd and 4th doses of sildenafil i.e. from 18 to 24 hours from the start of treatment. Data on the use of sildenafil in PPHN is currently very scarce with a few published case reports. In this study, a significant improvement of oxygenation after sildenafil treatment was indicated by a significant reduction of oxygenation index [OI] s and increase of PaO<sub>2</sub> ranging from 34.9 ± 9.6 to 13 ± 3.2 [p < 0.001], 42.4 ± 13.5 to 78 ± 11.5 [ $<0.01$ ], and reduction of FiO<sub>2</sub> from 1.22±0.45 to 0.3±0.06. Our results were comparable to Herrera et al. who also reported a significant improvement in OI in a group of infants who received sildenafil compared to a control group. Prospective randomized studies were all pilot in nature with a limited number of victims. In the treatment group, OI improved in all

infants within 6 to 30 hours, with a steady improvement in sildenafil group as regards to O<sub>2</sub> saturation, and in mortality. Similar results were reported in a couple of non-randomized reports [3, 18, 19]. Treatment groups had greater PaO<sub>2</sub> at 72 hours and shorter duration of ventilation. In line with this study, Baquero et al. conducted a pilot randomized blinded study in infants with severe PPHN with OI >25 who received oral sildenafil.

A Cochrane meta-analysis study was conducted by Shah and Ohlsson [9] to measure the effectiveness sildenafil in the treatment of PPHN. It was found that sildenafil was safe, effective, and easily administered. The low mortality rate among victims treated with sildenafil in our study was comparable to those reported by Baquero et al. [8] and by Shaltout et al [10]. In this study, sildenafil was not effective in 21.22% newborn victims with severe PPHN, 5 newborn were transferred to another center for iNO and/or ECMO and one newborn died with sepsis. In this study, sildenafil was well tolerated in newborn victims with no short term side effects for sildenafil particularly systemic hypotension as shown by non-significant difference of mean blood pressure between pre and post-sildenafil victims [p = 0.63]; as it was reported by other studies. However; it cannot be concluded that oral sildenafil improve survival of PPHN victims since we did not conduct a randomized trial.

**CONCLUSION:**

It was well tolerated and was not associated with short term side effects. We conclude that oral sildenafil could be a promising pulmonic vasodilator and effective for improving oxygenation in newborns with PPHN, particularly in medical facilities without iNO or ECMO. In our study incubational age was

38.5±8.39 weeks and birth weight was 3215±348 grams. Efficacy of oral sildenafil was noted in 78.78% patients while 21.22% was found to be non-effective. Our results are comparable with most of national and international studies. Large multicenter randomized controlled studies are recommended to determine the long term safety and neuro developmental outcomes of infants receiving this treatment.

#### **Strength & Weakness and Recommendation:**

Generalizations could also not be made since we use sampling that was non probable. Regardless, this was mitigated by the small number of newborns being tested including the fact that the durations of the follow ups were succinct. The study was further affected by the lack of outcome variables available in the study. Many factors with a direct connection to predictor and outcome variables were not included in the study which further weakened the strength of our study.

Furthermore, generalizations cannot be made since this study was performed in one single unit of a hospital. Since this study was conducted in a hospital setting, the findings do not truly represent the accurate frequency and extremity of the sickness.

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