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Profile Of Haemodynamically Significant Patent Ductus Arteriosus In Preterm Neonates (24-34 Weeks Gesation) With And Without Surfactant Replacement Therapy In A Tertiary Care Neonatal Centre- A Prospective Observational Study

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ABSTRACT
Background: Preterm birth is certainly a public health problem. According to the World Health Organization (WHO), prematurity is the leading cause of death among newborns and it comes in second between children below five years old, after pneumonia. Aside from being an important cause of mortality, premature birth increases the risk of serious lifetime disabilities. **AIM:** To determine the incidence of haemodynamically significant patent ductus arteriosus in babies between 24-34 weeks gestation among those receiving surfactant replacement therapy and on respiratory support and those on respiratory support and not receiving surfactant and to determine whether there is any significant difference among both the groups in other outcomes such as NEC, BPD, duration of hospital stay etc. **Methods**: This prospective observational cohort study enrolled 86 newborns, 43 in each group. First group included newborns who received surfactant therapy based on specified criteria in accordance with unit protocol and second group included newborns who did not receive surfactant but were on respiratory support. Both groups were monitored regularly for opening of ductus arteriosus. Echocardiography was done regularly from day 1 in both the groups for detection of haemodynamically significant ductus . Echo was repeated every alternate day in first week, twice weekly in second week , thereafter once every seven days till discharge to see for closure or reopening of the ductus in both the groups. Haemodynamically significant ductus was defined as per Echocardiographic as well clinical criteria. All patients with haemodynamically significant PDA were treated with paracetamol initially till 2 courses. If it still did not close, ibuprofen was used. All patients were followed up to discharge. **Results:** 101 babies were screened of which a total number of 84 sample size was taken. 42 babies received SRT with respiratory support while 42 received only respiratory support without SRT as per criteria. The baseline characteristics of both the groups were similar except for gestational age for which later binary logistic regression analysis was performed. Haemodynamically significant PDA was present in 54.7% babies in SRT group and 26.19% in the other group which was statistically significant.(p value = 0.008) Despite analyzing via binary logistics regression , the p value was 0.029 which was significant. **Conclusion**: The most common short term morbidities faced by neonatologists in preterm babies are respiratory and cardiovascular**.** Respiratory distress in newborn is one of the commonest conditions contributing to 30-40% of admissions in NICU **Keywords**: PDA, BPD, Surfactant, Ductus Arteriosus.

I. INTRODUCTION

Preterm birth is certainly a public health problem. According to the World Health Organization (WHO), prematurity is the leading cause of death among newborns and it comes in second between children below five years old, after pneumonia.Aside from being an important cause of mortality, premature birth increases the risk of serious lifetime disabilities.[1] Globally, Preterm Birth (PTB) is the single largest cause of neonatal deaths. A birth that takes place before the mother has been pregnant for at least 37 weeks construes a preterm birth. In India, among the total 27 million babies born annually, 3.6 million babies are born preterm, and over 300,000 of these preterm babies die each year because of associated complications. India, with its highest number of PTBs and the highest number of preterm deaths worldwide, contributes 25% of the overall global preterm

related deaths. Despite substantial efforts to introduce new therapies for prevention, it continues to contribute significantly to neonatal and infant mortality. The effects of PTB extend beyond the early infancy with substantial long-term consequences in late childhood and adult life.[2] Preterm births , apart from being a reason for mortality also lead to multiple morbidities which have to be dealt in both in the immediate neonatal period as well as later in infancy .Complications of prematurity are the underlying reasons for the higher rate of infant mortality and morbidity in preterm infants compared with full-term infants. The risk of complications increases with increasing immaturity. Thus, infants who are extremely preterm (EPT), born at or before 25 weeks of gestation, have the highest mortality rate (approximately 50 percent) and if they survive, are at the greatest risk for severe impairment. Complications of the preterm infant are divided into short-term complications (eg, respiratory and cardiovascular complications), which occur in the neonatal period, and long-term sequelae (eg, neurodevelopmental disabilities such as cerebral palsy) in patients who survive and are discharged from the neonatal intensive care unit (NICU) . Short-term complications increase the risk of long-term sequelae.[3] The most common short term morbidities faced by neonatologists in preterm babies are respiratory and cardiovascular**.** Respiratory distress in newborn is one of the commonest conditions contributing to 30-40% of admissions in NICU. In preterm infants, respiratory distress syndrome (RDS) being the most common cause (almost 90%) while in the late preterm and term infants, transient tachypnea of the newborn (TTNB) is the predominant cause (68%).[5]In the age group considered in our study of preterm babies (gestation 24-34 weeks) the common respiratory morbidities are RDS, TTNB and pneumonia, Respiratory distress syndrome or RDS , formerly referred as hyaline membrane disease, remains a dominant clinical problem encountered among preterm infants.The incidence of RDS is inversely proportional to gestational age: 95% to98% of infants born at 22-24 weeks gestation have RDS , decreasing to approximately 25% in infants with birth weights between 1251 and 1500gms .[6,7] In premature infants, respiratory distress syndrome develops because of impaired surfactant synthesis and secretion leading to atelectasis, ventilation-perfusion (V/Q) inequality, and hypoventilation with resultant hypoxemia and hypercarbia. Blood gases show respiratory and metabolic acidosis that cause pulmonary vasoconstriction, resulting in impaired endothelial and epithelial integrity with leakage of proteinaceous exudate and formation of hyaline membranes (hence the name).The relative deficiency of surfactant decreases lung compliance (see the image below) and functional residual capacity, with increased dead space. The resulting large V/Q mismatch and right-to-left shunt may involve as much as 80% of the cardiac output. However , in recent years, there has been significant improvement in the mortality and morbidity associated with RDS . This can be attributed primarily to the introduction of pharmacological acceleration of pulmonary maturity and development of exogenous surfactant replacement therapy, Patent ductus arteriosus remains a conundrum for the neonatologists. Hence it is important to identify the predisposing conditions which may lead to persistence of the patent ductus arteriosus. Whether administration of surfactant therapy in babieswith respiratory distress leads to increased incidence of Patent ductus arteriosus is not very clear till date. Various studies have reported incidence of PDA after administering surfactant to as much as 78% to some studies reporting no difference in opening of PDA after surfactant replacement therapy.

II. OBJECTIVES

To determine the incidence of haemodynamically significant patent ductus arteriosus in babies between 24-34 weeks gestation among those receiving surfactant replacement therapy and on respiratory support and those on respiratory support and not receiving surfactant.

III. REVIEW OF LITERATURE

WHO defines preterm birth as babies born alive before 37 weeks of pregnancy are completed. It is the leading cause of death worldwide for children below 5 years ofage. New global estimates show that in 2014, approximately 10.6% of all live births globally were preterm that is around one in ten babies born in this world are preterm. Worldwide, India tops the list of total number of preterm babies born in the world. In India, among the total 27 million babies born annually, 3.6 million babies are born preterm, and over 300,000 of these preterm babies die each year because of associated complications. India, with its highest number of PTBs and the highestnumber of preterm deaths worldwide, contributes 25% of the overall global preterm related deaths. Despite substantial efforts to introduce new therapies for prevention, it continues to contribute significantly to neonatal and infant mortality. The effects of PTB extend beyond the early infancy with substantial long-term consequences in late childhood and adult life. The

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morbidities of preterm babies are both immediate and long term. The most common morbidities in the immediate neonatal period are respiratory and cardiovascular. Respiratory distress in newborn is one of the commonest conditions contributing to 30-40% of admissions in NICU . Respiratory distress occurs in 2.2% of all newborns and in almost 60% of the infants below 1000 gram.(ELBW)[4] according to NNPD data (2002-03), 5.8% of the live born infants had respiratory morbidities. Gregory et al , in 1971,introduced continuous positive airway pressure to maintain functional residual capacity for infants with RDS. This was the first application of the respiratory physiology of RDS to improve outcomes in babies with RDS. Simultaneously, Ehnorning and Robertson,demonstrated feasibility of surfactant treatment for lung immaturity in animal models in the 1970's.Since the description of the pathophysiology of RDS, studies investigating remedies that supplement PS deficiencies in animal models of RDS have been conducted. In 1980, Fujiwara et al. performed treatment via the respiratory tract in 10 pediatric patients with RDS, using Surfactant-TA (Surfacten®; Mitsubishi Tanabe Pharma Corporation, Tokyo, Japan), an artificial PS preparation that was reconstituted by adding phospholipids (PLs) to PS extracted from bovine lung. This was the first successful treatment using artificial PS supplementation in humans, and has since resulted in improvement in oxygenation, treatment progress,and prognosis. This therapy has been further developed in the treatment of RDS, which was previously limited to conventional oxygen therapy, artificial ventilation therapy, and other symptomatic therapies. It was the first time that a treatment method of complementing PS with artificial preparations was used, which was a milestone in this field. Since then, this therapy has become the most important and definitive method of neonatal RDS therapy, A common cause of early systemic and pulmonary infections in the neonate is Group B Streptococcus (GBS). It affects approximately 1–4/1,000 newborn infants, and carries with it a substantial risk of mortality.28 Most infants with GBS infection exhibit signs of pulmonary compromise, often manifesting as respiratory failure requiring intubation and mechanical ventilation. The mechanism of action is believed to involve leakage of surfactant inhibitors and/or plasma proteins into the bronchoalveolar space, causing a secondary surfactant deficiency or inactivation. It has thus been postulated that surfactant replacement could improve clinical respiratory status by improving deranged pulmonary mechanics. Persistent patency of the ductus arteriosus in preterm infants with respiratory distress syndrome (RDS) has concerned physicians for long. Medical literature has documented the adverse consequences of delayed ductus closure since it waslinked to bronchopulmonary dysplasia (BPD), prolonged ventilation, mortality.

IV. MATERIAL AND METHODS

This is Prospective Longitudinal Cohort study -Neonatal intensive care unit in the neonatology department, Institute of Postgraduate Medical Education and Research (IPGME&R) and Seth Sukhlal Karmani Memorial Hospital (SSKM Hospital), Kolkata. Study period of July 2019 to November 2020, STUDY POPULATION-All preterm neonates between 24-34 weeks of gestation with respiratory distress with requirement of respiratory support like Continuous positive airway pressure(CPAP),Non invasive positive pressure ventilation(NIPPV) ,heated humidified high flow(HHHFNC)or invasive ventilation for atleast 24 hours and fulfilling inclusion and exclusion criteria

Inclusion Criteria

All neonates between 24-34 weeks of gestation requiring respiratory support like HHHFNC,CPAP, NIPPV or Invasive ventilation for more than 24 hours whose parents have given consent for participation in this study.

Exclusion Criteria

Congenital heart disease(exceptASDand PFO) Chromosomal abnormalities

Gross congenital anomaliesCongenital lung malformation, SAMPLE SIZE AND ITS CALCULATION Based on studies showing incidence of PDA in babies < 1500 gms and those treated with surfactant therapy as 70% and incidence in similar group not treated with surfactant as 40%, power as 80% and alpha error of 5Sample size have been calculated using the formula n > 2(Z α + Z 1-β) 2 x p*q/d 2 , where p = (p 1+ p 2)/2 , q = 1-p, and d is p 1 -p 2 Now assuming p value <0.05 to be significant and considering effect to be two sided, we get Z α =1.96; assuming power of study to be 80% we get Z 1-β =0.84. taking p 1 and p 2 as the incidence of PDA in babies < 1500 gms, in the 2 groups as 40%and 70% respectively using the above formula we get n = 35 in each group. Assuming a20% drop out rate 42 patients were included in each group. Hence Total Sample Size was taken as 84.% , a sample size of 42 in each group was taken and a total of 84.

This was a observational study in the NICU patients and investigator has collecteddata of

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relevant clinical events, examinations and investigations. The functional echocardiography examination is a non invasive procedure and has been maintaining strict asepsis protocol, without affecting haemodynamic status of the baby. The individual examination was always abandoned whenever there was slightest indication of haemodynamic instability.

V. RESULTS

The study was conducted in the department of Neonatology, IPGME & R ,SSKM Hospital after prior approval of the study protocol by the institutional ethics committee. The Neonatology unit of the SSKM hospital is a level III one with annual admission of around 3500 newborn. The study was conducted from July 2019 to November 2020. During this duration , 220 babies were admitted in the gestation age 24-34 weeks who required respiratory support in the initial 24 hours of life. By calculating attrition rate of 20%, 101 babies were screened of which a total number of 84 sample size were taken as per the study selection criteria and assessed for the requirement of Surfactant replacement therapy(SRT). 42 babies received SRT with respiratory support while 42 received only respiratory support without SRT as per criteria described above. All babies were followed up by repeated Echocardiography for development of hsPDA. Median maternal age in SRT group was 28.6 (24-31) years while in group notreceiving SRT was 27.5 (23.73- 31) years.11(26.5%) mothers in SRT group had PIH while 9 (21%) in the other group had PIH. P value 0.0847 (16%) mothers had GDM in SRT group while 1 (2.5%) in the other group had GDM. 3 (7.14%) mothers had history of APH in the SRT group while 4 (9.52%) hadhistory of APH in the antenatal period. P value 0.306Antenatal steroid coverage in SRT group was 34(81.4%) while the other groupwas 30(71.4%). P value 0.306Median antenatal steroid dose in SRT group was 1.48 (0.75-2.0) and in other group was 1.71 (0.0-3.0) . p value 0.525.

		GROUP				
		SRT	NO SRT	Total	p Value	Significance
PDA	NO	18(42.86)	25(59.52)	43(51.19)	0.127	Not Significant
	YES	24(57.14)	17(40.48)	41(48.81)		
Total		42(100)	42(100)	84(100)		

Pearson's Chi Square test for Independence of Attributes

		GROUP				
		SRT	NO SRT	Total	p Value	Significance
HSPDA	NO	19(45.24)	31(73.81)	50(59.52)	0.008	Significant
	YES	23(54.76)	11(26.19)	34(40.48)		
Total		42(100)	42(100)	84(100)		

Pearson's Chi Square test for Independence of Attributes

As gestational age was found to be having statistically significant difference between the two groups, binary logistic regression equation with dependent variable as hsPDA was analysed. In the group that did not receive SRT, there were 11(26.19%) babies who developed hsPDA. All these 11 ductus arteriosus were treated with paracetamol as per unit protocol. 9(81.8%) underwent closure after treatment while 2 (18.18%) required Ibuprofen for treatment. Both closed after treatment with ibuprofen. 6 babies had developed PDA but was non significant. They were followed up byserial echocardiography but not treated Out of the 6 babies who had developed PDA but were non significant, 5 (83.3%) underwent spontaneous closure. 1 baby's PDA persisted but was not haemodynamically significant hence baby was discharged and follow up echocardiography was done.The outcome parameters like death before 40 weeks of age, culture positive sepsis, IVH> gr 2,BPD, ROP, NEC>2 have been analysed by Chi square statistics. 2(4.76%) patients in the SRT group developed culture positive sepsis while none reported culture positive sepsis in the other group. P value was 0.147,which was not significant. Meningitis was equal in both the groups. Pulmonary haemorrhage was seen in 9(21.43%) in the SRT group while 5 (11.9%) developed it. P value 0.242. Regarding IVH, 2 patients (4.76%) developed IVH in the SRT group while 3 patients developed in the other group. P value was 0.668. NEC >stage 2 was seen in 6 (14.2%) in SRT group and 4(9.52%) in the other group. P value 0.50.ROP was seen in 1 baby in SRT group (2.39%) and in 2 babies(4.76%) in the other group. p value0.557.

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VI. DISCUSSION

The incidence of PDA after surfactant therapy has been an unanswered question for almost a decade. There are a few available literature which have retrospectively studied this topic but none prospectively. This present study with a sample size of 84 , 42 in each group studied prospectively the development of PDA after SRT administration in one group and without SRT but requiring respiratory support in the other group. The study population consisted of babies from the gestation 24- 34 weeks in both the groups. The mean gestation in the SRT group was 964 grams and 1070 grams. 19% babies were SGA in the SRT group while 33.33% were SGA in the other group. This difference , although statistically not significant , may have been present due to the fact that babies requiring SRT are lower in gestation and those of similar birth weight but not requiring SRT are usually SGA babies. 40% were male babies in the SRT group and 43% were male in the other group which was almost similar. Around 70% were born through caesarean section in the SRT group and around 58% in the non SRT group. Such a high rate of caesarean section may be seen as this is a tertiary care centre catering to high risk pregnancies referred from the neighbouring regions. The median gestational age in the SRT group was 29 weeks while in the other group was 31 weeks which was statistically significant , p value < 0.001. Despite our best efforts to match both the groups this difference has come. This may be possible as the babies requiring SRT are lower in gestation and those not requiring SRT tend to have attained lung maturity due to increased gestational age. The incidence of PDA was 57.14% in the SRT group and 40.48% in the other group which was not statistically significant. However haemodynamically significant PDA was present in 54.7% babies in SRT group and 26.19% in the other group which was statistically significant .This hs PDA incidence is slightly higher than other studies reported .However they have also reported significant difference in incidence of hs PDA after surfactant therapy. (40% in SRT group vs17 % in the other group.[154] As gestational age was found to be having statistically significant difference between the two groups, binary logistic regression equation with dependent variable as hsPDA was analysed. Despite analyzing via binary logistics regression , the p value was 0.029 which was significant. Hence, this study concludes that instilling surfactant leads to increased incidence of haemodynamically significant PDA. Biologically this may be possible due to sudden change in pulmonary graphics after SRT instillation leading decreased pulmonary vascular resistance and increased incidence of a hemodynamically significant PDA. This is similar to the other retrospective studies published on SRT and PDA. The requirement of invasive ventilation during the first 24 hours showed significant difference between the two groups. 61.9% of the babies in the SRTgroup were on invasive ventilation while in the other group only 21.4% babies received invasive ventilation. P value was <0.001 which was statistically significant. This difference can be explained by the fact that these babies receiving SRT were lesser in gestation as compared to the other group and hence the requirement of invasive ventilation in this group was more.

Amongst the rest of the secondary outcome parameters like IVH, BPD, culture positive sepsis, ROP and death is seen in this study. This study also reestablishes the fact that SRT administration doesn't lead to reduction in BPD.(57.14% in SRT group and 53.14% in the other group, p value 0.765)While causality may not be ascribed, the present study suggests an important association between surfactant replacement therapy and the ductus arteriosus asmanifested by increased incidence of hs PDA and longer duration required for closure. This study is one of its kind as it uses clear definition of hsPDA, the criteria defined for initiating treatment was clear and standardized and it was prospective in nature. The limitations of this study were that randomization was not possible hence purposive sampling was done and it had a small sample size. Also the development and clinical impact of a hsPDA may also relate to underlying disease as respiratory disease itself has been proposed as an important factor in the development of prolonged ductal patency in a previous study. The current management of RDS relies heavily on surfactant therapy due to its beneficial effects on oxygenation and pulmonary function. Despite significant advances in respiratory management and neonatal intensive care, the benefits of SRT have not translated into reduced rates of neonatal morbidities. The hemodynamic consequences of surfactant administration are likely to be complex but need further investigation. The purpose of the present study is not to dissuade neonatologists from administering surfactant to patients who are likely to benefit treatment, but to highlight the potential association of intervention to a hemodynamically significant ductus arteriosus. It is important, however, that the need for surfactant administration in preterm babies be individualized. Hence this study highlights the early use of functional echocardiography in patients administered with

surfactant.

VII. CONCLUSION

The most common short term morbidities faced by neonatologists in preterm babies are respiratory and cardiovascular**.** Respiratory distress in newborn is one of the commonest conditions contributing to 30-40% of admissions in NICU.

REFERENCES

[1] WHO; Howson C, Kinney M, Lawn J (Eds.). Born Too Soon: The Global Action Report on Preterm Birth. Geneva, Switzerland: World Health Organization, 2012.

[2] https://www.nibmg.ac.in/Ministry of Science & Technology, Government ofIndia
https://www.uptodate.com/contents/short-term-complications-of-the-preterm-infant/abstract/1

[3] NNPD working definitions. NNPD report 2002-03. NNPD network, ICMR; p67

[4] Rubaltelli FF, Dani C, Reali MF, et al. Acute neonatal respiratory distress in Italy: a one year prospective study, Acta Paediatr 1998:97;1261-68.

[5] Avery ME etal. Surface properties in relation to atelectasis and hyaline membrane disease.Am J Dis Child,1959;97:517

[6] Fanaroff AA,Store BJ,Wright LL,et al.NICHD Neonatal Resarch Network. Trends in neonatal Morbidity and mortality for very low birth weight infants, Am J Obstetrics Gynaecol. 2007; 196:147e 141-147e148

[7] Calkovska A, Mokra D, Drgova A, et al. Bronchoalveolar lavage with pulmonary surfactant/dextran mixture improves meconium clearance and lung functions in experimental meconium aspiration syndrome. Eur JPediatr. 2008; 167: 851–857

[8] Herting E, Gefeller O, Land M, et al. Surfactant treatment of neonates with respiratory failure and group B streptococcal infection. Members of the Collaborative European Multicenter Study Group. Pediatrics. 2000; 106: 957–964.

[9] Pandit PB, Dunn MS, Colucci EA. Surfactant therapy in neonates with respiratory deterioration due to pulmonary hemorrhage. Pediatrics. 1995; 95: 32–36

[10] Hentschel R, Jorch G. Acute side effects of surfactant treatment. J Perinat Med.2002;30:143–8

[11] Long W, Corbet A, Cotton R, et al. A controlled trial of synthetic surfactant in infants weighing 1250 g or more with respiratory distress syndrome. The American Exosurf Neonatal Study Group I, and the Canadian Exosurf Neonatal StudyGroup. N Engl J Med. 1991;325:1696–703

[12] fa naroff and martin, pathophysiology of rds

[13] Shimada S,Kasai T, Konishi M, Fujiwara T. Effects of patent ductus arteriosus on left ventricular output and organ blood flows in preterm infants with respiratory distress syndrome treated with surfactant. J Paed 1994; 275: 120-7

[14] Jeegathesan P, Lanus V, Buchch B, Yoon G BA et al. Increased indomethacin dosing for persistent patent ductus arteriosus in preterm infants: a multicentre randomized control trial.J Paediatric 2008 153:183-189

[15] Van Overmiere B, Chemtob S. The pharmacological closure of patent ductus arteriosus. Sem in fetal and neonatal medicine 2005 : 10-177-184.

[16] Northway Jr WH, Rosan RC, Porter DY. Pulmonary disease following respiratory therapy of hyaline-membrane disease. Bronchopulmonary dysplasia. N Engl J Med 1967; 276:357-368.