SHORT COMMUNICATION

Oral Sildenafil for PPHN in Neonates: Selection of patients Remains a Dilemma?

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Persistent pulmonary hypertension (PPHN) in neonates has varied etiologies.1-4 It remains a condition with high mortality. The mortality reported from Western literature is 10-15%, which may be significantly more in Indian subcontinent due to non-availability of inhaled nitric oxide and extracorporeal membrane oxygenation.1 Multiple pharmacological approaches have been suggested for its management.4 Sildenafil, a phosphodiesterase inhibitor shows promise in our settings due to ease of availability, administration and low cost. However, it’s off label use is still not allowed due to inconsistent responses.5 We share our experience of failure to demonstrate any beneficial response with oral sildenafil in two outborn neonates.

Case 1: A 1450 grams near term small for gestational age, male baby was delivered at a small peripheral health facility by emergency cesarean section, for severe oligohydramnios and prolonged rupture of membranes, was brought in respiratory distress having a positive sepsis screen at admission. Chest X-ray revealed low volume lungs with generalized opacity suggesting pulmonary hypoplasia and a small right pneumothorax. Baby was given surfactant at eight hours of age and ventilated on Synchronized Intermittent Mechanical Ventilation (SIMV) mode with pressure support (Maquet, Servo I, Sweden). He required very high pressures PIP 28/5 rates 60 and 100 FiO2. Sequential X-rays showed an enlarging right pneumothorax that was managed with chest drainage. After a transient response, blood gases showed persistent severe hypoxemia (PO2 25-34 mmHg). Echocardiography confirmed PPHN with suprasystemic pulmonary pressures (gradient 25 mmHg). Baby was started on maximum vasopressor support, hyperventilated and given sodium bicarbonate in vain. Oral Sildenafil 0.5 mg/kg was tried at 18 hours of age and was repeated in 30 minutes with no response. Baby died at 36 hours of age from persistent hypoxemia and circulatory failure.

Case 2: A full term 3250 grams female newborn was born by emergency LSCS for fetal bradycardia. There was a history of maternal antepartum hemorrhage one-week prior, that was managed conservatively. Mother had poor nutritional status with severe anemia (Hb 4.4 g%) and was delivered with thick old meconium. Baby required direct tracheal suction and IPPV with Apgar scores of 4, 7, 8 at 1, 5 and 10 minutes respectively. At 20 minutes of age, baby developed respiratory distress and prolonged capillary filling time. Baby was thus, referred to us. At 4 hours of age, baby was initiated on mechanical ventilation for desaturations and increasing respiratory distress (Blood gas at this stage showed hypoxemia PO2 42 mmHg without hypercapnia or acidosis). Sepsis screen, hematocrit (45%) and USG cranium was normal. Chest X-ray done was consistent with meconium aspiration syndrome. Baby remained hypoxic with maximum ventilation (30/5 rate 65 and FiO2 100%). A dose of surfactant was given with no response. Echocardiography ruled out cyanotic congenital heart disease but showed suprasystemic pulmonary pressures. Baby was managed with hyperventilation, alkalinization and vasopressor support with persistent hypoxemia. A rescue dose of oral sildenafil was given at a dose of 1.5 mg/kg at 10 hours of age without any improvement in oxygenation index. Baby died at 16 hours of age due to refractory shock. We used oral sildenafil as a rescue measure after discussions with the family and verbal consent. We discussed in detail about the unavailability of inhaled nitric oxide and ECMO at other higher centres, and instability of the babies for transport. In both the babies oral sildenafil was used once the criteria for extracorporeal membrane oxygenation were met (Oxygenation index > 40). We prepared sildenafil (25 mg) by dissolving in 10 ml distilled water and gave the solution through oro-gastric tube. Both the cases represent common scenarios faced by neonatologists in India and other developing countries.6,12 Three major patho-physiological derangements in PPHN have been described: underdevelopment of the lung, mal-development of the lung and mal-adaptation of the lung with the latter group showing the best response to vasodilator therapy.4 A search of electronic databases (MEDLINE, EMBASE, PsyclINFO AND CINAHL) was done using key words sildenafil and neonates and sildenafil and PPHN. Reports in which sildenafil was used for PPHN in only in neonatal age group (excluding children) were retrieved. Case reports in which sildenafil was used for PPHN secondary to congenital heart disease and bronchopulmonary dysplasia were excluded. Thus, only five publications were left, which included one recent placebo randomized controlled trial enrolling 13 newborns with use of oral sildenafil in seven...
newborns. Overall combining all reports, oral sildenafil have been used in 12 new borns with PPHN reporting dramatic responses in 11 babies who survived. One report highlighted successful use of intravenous sildenafil. The dose of oral sildenafil used has been 0.5 mg/kg to 1.5 mg/kg/dose. In animal studies, a dose of 3 mg/kg have been suggested. Simiyu et al. and Juliana et al. have shown good response in PPHN secondary to birth asphyxia. Chaudhari et al. has shown survival in impaired alveolarisation that was proven by lung biopsy. However, in the first case, we could not confirm pulmonary hypoplasia and poor response may be due to slightly delayed and low dose of sildenafil use. Some studies have suggested repeat dose of sildenafil at six hours, but was not used because the perfusion had became markedly deteriorated and second oral dose of drug would be futile. Baquero has shown good response in meconium aspiration syndrome in their trial. However, we could not demonstrate response in the second case also, probably we used it slightly late again (10 hours) (Table I).

Table I: Ventilator indices pre and *post sildenafil

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*Post indices are 30 minutes after oral administration of sildenafil

Other confounding variables like status of the baby at birth, out-born status, poor transport system and low birth weight in the first case may have contributed to poor outcomes. There is an urgent need for multicentric randomized controlled trials from the Indian subcontinent. A clinical prediction rule needs to be developed, which includes neonatal variables (age, sex, weight, and gestational age, condition of baby at birth and admission, diagnosis), maternal variables, ventilator indices and parameters into account.

REFERENCES

12. Patole S, Travadi J, Sildenafil for "blue babies": Ethics, conscience, and science have to be balanced against limited resources. BMJ 2002; 325:1174.

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