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INTRAVENOUS SILDENAFIL THERAPY IN PERSISTANT PULMONARY HYPERTENSION OF THE NEWBORN IN A RESOURCE LIMITED HOSPITAL SETTING

Neonatology

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ABSTRACT

Objective: The aim of the study was to determine the effectiveness (oxygenation) and immediate outcome of intravenous (IV) sildenafil therapy in persistant pulmonary hypertension of the newborn (PPHN).

Design: Retrospective medical records review

Setting: Neonatal intensive care unit (NICU) of a tertiary Hospital Delhi, India

Method: case records of Newborns who received IV Sildenafil between October 2015 and October 2016 at NICU of Hindu Rao Hospital, Delhi were reviewed .Inclusion criteria for the study was Newborns with Echocardiography (ECHO) proven PPHN .Exclusion criteria were presence of congenital heart disease and any evident major congenital anomaly. Informed consent was obtained from all the parents of neonates prior to starting IV sildenafil with emphasis of non availability of iNO (inhaled Nitric Oxide) and ECMO (Exra corporeal membrane oxygenation) in our setup.

Result: Neonates who presented with severe hypoxemia underwent screening with ECHO. Out of 22 newborn babies screened 15 were diagnosed to be PPHN. Median gestation of the newborns was 39 weeks. All the babies had a response to the IV sildenafil therapy in the form of improvement in oxygen saturation by the time loading dose was given @0.4 mg/kg/ over 3 hours. The mean duration of IV sildenafil given was 4 days and the maximum duration given was 14 days. All newborns received ionotropes dopamine, dobutamine, epinephrine either alone or both or all three respectively to provide blood pressure support. The survival rate in babies given IV sIldenafil was 73.33%.

Conclusion: IV Sildenafil is an effective therapy in improving oxygenation of babies diagnosed with PPHN especially in limited resource centres where iNO /ECMO is unavailable.

KEYWORDS

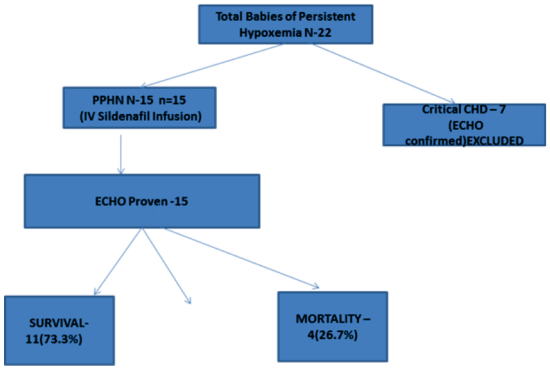
Hypoxemia, Sildenafil, pulmonary Hypertension, Newborn

INTRODUCTION:

Persistant pulmonary hypertension of the newborn (PPHN) is a disorder that was previously referred to as persistant fetal circulation .This condition often occurs due to an unsuccessful pulmonary transition at birth[1].The incidence of PPHN is 1.9 per 1000 live births with mortality ranging between 4-33%[2].The primary objective of treatment in neonates with PPHN is effective pulmonary vasodilatation. Inhaled nitric oxide (iNO) is an established mode of treatment in PPHN and it also reduces the need for Extracorporeal membrane oxygenation (ECMO)[3].i NO is efficacious but not available in developing countries hence adjunct therapies which are more affordable are being sought .Even when iNO is available in selective centres most of the babies of PPHN require supportive Mechanical ventilation, ionotropes, intravenous fluids making the transport of the sick newborn very difficult. Many alternative therapies have been used in PPHN like iloprost[4],oral sildenafil[5], milrinone[6] ,magnesium sulfate[7] with varied results. The aim of this study was to delineate short term outcome with intravenous sildenafil in newborns with Echocardiography (ECHO) proven PPHN.

METHODS:

A retrospective case records review was performed in neonates who received intravenous Sildenafil for treatment of PPHN. The therapy was given between October 2014 to October 2016 at Neonatal Intensive Care Unit (NICU) in a tertiary care center, Delhi. The inclusion criteria Were 1.Pre to post ductal saturation difference of> 10% on pulse oximetry (SpO2)2. Diagnosis of PPHN by ECHO[8][9] Exclusion Criteria : included presence of congenital heart disease ,any gross congenital anomaly. Informed consent was taken from parents of all babies included prior to giving intravenous sildenafil. The primary outcome was monitored in terms of improvement in oxygenation as reflected by SpO2.other parameters were duration of ventilator support, requirement of ionotropic supportand mortality.



Table/fig -1

Our NICU is not equipped with High frequency oscillatory ventilation (HFOV), ECMO and iNO. Henceforth all babies diagnosed with PPHN (done by ENVISOR-C, PHILIPS, Model 2004 color Doppler using Pediatric probe) were treated initially with conventional therapies such as dopamine, dobutamine, intravenous fluids, antibiotics and sedation as required prior to starting intravenous sildenafil. The 2-D ECHO parameters considered for diagnosing PPHN were Pulmonary artery peak systolic pressure > 35mmHg,Tricuspid regurgitation jet maximum velocity of > 2.5 m/s.[8][9].The Intravenous sildenafil preparation (10mg/12.5ml) wasgiven @ 0.4mg/kg over 3 hours as a loading dose diluted in isotonic saline followed by maintenance dose of 0.03-0.06mg/kg/hour, administered by infusion pump upto a maximum of 0.1mg/kg/hr[10] .The dosage was titrated depending on the clinical improvement, blood pressure, requirement of assisted ventilation. The decision for mode of ventilation, type of ionotroic agent used, antibiotics commencement and additional vasodilator support like magnesium sulphate was the sole discretion of attending consultant as per the

existing NICU protocols of the Hospital.

The parameters retrieved from the case records were gestational age, evidence of asphyxia and sepsis, initiation of IVsildenafil, minimum and maximum duration of therapy, underlying risk factors, mode of delivery, number of ventilation days .Before discharge all the babies underwent repeat ECHO and cranial ultrasonography .

RESULTS:

During the study period 22 neonates had persistant hypoxemia who underwent screening with ECHO out of which 15 babies were included in the study when proven with ECHO as PPHN, while remaining 7 newborn were diagnosed to be critical congenital heart disease (CCHD) hence excluded. Of the 15 babies who received IV sildenafil none of the baby was referred or there was any dropout due to any side effects like hypotension.

TABLE/fig -2 : BASIC PROFILE OF STUDY SUBJECTS

Total number of babies (n)	Responders (Survived)	Non responders (Expired)	P value
	N (%)	N (%)	
Total Babies(15)	11 (73.33)	4 (26.66)	
Male (%)	6(54.5%)	2(50%)	
Female (%)	5(45.5%)	2(50%)	
#Gestational age in weeks	39(37-41)	38(37-40)	
Mode of Delivery cesarean section (%)	7(63.6%)	2(50%)	
Mode of Delivery Vaginal (%)	4(36.4%)	2(50%)	
#Birth weight in gms	3000(1850-4400)	2950(2800-3500)	-
Meconium Aspiration syndrome (%)	5(45.4%)	3(75%)	
Severe birth asphyxia (%)	2(18.1)	3(75%)	
Moderate birth asphyxia (%)	5(45.4%)	1(25%)	
Sepsis (culture proven) (%)	3(27.2%)	Nil	
Mechanical Ventilation (%)	7(63.6%)	4(100%)	
#Total ventilation days	20(1-17)	11(1-4)	-
Hypoplasia of lung (%)	1(9%)	Nil	-
Surfactant (%)	Nil	1(25%)	
#Age at start of IV Sildenafil(hrs)	28(6-96)	20(18-48)	
Mean duration of IVSildenafil (days)	4(3-14)	2(1-4)	-
Mean duration for normalization of PPHN (days)	4 (2-14)	-	-
Ionotropes (%) Dopamine Dopamine +Dobutamine Dopamine +dobutamine+epinephrine	8(72.8%) 3 (27.2%) Nil	NIL NIL 4(100%)	-
Pneumothorax (%)	NIL	1(25%)	
Oxygen saturation (SpO2) (%)	40-99	30-92	-
Oxygenation index	24(20-36)	54(38-106)	<0.005

#median, PPHN-Persistant Pulmonary Hypertension of the Newborn Newborns included in the study were all inborn babies either booked or unbooked. All the babies included n the study were term babies with gestational age more than 37 weeks. Before and after starting IV Sildenafil all the babies had complete blood count, kidney function test and serum electrolytes which were essentially normal.10 babies (66.6%) had probable sepsis with a positive Creactive protein of which only 3 had culture proven sepsis (20%).

There was lung hypoplasia in 1(6.6%) baby who was discharged and referred to higher center when PPHN got resolved. The Most common etiology was found to be Asphyxia (73.3%) followed by Meconium Aspiration Syndrome (53.3%). All the neonates required ionotropes of which 6(40%) neonates required only Dopamine, 5(33.3%) required dopamine and dobutamine and 4(26.7%) required dopamine, dobutamine and epinephrine respectively.

Mortality occurred in 4 babies of which 3 babies had severe birth asphyxia .one neonate was unbooked. All the babies who died required iontropes dopamine, dobutamine and epinephrine. None of the baby who expired had proven sepsis.

All the surviving newborns were discharged with no medications or oxygen support. There was no evidence of any flushing, diarrhoea, pyrexia or hyperactivity.

DISCUSSION:

Advances in the understanding of the physiology of PPHN has revealed that when phosphodiesterase 5 is inhibited there is an increased concentration of cyclic –AMP and GMP locally which enables relaxation of pulmonary vasculature smooth muscles[11]. Currently sildenafil a phosphodiesterase 5 inhibitor is used in neonates as an adjuvant to i NO and while weaning off from it or as a primary treatment where i NO is not available. In Cochrane Database 2017 it was concluded by authors that sildenafil when used in treatment of PPHN improves oxygenation in neonates and reduces mortality[12].In our study all the 15 neonates who were given IV Sildenafil had improvement in oxygenation by the time loading dose was given. In this study all the neonates required one or more ionotropic medication support as has been seen with other adjunct therapy like iloprost[4], but our study included all the grades of PPHN unlike their study who included only severe PPHN. Babies who required higher settings of ventilation and were requiring ionotropes for prolonged duration were given Magnesium sulphate in addition to IV sildenafil. None of the babies deteriorated or expired in this group unlike in a study done by uslu [13] where the neonates who were given magnesium sulphate required more mechanical ventilation days and also required more ionotropeswhen given alone without sildenafil. The effect of sildenafil was seen in 7hours in a study done in mexico by Vargas –Origel as compared to within 3 hours in our study[15].

TABLE/FIG -3 Comparative study of sildenafil in PPHN

AUTHOR/YEAR	TYPE OF STUDY	LOCATION	NO OF PARTICIPANTS	INTERVENTION	OUTCOME
Baquero/ 2006[15]	Single centre randomized double blind controlled trial	Colombia	7-oral sildenal 6-placebo (Term and near term)	Oral sidenafil given @0.5ml-1ml/kg	Well tolerated with improvement in OI
Uslu/2011 [16]	Single centre randomized double blind controlled trial	Turkey	31- oral sildenafil 34-MgSO4 Both term and near term	0.5mg/kg every 6hours Of sildenafil 300mg/kg of MgSO4 f/b20mg/kg of maintenance dose	Sidenafil was better in terms of clinical response ,duration of MV and ionotropic support , 3babies had gastric bleeding
Khorana M/2011[17]	Single centre randomized trial	Thailand	40 –oral sildenafil Near term and term	0.25 -0.5 mg/kg	One baby given iloprost due to hypotenson , another baby given iNO/improvement in oxygenation in all other babies

Vargas-origel/2010[13]	Double blind randomized clinical trial	Mexico	31-oral sildenafil 20-placebo Term and post term	3mg/kg every 6hours	Effect of sildenafil after 7 hours High mortality in placebo group
Al –Omar/2016[18]	Single center randomized clinical trial	Qatar	13-oral sildenafil +iNO 11-placebo+Ino Preterm and term	2mg/kg/dose every 6 hours	No side effects seen with sildenafil group
Steinhorn RH /2009[19]	Single center randomized clinical trial		36 neonates given IV sildenafil +iNO	Continuos IV infusion given for 48hrs-7days	IV Sildenafil was well tolerated, response seen in 4hours
Present study	Single centre retrospective study	Delhi	15 – all IV Sildenafil All term babies	Loading dose 20.4mg/kg f/b 0.03-0.1mg/kg for a duration of minimum 3days -14 days	Well tolerated, response time within 3hours.Spo2 increased and OI decreased

MgSO4-Magnesium Sulphate, MV –Mechanical Ventilation, i NO-Inhaled Nitric oxide, OI-oxygenation index Meconium has the potential to partially or completely obstruct the airway and also deficiency of surfactant. This causes decreasing ventilation perfusion ratios and increasing intrapulmonary right-to-left shunt[1].one of the newborn in the nonresponder group required surfactant which was given due to requirement of higher ventilator settings.

There was a single case(6.6%) of pulmonary hypoplasia in our study.In a study by Gustavo [20]out of 78 of PPHN 2 newborns(2%) had pulmonary hypoplasia .

The results in our study was similar to done by Khorana etal [17] where the OI was significantly high in non responder group given oral sildenafil ,their median range for non responder was 46.12 versus 29.31 in responder group.

LIMITATIONS AND RECOMMENDATION:

The study had several limitations. There was no control group as it was a retrospective study. The sample size of the population included is small hence evaluation of efficacy is suboptimal. The long term follow up for monitoring growth and neurodevelopmental outcome is not done .A randomized clinical trial including large population of neonates is required to study the safety profile, efficacy as a preliminary drug in resource limited centers.

Conclusion:

Intravenous sildenafil is an effective modality of treatment in PPHN and it should be considered especially in resource limited centers where there is no provision of iNO, ECMO available. No immediate side effects have been observed which may be a cause of concern but blood pressure should be diligently monitored.

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