International Journal Dental and Medical Sciences Research
Volume 4, Issue 2, Mar-Apr 2022 pp 151-157 www.ijdmsrjournal.com ISSN: 2582-6018

Association of Early Hyperoxemia in Perinatal Asphyxia with Hypoxic-Ischemic Encephalopathy in Neonates

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Submitted: 15-03-2022 Accepted: 23-03-2022

ABSTRACT

The study aimed to determine association between early hyperoxemia in perinatal asphyxia and development of moderate to severe hypoxic ischemic encephalopathy (HIE). A cross sectional study was conducted in the Neonatology Department, Children Hospital, Pakistan Institute of Medical Sciences (PIMS), Islamabad from September 2017 to March 2019. A total of 374 neonates were enrolled.All inborn babies of gestational age ≥ 36 weeks with perinatal asphyxia having pH (Power of Hydrogen Ions) of Arterial blood of ≤ 7.0 within first hour of life OR those having Base Deficit of Arterial blood of ≥ 12mmol/L within first hour of life were included. Study was approved by hospital ethics committee. Study outcome was assessed in terms of association of early hyperoxemia with development of severity of HIE. Data was analyzed in SPSS version 20.0. Age and sex of babies was similar in hyperoxemic and non-hyperoxemic groups. Apgar score at 1 minute and 5 minutes was found significantly low in hyperoxemia patients. (p-value, <0.001). Out of 157 non-hyperoxemia cases, 94 (59.9%), 29 (18.5%) and 34 (21.7%) whereas out of 217 neonates with hyperoxemia, 99 (45.6%), 68 (31.3%) and 50 (23.0%) neonates had HIE-I, HIE-II and HIE-III, respectively. Hyperoxemia was significantly associated with moderate to severe Hypoxic Ischemic Encephalopathy (p-value, 0.009). The final predictors of hyperoxemia weremoderate to severe HIE, low APGAR score at 5 minutes and hypocapnia.Moderate to severe HIE is significantly associated with hyperoxemia during the first hour of life in neonates with perinatal asphyxia

Keywords; Perinatal asphyxia, early hyperoxemia, Hypoxic Ischemic Encephalopathy

I. INTRODUCTION

Birth asphyxia or still births is the fifth most common cause of death among children under age 5 years worldwide[1]. Approximately, 4 million newborns experience birth asphyxia each year, accounting for an estimated 1 million deaths and 42 million disability-adjusted life years. Most of them have brain injury and long-term sequelae, cerebral palsy, epilepsy, and sensory deficits[1].

Hyperoxemia and hypocapnia occurs unintentionally in severely asphyxiated neonates in the first postnatal hour[2].

In severely asphyxiated infants it is difficult to maintain the correct balance between hyperoxemia and hypoxemia. Oxygen supplementation and/or ventilation may be inadequate or excessive because of variable postnatal cardio-respiratory adaptation and responses to therapeutic interventions, difficulty in monitoring and interpreting blood gas measurements, and inability to implement corrective action rapidly. The excessive respiratory support result in hyperoxemia which may increase the risk of injury to brain mediated primarily by the production of free oxygen radicals[3]. Many of these infants sustain significant brain injury and develop long-term sequelae[4].

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The perinatal transition from low oxygen (with PaO2 of 25 to 30 mmHg) to the significantly higher oxygen environment after birth (with PaO2 of 580 to 100 mmHg) makes even the healthy newborn vulnerable to free radical production and oxidative stress[5]. The additional use of supplemental oxygen during resuscitation may result in early hyperoxemia after a perinatal insult leading to further reproduction of free radicals and higher oxidative stress, potentially worsening brain injury[6].

Observational studies in adults and children have demonstrated an association between hyperoxemia after resuscitation from cardiac arrest and mortality. The few published studies to date that have examined the association between hyperoxemia and neurodevelopment outcomes in asphyxiated neonates have reported conflicting results[7,8].

As reported by Kapadia VS et al the rates of moderate HIE was high in the hyperoxemia group and the incidence was directly related to the degree of hyperoxemia exposure on admission. The authors found out those 58.3% neonates who experiencedhyperoxemia developed HIE compared to 27.3% patients who were non-hyperoxemic[9].

Newly born infants with post-asphyxial HIE often have episodes of hyperoxemia and or hypocapnia between birth, transfer in the neonatal intensive care units and early postnatal hours of life. The aim of this study was to determine, if hyperoxemia add to the risk of brain injury after asphyxial event.

II. MATERIAL AND METHODS

The was a cross sectional study carried out in the Neonatology Department, Pakistan Institute of Medical Sciences (PIMS), Islamabad for 18 months from September 2016 to March 2018. A total of 374 neonates with perinatal asphyxia were enrolled. The sample size was calculated by using the WHO sample size calculator with the statistical assumptions of confidence interval of 95%, alpha error of 5% and anticipated population proportion of 58.3%[10]. A non-probability consecutive sampling technique was applied.

Hyperoxemia was defined as Partial Arterial Pressure of Oxygen (PaO2) > 100 mmHg detecting on arterial blood gas analysis within first hour of life. Hypocarbia was defined as Partial Arterial Pressure of Carbon Dioxide (PCO2) < 35mmHg detecting on arterial blood gas analysis within first hour of life. Similarly, hypercarbia was defined as Partial Arterial Pressure of Carbon Dioxide (PCO2) > 50mmHg detecting on arterial blood gas analysis within first hour of life. Perinatal asphyxia was defined as a condition of impaired blood gas exchange leading to progressive hypoxemia and hypercapnia with a significant metabolic acidosis evidenced by pH less than 7.00, base deficit greater than or equal to 12 mmol/L in fetal, cord or early neonatal blood samples.Hypoxic Ischemic Encephalopathy (HIE) was confirmed if babies have the spectrum of clinical findings on Sarnat and Sarnat AND convincing evidence of antepartum or intrapartum hypoxia using criteria outlined by International Cerebral Palsy Taskforce[11].

All inborn babies of gestational age ≥ 36 weeks with perinatal asphyxia having pH (Power of Hydrogen Ions) of Arterial blood of ≤ 7.0 within first hour of life OR those having Base Deficit of Arterial blood of ≥-12mmol/L within first hour of life were included. Those babies who received supplemental oxygen at birth and agreed to participate on informed consent were to be included. Babies were excluded if they were out born, those with congenital malformations (cardiac or metabolic), delivered with gestational age of less than 36 weeks, and those inborn babies who didn't receive supplemental oxygen at birth.

The study was approved by the hospital ethical committee. The babies with perinatal asphyxia, got admission within first hours of life and those fulfilling the study criteria were included in the study. On the basis of baseline ABGs taken on admission, newborns were further divided into two groups i.e. arterial PaO2 value as Hyperoxemia group (PaO2 more than 100mmHg) and Non-Hyperoxemia group (PaO2 less than 100mmHg). Both categories were followed upto six hours of life to check severity of Hypoxic ischemic encephalopathy using modified sarnat and sarnat staging criteria. Babies were also assessed for study outcome in terms of association of early hyperoxemia with development of severity of HIE.

Study data was analyzed in SPSS version 20.0. As per primary objective the severity of HIE was associated with hyperoxemia using Chi square test. The association between hyperoxemia and other risk factors was done by usingunivariate logistic regression analysis.

III. RESULTS:

The baseline characteristics of patients were found similar in hyperoxemia and non-hyperoxemia group. The mean (± SD) gestational age of neonates in non-hyperoxemia group was 38.5 (±1.6) weeks, whereas, it was 38.9 (±1.6) weeks in hypoxemic neonates. There were 97 (61.8%) males, while 60 (38.2%) females in non-hyperoxemia group whereas inhyperoxemia group,

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132 (60.8%) were males and 85 (39.2%) were females. The mean (± SD) birth weight of neonates in non-hyperoxemia group was 2.81 (±0.59) Kg, compared to 2.83 (±0.61) Kg in hyperoxemia, however, this difference was not statistically significant (p=0.684). In non-hyperoxemia, 56 (35.7%) neonates had fetal heart rate (FHR) deceleration, while in hyperoxemia, 72 (33.2%) had FHR deceleration. Similarly, nuchal cord and breech presentation were found similar between the two groups. (Table 1)

Furthermore, the clinical characteristics were compared between two groups. Apgar score at 1 minute and 5 minutes was found significantly low in hyperoxemia patients. (p-value, <0.001).

The mean (± SD) pH level was 6.87 (±0.14) non-hyperoxemiacompared to 6.92 (±0.15) in hyperoxemic neonates.

The mean (± SD) base deficit was -15.20 (±2.52) non-hyperoxemia group, whereas, it was -15.33 (±2.58) in neonates with hyperoxemia and this difference was not statistically significant (p=0.750). The mean (± SD) PaCO2 of neonates was found significantly low in hyperoxemia group (p-value, <0.001). Out of 157 neonates with non-hyperoxemia, 20(12.7%) had hypercapnea, while out of 217 neonates with hyperoxemia, 12(5.5%) had hypercapnea and the difference was significant (p-value, <0.025).On the other hand, hypocapnea was found significantly more frequent in hyperoxemia patients (p-value, <0.001). The mean (± SD) PaO2 68.6 (±18.5) in non-hyperoxemia, compared to 156.2 (±43.3) in neonates with hyperoxemia (p-value, <0.001). The mean (± SD) SPO2 and MAP levels were found similar in both groups (p-value, 0.146). Similarly, no difference in mean (± SD) temperature was noted. (Table 2)

Furthermore, the outcome of neonates between two groups. Out of 157 neonates with non-hyperoxemia, 94 (59.9%), 29 (18.5%) and 34 (21.7%) whereas out of 217 neonates with hyperoxemia, 99 (45.6%), 68 (31.3%) and 50 (23.0%) neonates had HIE-I, HIE-II and HIE-III, respectively. Hyperoxemia was significantly associated with moderate to severe Hypoxic Ischemic Encephalopathy in neonates with perinatal asphyxia (p-value, 0.009).(Figure I)

The final predictors and outcome of hyperoxemia were assessed by applying logistic regression analysis. Moderate to severe HIE, low APGAR score at 5 minutes and hypocapnia were all found significantly related to hyperoxemia. (Table 3)

Table 1: Baseline characteristics of patients in two groups

	Non-hyperoxemia (n=157)	**Hyperoxemia (n=217)**	**p-value**
Age at admission (in minutes)			
Mean ± SD	23.2±4.4	23.7±5.6	0.352
Age categories at admission			
Upto 20 minutes	61 (38.9%)	77 (35.5%)	1.00
21 - 30 minutes	94 (59.9%)	131(60.4%)	0.731
More than 30 minutes	2 (1.2%)	9 (4.1%)	0.173
Gestational Age (weeks)			
Mean ± SD	38.5±1.6	38.9±1.6	0.140
Sex			
Male	97 (61.8%)	132 (60.8%)	0.937
Female	60 (38.2%)	85 (39.2%)	
Birth weight (kg)			
Mean ± SD	2.81±0.59	2.83±0.61	0.684
FHR decelerations	56 (35.7%)	72 (33.2%)	0.969
Nuchal cord	7 (4.5%)	6 (2.8%)	0.551
Breech presentation	17 (10.8%)	24 (11.1%)	1.00

International Journal Dental and Medical Sciences Research
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Table 2: Clinical feature in the two groups

	Non-hyperoxemia (n=157)	Hyperoxemia (n=217)	p-value
Age at ABGs obtained(minutes)			
Mean±SD	44.48±4.8	44.65±8.8	0.818
pH			
Mean±SD	6.87±0.14	6.92±0.15	0.287
Base deficit			
Mean±SD	-15.20±2.52	-15.33±2.58	0.750
PaCO2			
Mean±SD	34.1±14.3	28.0±13.6	0.0001
Hypercapnea	20(12.7%)	12(5.5%)	< 0.025
Hypocapnea	96(61.1%)	181(83.4%)	<0.001
PaO2			
Mean±SD	68.6±18.5	156.2±43.3	0.0001
Mean arterial pressure (MAP)			
Mean±SD	39.2±7.8	39.1±8.9	0.930
SPO2			
Mean±SD	90.78%±6.64%	92.08%±6.51%	0.146
Temperature (^{0}F)			
Mean±SD	98.0±0.23	98.0±0.20	
APGAR score 1 min			
Mean±SD	4.11±2.01	3.41±2.16	0.001
APGAR score 5 min			
Mean±SD	6.45±1.66	5.68±1.98	0.0001

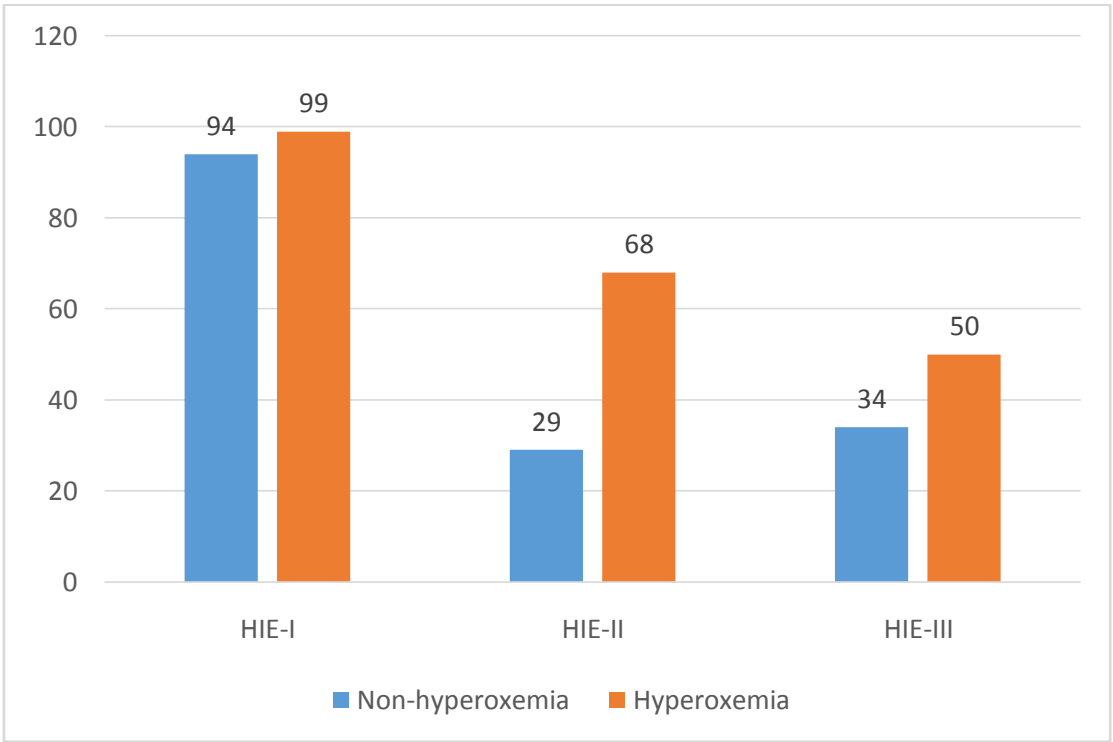

Figure I: Association of hyperoxemia with HIE

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Table 3: Final predictors and outcomes of hyperoxemiain perinatal asphyxia according to logistic regression analysis

Factors	Adjusted OR	95% CI	p-value
Moderate to severe HIE	1.70	1.05 – 2.76	0.030
APGAR score (5 minutes)	0.80	0.70 – 0.91	0.001
Hypocapnia	4.60	2.03 – 10.41	0.0001

IV. DISCUSSION:

This study found out that there is a significant relationship between moderate to severe HIE and hyperoxemia. A severe episode of perinatal asphyxia is associated with a wide spectrum of neurodevelopmental and neurological disorders and lifelong disability[12]. Hypoxic ischemic encephalopathy (HIE) is potentially a preventable condition that can result in death or disability in 60–70% of infants with moderate or severe (moderate-severe) encephalopathy[13,14].

In the present study 40.1% neonates with non-hyperoxemia had mild to moderate HIE compared to 54.4% of hyperoxemia cases, thus, there was a significant association between severity of HIE and hyperoxemia. Similar findings have been witnessed by Kapadia et al in US where they witnessed that incidence of HIE was significantly much higher in infants with hyperoxemia compared to those without hyperoxemia (58% vs 27%, p-value, 0.003)[9]. In a retrospective cohort study Klingers and colleagues found out that severe hyperoxemia and severe hypocapnia were associated significantly with neurodevelopmental deficit, thus, pointing towards severe HIE and moreover, they also found high neonatal deaths after severe hyperoxemia[2].A recent study by Negro S from Italy also revealed that neonates with perinatal asphyxiahaving severe HIE were mostly related to low apgar score, low pH and low BE and had significantly higher levels of Advanced oxidation protein products (AOPP), nonprotein-bound iron (NPBI) than in those with mild to moderate HIE[15].

In this study not only association of early life hyperoxemia was proven with severity of HIE but low Apgar score at 5 minutes (<5) and hypocapnia were found as predictors of early hyperoxemia and severe HIE. Negro S and colleagues also witnessed that low Apgar score at 5 minutes of life plus low pH and BE were significantly associated with perinatal asphyxia and severity of HIE[15]. Many others have also witnessed similar findings and have suggested that neonates with admission hyperoxemia have higher incidence of HIE. Investigators concluded that judicious use of oxygen during and after resuscitation should only be warranted[16,17].

Evidence suggests that severe HIE has a greater chance of mortality with rates ranging between 50 to 75%. Majority of infants, who survive severe HIE episode, develop serious complications. Data from Pakistan has shown that it is one of the leading causes for admission in a neonatal unit[18]. It has also been witnessed that most causes of neonatal morbidity in Pakistan are preventable[19].

Keeping in view the lower middle income status of the country and cash strapped status as well as very low budgetary allocation for health, avoidance of the burden on healthcare settings and workers should be the priority. In this regard birth asphyxia is clearly a problem where prevention should be the aim.

This study has many advantages; firstly, it is one of first attempts in the local settings and a rare one in the international context. Secondly, detailed baseline characteristics of neonates and their clinical presentation was assessed. Thirdly, though death rate was almost similar between neonates with hyperoxemia and non-hyperoxemia, however, the neurological deficit in terms of HIE severity was significant and previous reports on this are validated by this report. On the other hand, no significant limitations of the study were noted.

V. CONCLUSION:

Based on the findings of current study it is concluded that moderate to severe HIE is associated with hyperoxemia during the first hour of life in neonates with perinatal asphyxia. The effect of hyperoxemia on moderate to severe HIE remained present after adjusting for other risk factors at our clinical settings. Our findings are comparable to other international studies, however, further large scale investigations with rigorous research methods are suggested before generalization of these inferences.

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