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Original Article

Comparisons of mortality and pre-discharge respiratory morbidities in small for gestational age and appropriate-for gestational age premature infants - An Indian Experience

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ABSTRACT

***Background*:** There is an assumption that fetus with restricted growth with an inappropriate intrauterine environment lies under stress. Although small-for-gestational-age (SGA) infants have higher mortality, difference in the outcome of SGA and appropriate-for-gestational-age (AGA) infants regarding respiratory morbidity is controversial. It seems that respiratory morbidities in SGA neonates is different from neonates with AGA. In this study, we intend to compare the mortality and respiratory morbidity rates between the preterm small for gestational age (SGA) and appropriate for age (AGA) neonates of less than 34 weeks of gestation.

***Methods*:** This analytical cross-sectional study was conducted on 498 preterm neonates with gestational age of < 34 weeks, admitted to the Neonatal Intensive Care Unit. These neonates were categorized into two groups of SGA (n=210) and AGA (n=286). The data analysis was performed, using Student's t-test and Mann-Whitney U test for parametric variables and Chi-square and Fisher's exact tests for nonparametric data.

***Results*:** According to the results of the study, the two groups were significantly different in terms of their birth weight (P<0.001), pregnancy-induced hypertension (P<0.001), and antenatal steroid usage (P=0.011). Furthermore, respiratory distress syndrome (RDS) was found to be more prevalent in the premature AGA neonates than the SGA ones (P=0.011). In addition, surfactant usage was significantly less in the SGA group (P=0.0006). Bronchopulmonary dysplasia (BPD) developed in 14% and 9% of the premature AGA and SGA neonates, respectively (P=0.094). However, there was no significant difference between the two groups regarding the mortality rate, intra-ventricular hemorrhage, and necrotizing enterocolitis. Among the survived neonates, mean length of hospital stay was significantly higher in the premature SGA newborns born within 26-36 weeks of gestation than their AGA counterparts.

Conclusion: As the findings of the current study demonstrated, the mortality rate was similar in the SGA and AGA groups; however, the respiratory morbidities such as RDS and BPD were more prevalent in the AGA neonates.

Keywords: AGA, BPD, Preterm, RDS, SGA

Introduction

Intrauterine growth restriction (IUGR) complicates 10-25% of the preterm births, which increase the morbidities (1). Small for gestational age (SGA) newborns represent a significant proportion of the neonates admitted to the Neonatal Intensive Care Unit (NICU) in developing countries. Prematurity and SGA are two important pregnancy complications, often co-existing, resulting in high mortality and morbidity rates in the NICU. There are reports indicating the higher risks of mortality and morbidity during the perinatal period (2).

Although there is a consensus that the premature SGA neonates have higher mortality rate than the appropriate for gestational age (AGA) newborns, the differences in outcomes regarding the respiratory morbidity are not clear. Treatments such as antenatal steroids, early continuous positive airway pressure (CPAP), gentle ventilation, early surfactant, and caffeine increase the survival of the SGA neonates.

There are a number of studies comparing the premature SGA newborns with the AGA ones in terms of their mortality and morbidity rates (3-7). However, the number of the studies comparing the

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respiratory outcomes in the SGA and AGA neonates is limited, especially in developing countries with improved respiratory practices. With this background in mind, the aim of the present study was to compare the short-term respiratory outcomes between the premature SGA and AGA neonates of less than 34 gestational weeks.

Methods

This analytical cross-sectional study was conducted at a tertiary care center in the Western Maharashtra. The population of this study consisted of all the neonates with less than 34 weeks of gestation, admitted to the NICU of the hospital during the 1st of January 2013-1st of January 2015. The newborns with major congenital anomalies, chromosomal syndromes, and gestational age of more than 34 weeks were excluded from the study. The study was approved by the ethics committee of the hospital. Furthermore, informed parental consents were obtained from those who met the inclusion criteria.

The gestational age was determined based on the date of the last menstrual period or the first trimester ultrasound examination in case the last menstrual period was not available. To ensure the accuracy of this estimate, it was also assessed by the Expanded New Ballard Score (NBS) (8). In case of observing the discrepancy of more than two weeks, the latter (i.e., NBS) was taken as the gestational age.

The patients were divided into two groups of premature SGA and AGA. Based on the modified Fenton's growth chart, the neonates in the SGA group had a birth weight below the 10th percentile for the gestational age, whereas the birth weight of those in the AGA group was between the 10th and 90th percentile for the gestational age (9). IUGR is a clinical definition, which is applied to the neonates with clinical evidence of malnutrition.

Respiratory distress syndrome (RDS) is a breathing disorder in the premature neonates with such clinical manifestations as: respiratory rate > 60, grunting respirations, retractions, nasal flaring, cyanosis, and increased oxygen requirement. The neonatal RDS can be diagnosed with the onset of the symptoms shortly after birth and chest radiography (10).

The neonates were examined immediately after birth for the presence of respiratory distress, using Silverman-Anderson index. The criteria for CPAP application, intubation, extubation, CPAP failure, and surfactant use were predefined prior to the administration of the study. The newborns with scores of 4 or higher were initially put on nasal CPAP pressure of 5 cmH_2O (11).

The neonates who began CPAP therapy were intubated and ventilated if they met $\geq$ 1 of the following criteria.

Criteria for intubation (12)

Blood Gases

1. Severe hypoxemia (PaO_2<50 mmHg with $FiO_2 \geq 0.60$)
2. Severe hypercapnia ($PaCo_2$>65 mmHg more than once)

Clinical

1. Prolonged or recurrent apnea (>2 episodes within 24 h associated with bradycardia) and any episode requiring bag and mask ventilation
2. Marked retractions that did not improve with CPAP therapy
3. Severe metabolic acidosis (pH<7.2) or shock requiring inotropic support.

Criteria for extubation (13)

1. $FiO_2 \leq 0.4$, $PaCO_2 \leq 60$ mmHg, peak inspiratory pressure less than 20 cmH_2O on ventilator, ventilator rate of 20 breaths per min
2. Spontaneous breathing with minimal or no retraction on ventilator

• Re-intubation is performed according to the intubation criteria.

Trial off CPAP criteria (13)

1. Acceptable saturation levels (>90%) in room air on CPAP
2. No tachypnea or retractions
3. No apnea or bradycardia

The CPAP was restarted in case of observing the following conditions:

$FiO_2 > 0.3$

SAS > 3

• Prolonged or recurrent apnea (>2 episodes within 24 h associated with bradycardia) and any episode requiring bag and mask ventilation

Surfactant therapy was performed according to the recommendations of the Canadian Pediatric Society (2012) (14). Surfactant was given to the neonates on positive pressure support, who had FiO_2 requirement > 0.4. Mortality was based on death prior to hospital discharge. Length of hospital stay denoted the total number of days that a neonate was in the NICU before being discharged. Bronchopulmonary dysplasia (BPD) was defined as the dependency on supplemental oxygen or mechanical respiratory support at 28 days of birth or 36 weeks' post menstrual age (15). Cranial ultrasound examination was performed on all the neonates at the first 5-7 days of their delivery for the diagnosis of intra-ventricular hemorrhage by a pediatric

radiologist. In addition, patent ductus arteriosus was diagnosed based on the presence of compatible clinical signs associated with echocardiography findings and Doppler measurements, interpreted by a pediatric cardiologist.

Data analysis was performed, using descriptive statistics, Fisher's exact test ([two-sided] to detect the statistically significant nonrandom associations between the pairs of the categorical variables), Student's t-test (to assess the differences in means), and Mann-Whitney U test (to determine the statistically significant differences in the median values of the continuous variables) through SPSS version 20. P-value less than 0.05 was considered statistically significant.

Results

Patient demographics characteristics

In total, 517 neonates were enrolled in the study, 21 of whom were excluded (two neonates were large for gestational age and 19 patients were discharged based on their parents' requests against medical advice). Consequently, 210 neonates (42.3%) were classified as SGA and 286 newborns (57.6%) were grouped as AGA. The mean gestational ages of the subjects were 31.7±2.1 and 31.2±2.5 weeks in the SGA and AGA groups, respectively (P=0.24). Demographic characteristics of the subjects are illustrated in Table 1. The most common causes of prematurity in the SGA and AGA groups were pre-eclampsia (62.86%) and preterm premature rupture of membranes (PPROM; 29.37%), respectively. Furthermore, antenatal steroid coverage was almost similar in both groups (P=0.066).

The overall mortality rates in the SGA and AGA groups were 7.6% (16 cases) and 6.9% (20 cases), respectively (P=0.94). Distribution of the pre-discharge mortality rate based on the gestational age is shown in Figure 1.

As shown in Table 1, in the SGA and AGA groups, 71 and 130 patients were admitted with diagnosis of RDS, respectively (P=0.011). Surfactant therapy was found to be more frequent in the AGA group than the SGA one (P=0006). In addition, the needs for ventilation (P=0.18) and CPAP (P=0.27) were similar between the two groups. The distribution of the prematurity complications between the two groups

Table 1. Demographic characteristics of the patients

Characteristics	AGA (n=286)	SGA(n=210)	P-value
Gestational age	31.35±2.51	31.69 ±2.11	0.092
Birth weight	1485.34±426.93	1220.62±323.861	<0.001
Male	177(61.8)	119(56.6)	0.26
LSCS	178(62.2)	178(84.7)	NS
Low Apgar score	28(9.7)	16(7.6)	0.429
Antenatal steroids	112(39.1)	100(47.6)	0.066
Pregnancy induced hypertension	62(21.68)	132(62.86)	<0.001
Antepartum hemorrhage	16(5.59)	6(1.9)	0.062
Multiple gestation	28(9.79)	15(7.14)	0.335
Clinical chorioamnionitis	9(3.15)	1(0.48)	0.049
PPROM	84(29.37)	19(9.05)	0.001
Neonatal sepsis	32(11.19)	32(15.24)	0.232

Data are shown as frequency (%) or mean±SD

SGA: small for gestational age, AGA: appropriate for gestational age, LSCS: lower (uterine) segment Caesarean section, PPROM: preterm premature rupture of membranes, NS: non-significant

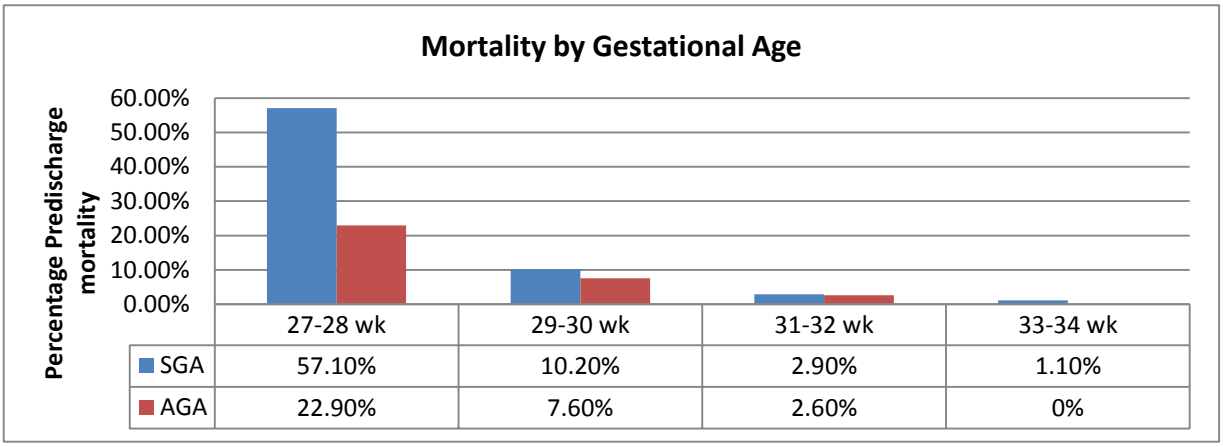

Figure1. Different gestational age periods

The figure illustrates the mortality rate in each gestational age group. The AGA neonates are represented by the brown bars and the SGA newborns are displayed by the blue bars

Table 2. Distribution of pre-discharge respiratory and non-respiratory morbidities

Morbidities	SGA (n=210)	AGA (n=286)	P-values
Pre-discharge mortality	16(7.6%)	20(6.9%)	0.94
Respiratory distress syndrome	71(33.8%)	130(45.45%)	0.011
Need for ventilation	71(33.8%)	114(39.8%)	0.189
Need for CPAP	94(44.7%)	143(50%)	0.275
Incidence of CPAP failure	34(16.1%)	34(11.8%)	0.187
Duration of ventilation	4(2,7)	3(2,6)	0.434
Duration of CPAP	3(1,6)	3(1.7,7)	0.385
Duration of oxygen dependency	5(2,14)	5(2,12)	0.935
Postnatal corticosteroid usage	6(2.8%)	11(3.8%)	0.228
Surfactant (%)	33(15.7)	84(29.3)	0.0006
Air leak syndrome (pneumothorax, pulmonary interstitial emphysema)	3(1.4%)	11(3.8%)	0.16
Broncopulmonary dysplasia	19(9%)	41(14.3%)	0.094
Intraventricular hemorrhage	19(9%)	43(15%)	0.80
Necrotizing enterocolitis	22(10.4%)	19(6.6%)	0.44
Patent ductus arteriosus	56(26.6%)	88(30.7%)	0.36
Duration of hospital stay	20(13,30)	15(8.7,28.5)	0.003

Data are shown as frequency (%), mean±SD or median (25^{th}-75^{th} percentile) SGA: small for gestational age, AGA: appropriate for gestational age, CPAP: continuous positive airway pressure

is displayed in Table 2. The median durations of hospital stay were 20 and 15 days in the SGA and AGA groups, respectively (P=0.003).

Discussion

It is a commonly held assumption that growth-restricted fetuses are "stressed" by the unfavorable *in utero* environment and have accelerated lung maturation and lower incidence of pulmonary complications, compared to the appropriately grown neonates (16, 17). According to the literature, between 11% and 22% of the prematurely born newborns have evidence of IUGR (18, 19), yet the influence of fetal growth restriction on respiratory morbidity remains controversial. However, different studies presented conflicting reports on the outcomes of the prematurity in the SGA and AGA newborns. While some studies reported increased mortality and morbidity rates in the SGA preterm neonates (3, 4, 6, 20, 21), a number of other studies demonstrated decreased rates in this regard (22). Furthermore, there are several studies reporting no changes in the mortality and morbidity of the preterm SGA neonates, compared to their AGA peers (23, 24).

According to the findings of the present study, the pre-discharge mortality rates were similar in both groups with gestational age of ≤ 34 weeks (as shown in Figure 1). However, this rate was higher in the preterm SGA neonates with gestational age of ≤ 28 weeks, compared to their AGA counter-parts (OR =4.47, 95% CI: 1.32, 15.0; P=0.020). These findings are consistent with those observed in some of the previous studies (23, 24).

Furthermore, the premature AGA newborns had higher incidence of RDS than the premature SGA neonates (OR=1.63, 95% CI: 1.12, 2.35; P=0.011). Likewise, Procianoy et al. (22) demonstrated lower incidence of RDS in the SGA newborns with ≤ 32 weeks of gestation, compared to their AGA peers. Nevertheless, other studies reported either no difference between the two groups (3, 4, 20) or an increased incidence and severity of RDS in the premature SGA neonates (21, 25).

The analysis of the need for surfactant and days on mechanical ventilator represents the severity of interstitial lung disease. In the current study, the need for surfactant was significantly lower in the preterm SGA newborns, compared to the preterm AGA ones, supporting the concept of accelerated lung maturation in response to stress. This concept was supported by several studies demonstrating improved biochemical pulmonary profile in the growth-restricted neonates, which showed similar need for surfactant in the SGA and AGA newborns of < 27 weeks of gestation (26, 27).

As the findings of the current study indicated, RDS was less prevalent in the SGA neonates, compared to the AGA ones However, the total number of ventilation days was not different between the two groups, indicating that the advantage of "stressed" lung is transient (SGA=4[2, 7]; AGA=3[2, 6]; P=0.434).

Furthermore, BPD was observed to have an increasing trend in the AGA group with the postmenstrual age of 36 weeks, compared to the SGA neonates; however, it was not statistically significant (P=0.094). These findings are inconsistent with

those of the previous studies, which reported that the premature SGA neonates have increased incidence of BPD (1, 3). It needs to be emphasized that the etiology of bronchopulmonary disease is multifactorial. Various factors such as chorioamnionitis, prolonged rupture of membranes, severity of RDS, duration and degree of ventilator support, patent ductus arteriosus, higher oxygen concentration exposure of the neonate, and nutrition play a significant role in BPD.

In addition, higher incidence of RDS, PPROM, and chorioamnionitis in the AGA group may be responsible for BPD. In our study, the preterm AGA neonates were more exposed to chorioamnionitis (P=0.049) and prolonged rupture of membranes (P=0.001), which may account for the higher incidence of BPD in this group. Similarly, in a study conducted by Lee et al., PPROM was reported as an independent risk factor for BPD (28). In addition, in a meta-analysis carried out by Hartling et al., the association between BPD and chorioamnionitis was highlighted (29).

There were no significant differences in intraventricular hemorrhage, necrotizing enterocolitis, and mortality rates between the SGA and AGA groups, which may be due to better antenatal steroids in the SGA group. Although the two groups had similar short-term morbidity pattern, the AGA neonates were discharged earlier than their SGA counterparts, highlighting the compromised intrauterine nutrition and growth as important determinants of long-term morbidity.

Moreover, BPD was observed to be more prevalent in the AGA group than the SGA one. This finding indicates the important role of antenatal infection in the severity of investigated in a larger prospective trial. The limitation of the present study was focusing on the short-term pulmonary outcomes in the SGA and AGA neonates. Future studies are recommended to investigate the late pulmonary outcomes in the SGA newborns using long-term follow-ups.

Conclusion

The premature AGA neonates had lower need for surfactant than their SGA peers. This finding supports the concept of accelerated lung maturation in response to stress. However, this benefit was reported to be transient since the need for ventilation and duration of respiratory support (including invasive ventilation and CPAP) were similar in both groups. Furthermore, the higher incidence and severity of RDS, increased chorioamnionitis, and PPROM indicated that IUGR alone may not predict the short-term pulmonary morbidity in the form of BPD.

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Conflicts of interests

None declared.

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