PREDICTORS OF PERSISTENT PULMONARY HYPERTENSION OF THE NEWBORN AMONG PATIENTS WITH MECONIUM ASPIRATION SYNDROME; A TERTIARY CARE HOSPITAL BASED CROSS-SECTIONAL STUDY FROM EASTERN INDIA

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ABSTRACT

Background: Meconium aspiration syndrome(MAS) is a common cause of respiratory distress in neonates. One third of such cases develop persistent pulmonary hypertension of the newborn(PPHN), which is also a major cause of mortality.

Aims: To evaluate characteristics in neonates with MAS associated with increased risk of development of PPHN.

Settings and design: This cross-sectional observational study was conducted in the neonatal unit of a tertiary level paediatric hospital of Eastern India.

Materials and Methods: Data was collected from June 2012 to June 2014. Clinical, radiological and echocardiographic parameters of patients with Meconium Aspiration Syndrome(MAS) were recorded .Patients having congenital heart diseases were excluded.

Statistical analysis used: Statistical software R and MS Excel were used for statistical analysis. Comparisons between categorical variables were performed using Fischer's exact test for count data and 2-sample test for equality of proportions. In these tests, a p value less than 0.05 was considered significant.

Results: Out of 103 MAS,18(17.4%)had PPHN.Among MAS patients ,gestational age of 38 weeks or above, presence of moderate to severe hypoxic ischemic encephalopathy, prolonged oxygen requirements, hyperexpansion in chest xray, Tricuspid Regurgitation ,Patent Ductus Arteriosus,right ventricular dilatation and/or hypertrophy were significantly associated with patients with development of PPHN among MAS patients($p<0.05$).Combination of characteristics like age of 38 weeks or above ,with hypoxia and hyperexpansion have high sensitivity, specificity in predicting PPHN.

Conclusion: Combined characteristics like age of 38 weeks or above, with prolonged oxygen requirements and hyperexpansion may be used at even at centres where echocardiography facilities are not available for prediction of PPHN.

***Keywords** : Meconium aspiration syndrome,Neonate,Persistent pulmonary hypertension of newborn,Risk factors*

MAIN DOCUMENT

Introduction

Meconium aspiration syndrome (MAS) is a common cause of respiratory distress in neonates, which is associated with high incidence of morbidity and mortality **[1]** .Approximately 5% of neonates born through meconium stained amniotic fluid (MSAF) aspirate meconium and one third cases of MAS is associated with persistent pulmonary hypertension of newborn (PPHN), which is a major cause of mortality associated with this syndrome **[2].**

Persistent pulmonary hypertension of newborn is defined as a failure of normal pulmonary vascular adaptation at or soon after birth. This results in a persisting high pulmonary vascular resistance, such that the pulmonary blood flow is diminished and deoxygenated blood is shunted to systemic circulation through open foramen ovale and/or ductus arteriosus **[3].** It occurs in approximately 1.9 per 1000 live births (0.4-6.8/1000 live births) **[4].** PPHN has a reported mortality ranging from 4-33% **[5].** It is also associated with long term complications of chronic pulmonary disease, adverse neurodevelopmental outcome in the form of seizures, cerebral palsy and mental retardation **[6].**

This cross-sectional observational study was undertaken to evaluate the patient characteristics in neonates with MAS that are associated with increased risk of PPHN considering the significant incidence of the disease, its implication in terms of morbidity and mortality of the newborns affected and the scanty literature available on this subject, particularly from this region.

Materials And Methods

Required permission of ethical committee of the institution was taken. This cross-sectional observational study was conducted in the neonatal unit of a tertiary level pediatric hospital of Eastern India. Data was collected from June 2012 to June 2014. All neonates with documented history of delivery through meconium stained amniotic fluid (MSAF) with onset of respiratory distress within few hours of birth whose symptoms cannot be otherwise explained, with characteristic chest X-ray changes were included in the study after taking informed consent from the parents **[7].** Patients with congenital heart diseases documented by echocardiography were excluded.

Hypoxic ischemic encephalopathy (HIE) was classified according to Levene's classification**[8].** An oxygen requirement for more than three days was considered as persistent hypoxemia**[9].** Documented birth weight and gestational age of neonates were plotted on the intrauterine growth charts to categorize them as appropriate for gestational age(AGA), small for gestational age (SGA) or large for gestational age (LGA).Two chest X-ray findings i.e,bilateral nodular/ patchy opacities and hyperexpansion were statistically analysed as they were the most common findings **[10].**

Tricuspid valve regurgitation(TR) was taken as a marker of pulmonary hypertension .Pulmonary artery pressure(PAP) was evaluated using continuous wave Doppler sampling of the velocity of tricuspid regurgitation jet, when present**[2].** In this study,PPHN was defined by echocardiographic finding of peak velocity of a tricuspid regurgitant jet with a peak pulmonary pressure gradient >20mmHg and/or either bidirectional or R-L shunting of blood through Patent Ductus Arteriosus(PDA) or Patent foramen ovale(PFO)**[1,11].**

All data were compiled and tabulated. Statistical software R and MS Excel were used for statistical analysis. Comparisons between categorical variables were performed using Fischer's exact test for count data and 2-sample test for equality of proportions. In these tests, a p value less than 0.05 was considered significant.(Se- standard error,CL-confidence limit,LCL-lower CL,UCL-Upper CL)

Results

Table 1 shows presence of different characteristics in 103 neonates with MAS .Most of the patients were of gestational age 38 weeks and above.Among all the patients with MAS,boys were more in number. 65.05% ± 4.70% patients had prolonged hypoxemia. Chest X-ray findings of bilateral nodular/ patchy opacities were more than hyperexpansion of lung among all MAS patients.

Table-1: Presence of different characteristics in neonates with MAS

Characteristics	Mean ± Se (n=103)	95% confidence interval	
		LCL	UCL
Boy	67 (65.05% ±4.70%)	55.84%	74.26%
AGA	93 (90.29% ±2.92%)	84.57%	96.01%
LUCS	44 (42.72% ± 4.87%)	33.17%	52.27%
Gestational age			
38 weeks & above	81 (78.64% ± 4.04%)	70.73%	86.56%
Co-morbidities			
Moderate to severe HIE	45 (43.69% ± 4.89%)	34.11%	53.27%
Culture proven sepsis	13 (12.62% ± 3.27%)	6.21%	19.03%
Prolonged hypoxemia	67 (65.05% ± 4.70%)	55.84%	74.26%
CRP Positive	45 (43.69% ±4.89%)	34.11%	53.27%
Chest X-ray findings			
Hyperexpansion	26 (25.24% ± 4.28%)	16.85%	33.63%
Bilateral nodular/ patchy opacities	62 (60.19% ± 4.82%)	50.74%	69.65%
Echocardiography findings			
RV Dilation with Hypertrophy	7 (6.80% ± 2.48%)	1.94%	11.66%
Tricuspid Regurgitation (TR)	51 (49.51% ± 4.93%)	39.86%	59.17%
PDA	16 (15.53% ±3.57%)	8.54%	22.53%

Out of total 103 neonates under study,86 were delivered in institution,17 were non institutional.Number of patients delivered by Caesarean section were 44 i.e,(51.16% ± 5.39%), 95% CI (40.60%, 61.73%), out of all the institutional deliveries.

Table 2 shows comparison of associated factors in PPHN and Non-PPHN neonates.

Univariate logistic regression analysis showed characteristics like higher gestational age(38 weeks and above),moderate to severe HIE,prolonged hypoxemia, chest X-ray finding of hyperexpansion ,echocardiographic findings of RV abnormality(dilation/hypertrophy),TR,PDA have significant association with development of PPHN in MAS patients .However, association was not found between gender, mode of delivery and culture proven sepsis among MAS patients who developed PPHN.

Table -2: Comparison of Associated characteristics between PPHN and Non-PPHN neonates with MAS

Major characteristics	PPHN (Mean ± Se) (n = 18)	Non-PPHN (Mean ± Se) (n = 85)	P value (greater than)	Odds Ratio	LCL (95% CI Odds Ratio)
Sex					
Boy	77.78% ± 9.80%	62.35% ± 5.26%	0.165	2.099	0.697
Girls	22.22% ± 9.80%	37.65% ± 5.26%	0.9398	0.4764	0.134
Mode of delivery					
LUCS	55.56% ± 11.71%	40.00% ± 5.31%	0.2957	1.863	0.594
Normal Vaginal Delivery	44.44% ± 11.71%	60.00% ± 5.31%	0.9292	0.537	0.197
AGA	94.44% ± 5.40%	89.41% ± 3.34%	0.447	2.002	0.309
Gestational age					
38 weeks & above	100% ± 0.00%	74.12% ± 4.75%	0.0083 (< 0.05)	∞	1.755
Co-morbidities					
Moderate to severe HIE	72.22% ± 10.56%	37.65% ± 5.26%	0.008 (< 0.05)	4.244	1.497 (>1)
Culture Proven sepsis	11.11% ± 7.41%	12.94% ± 3.64%	0.710	0.842	0.123
Prolonged hypoxemia	100%	57.65% ± 5.36%	0.001 (< 0.05)	∞	3.743 (>1)
CRP Positive	61.11% ± 11.49%	40.00% ± 5.31%	0.084	2.337	0.872
Chest X-ray findings					
Hyperexpansion	77.78% ± 9.80%	14.12% ± 3.78%	2.49e-07 (< 0.05)	20.308	6.302 (>1)
Bilateral nodular/ patchy opacities	16.67% ± 8.78%	69.41% ± 5.00%	1	0.09	0.021
Echocardiography findings					
RV dilation with Hypertrophy	38.89% ± 11.49%	0.00%	1.61e-06 (<0.05)	∞	12.136 (>1)
TR	94.44% ± 5.40%	40.00% ± 5.31%	4.12e-05 (< 0.05)	24.864	4.363 (>1)
PDA	50.00% ± 11.79%	8.24% ± 2.98%	0.00012 (<0.05)	10.724	3.392 (>1)

Multivariate logistic regression (forward, step-wise) with binomial population model was done using eight factors namely gestational age of 38 weeks & above, hyperexpansion, Tricuspid Regurgitation,

prolonged hypoxemia, HIE, PDA and RV abnormalities (dilation /hypertrophy) to identify factors significantly associated with PPHN in neonates with MAS. A '*P*' value of <0.05 is considered significant. The best prediction model is on Gestational age of 38 weeks & above, hyperexpansion, prolonged hypoxemia and Tricuspid Regurgitation, which identifies hyperexpansion (P value 0.00039) increase the odds (Adjusted Odds Ratio 28.00, 95% CI (5.28, 236.00)) of developing PPHN in neonates with MAS. All these factors taken together has a Sensitivity of 77.78%, Specificity of 97.65%, and Positive Predictive Value (PPV) of 87.50% and Negative Predictive Value (NPV) of 95.40%.

Factors like neonates with gestational age ≥38 weeks, oxygen requirement for more than 3 days, and Chest X-ray finding of hyperexpansion taken together has also high sensitivity of (77.78%) and specificity (95.29%).

Table – 3: Sensitivity and Specificity of different characteristics associated with PPHN in neonates with MAS

Characteristics	PPV	NPV	Sensitivity	Specificity	J - Young Index
Hyperexpansion	53.85%	94.81%	77.78%	85.88%	63.66%
Tricuspid Regurgitation	31.03%	100%	100%	52.94%	52.94%
Gestational age ≥ 38 weeks & Hyperexpansion	70.00%	95.18%	77.78%	92.94%	70.72%
Gestational age ≥ 38 weeks Hyperexpansion & prolonged hypoxemia	77.78%	95.29%	77.78%	95.29%	73.07%
Gestational age ≥ 38 weeks, Hyperexpansion, prolonged hypoxemia & Tricuspid Regurgitation	87.50%	95.40%	77.78%	97.65%	75.42%

Discussion

Fetal hypoxia and perinatal asphyxia, often associated with meconium aspiration disrupts normal transition from fetal to adult circulation, from pulmonary vasoconstriction to dilation. In severe intrauterine asphyxia, there may be vasoreactivity manifested as muscularization of most distal pulmonary arteries resulting in PPHN(especially in term babies) **[12].** In this study ,PPHN was found to be associated with higher gestational age group i.e. 38 weeks and above,as it is also is found in literature **[13]**. Patients with PPHN were also found to be significantly associated with moderate to severe hypoxic ischemic encephalopathy and prolonged hypoxemia**[1,14].** So, intrapartum monitoring and timely intervention , as the gestational age progresses is extremely important to prevent the complications associated with MAS . Unlike previous studies in some developed countries, characteristics like birth by Caesarian section or male gender were not significantly greater in PPHN group in this study**[4,6].**

In this study, chest X-ray finding of hyperexpansion is significantly higher in the PPHN group. It also has a high sensitivity and specificity in prediction of associated PPHN in MAS patients.Gestational age more than 38 weeks in neonates with MAS with Chest X-ray findings of hyperexpansion and oxygen requirement more than 3 days had both high sensitivity and specificity in predicting development of PPHN in them .By using these combination of characteristics it may be possible to predict development

of PPHN in centres where echocardiography facility is not available. However,these findings need to be confirmed with a study taking a larger sample.

This echocardiographic finding right ventricle abnormality(dilation/hypertrophy),was seen to be more associated with MAS patients with PPHN than those without pulmonary hypertension. The right ventricle changes in PPHN patients in the present study could be due to the increased pulmonary vascular resistance that increases right ventricular after load,which is manifested acutely by right ventricular dilatation or reduced right ventricular wall thickness**[15].**In previous studies, 70% of PPHN patients had Tricuspid regurgitation, permitting systolic PAP estimation, in this study incidence of TR is much higher in the PPHN group.In the present study the incidence of PDA in PPHN patients is higher than non PPHN . **[9,16].**

To conclude a significant number of MAS patients develop PPHN. It remains unclear whether some of these factors as stated above are direct risk factors of persistent pulmonary hypertension of the newborn or are simple associations with PPHN. However, whenever such associated factors are noticed in a patient with meconium aspiration syndrome,clinicians must monitor and intervene appropriately.Echocardiography is necessary diagnostic tool for detecting PPHN.In centres where echocardiography facility is not available, prediction for development of PPHN may be possible using characteristics like, gestational age of 38 weeks or more, prolonged hypoxemia and Chest X-ray changes of hyperexpansion.

Acknowledgements: We are grateful to Prof(Dr) Mala Bhattacharya,Principal and Dr Dilip Kumar Paul,MSVP of Dr B C Roy Post Graduate Institute of Pediatric Sciences for allowing us and providing us all the support to do this study .We are thankful to Dr Arindam Kundu for helping us with the statistical analysis,Dr Kunal Biswas and Dr P K Tiwary for their help regarding echocardiography.

Competing Interest: None

Funding: None

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