Neurodevelopmental Outcomes of Preterm Small for Gestational Age and Appropriate for Gestational Age Babies at One Year of Age

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ABSTRACT

BACKGROUND

It is well known that prematurity causes several complications during the neonatal period and affects the neurodevelopment. But comparison of small for gestational age (SGA) and appropriate for gestational age (AGA) on prematurity-associated outcome has been disputed due to inconsistent results in the literature. The objective of this study was to compare the neurodevelopmental outcome at 1 year between preterm SGA and AGA infants. We also aimed at investigating short-term neonatal outcome variables in SGA-infants compared with AGA-infants.

METHODS

A prospective study was done among 213 infants born without congenital anomalies between 30 weeks and 34 weeks of gestation and admitted to the neonatal intensive care unit (NICU), Govt Medical College, Kozhikode, during a period of six months. Modified Fenton chart was used to classify neonates as SGA (< 10th percentile for GA) or AGA (10th - 90th percentile for GA). Infants were grouped into SGA (n = 80) and AGA (n = 133). Neonatal complications like RDS (Respiratory Distress Syndrome), hypoglycaemia, polycythaemia, hypocalcaemia, thrombocytopenia, neonatal hyperbilirubinaemia, sepsis, DIC (Disseminated Intravascular Coagulation), Necrotizing Enterocolitis (NEC), PDA (Patent Ductus Arteriosus), Intra Ventricular Haemorrhage (IVH), apnoea, pulmonary haemorrhage and mortality were compared. Neurodevelopmental outcome at 1 year was assessed using Bayley Scales of Infant and Toddler Development 3rd edition. Analysis was done using SPSS statistical program.

RESULTS

Proportion of preterm SGA infants with hypoglycaemia (AGA: 20.3 %, SGA: 55 % p = < .001), hypocalcaemia (AGA: 3.8 %, SGA: 16.2 % p = .002) and NEC (AGA: 9.8 %, SGA: 20 % p = .035) were significantly higher than AGA infants. Need for surfactant therapy in RDS is more for preterm AGA infants than SGA infants (AGA: 16.5 %, SGA: 13.8 % p = 0.841). Development of thrombocytopenia, neonatal hyperbilirubinaemia, sepsis, DIC, apnoea and pulmonary haemorrhage is observed more with SGA infants than AGA infants but lacks statistical significance. 6 % of AGA infants had PDA while for SGA it was 2.5 %. No significant difference was noticed in the occurrence of polycythaemia and IVH among the groups. Mortality was also comparable (AGA: 11.3 %, SGA: 10 %). SGA infants perform significantly lower when compared to AGA infants in cognitive, language and motor outcomes at 1 year. Severe developmental delay was also observed significantly more commonly with SGA infants.

CONCLUSIONS

Being born small for gestational age is additionally associated with neurodevelopmental delay for preterm babies at the age of 1 year. NEC and metabolic complications like hypoglycaemia and hypocalcaemia are significantly increased in preterm SGA babies when compared to preterm AGA babies. Several other neonatal complications except for severe RDS are also more common among preterm SGA infants although they lack statistical significance.

KEY WORDS

Infant, Small for Gestational Age, Preterm, Neurodevelopment

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BACKGROUND

There is six times higher risk in underdeveloped / developing countries for a baby to be born as SGA when compared to that in developed countries. Amongst the Asian countries, India stands second in the incidence for Low Birth Weight (LBW) and Intra-Uterine Growth Restriction (IUGR), IUGR-LBW.¹

Although premature SGA infants have higher mortality than AGA infants, the differences in respiratory and non-respiratory morbidity are controversial.² Studies done by Gluck L et al, Procianoy RS et al and Yamaguchi K et al showed that SGA infants have fewer respiratory complications in the neonatal period than AGA infants.^{3,4,5} But the outcome of studies conducted by Robertson CMT et al, Sung IK et al, Pena IC et al and Ruys Dudok van Hell et al were inconclusive.⁶⁻⁹ Within each gestational age group from 25 to 32 weeks, IUGR was associated with increased mortality, necrotizing enterocolitis, chronic lung disease, and retinopathy of prematurity. IUGR was shown to be a serious problem that is associated with increased morbidity and mortality among prematurely born neonates. Antenatal diagnosis of IUGR correlated well with neonatal diagnosis of SGA and was correlated with the same adverse outcomes.¹⁰

Studies by Punnet Sharma et al, Procianoy et al, Yoon J J et al, Warshaw J B et al showed that, the premature SGA infants were at a lower risk for RDS than premature AGA infants.^{2,4,11} However, other studies by Bardin C et al, Gortner et al, Pena et al and Simchen MJ had found no difference between the two groups^{8,12}. But an increased incidence and severity of RDS in premature SGA infants was noted in the studies by Tyson JE et al and Thompson P J et al^{13,14}. The postulation, that growth restricted fetuses have accelerated lung maturation resulting from intra uterine "stress" and thus lower incidence of RDS when compared to AGA infants, lacks evidence. In the study by Zaw W et al, a higher incidence of RDS among SGA infants was noted with use of the fetal growth standard but no difference was noted between SGA and AGA infants with use of the neonatal growth standard. The study done by Puneet Sharma et al revealed that while the incidence of RDS in SGA infants was lower as compared to AGA infants, the total number of ventilator days in both the groups is not different.⁴

Studies done by Bardin et al, Thompson et al, Teberg et al and Chen et al found an increased incidence of sepsis and related mortality among SGA compared to AGA babies.^{12,14} In the study by Bardin et al, infection was suspected or confirmed more frequently in SGA infants, especially during the first week of life.

The study by Bardin et al showed that even though the incidence of necrotizing enterocolitis was not significantly different between the two groups, the SGA infants had more difficulties with enteral feedings.¹²

Study by Procianoy et al suggested that an SGA infant with the same risk factors for IVH as an AGA infant has a lower probability of developing clinical IVH.⁴

Developmental delay rather than survival is now recognized as the main problem in children born preterm and SGA¹⁵ MRI studies in preterm children suggest that IUGR is associated with a decreased cortical grey matter volume in the neonatal brain.¹⁶ Moreover, structural brain alterations in IUGR newborns have been pointed out by a recent study on the hippocampal volume using 3D MRI.¹⁷ The hippocampus is known to be highly vulnerable to environmental factors as

hypoxia and ischaemia during brain development.¹⁷ In addition, the number of proliferating neurons and the maturation of neurons in the brain were found to be reduced in animal studies as a result of IUGR. Possible mechanisms are decreased expression of neuronal growth factors like the Brain Derived Neurotrophic Factor (BDNF) and the glial neurotrophic factor S-100 beta.¹⁸ It is not evident, whether the effects on neuronal proliferation and maturation, and changes in MRI are transient or result in subtle brain dysfunction like minimal cognitive impairment. As mentioned above, in addition to neonatal complications and changes in brain maturation, the socioeconomic background and the mother's educational level seem to influence the development of preterm infants.¹⁹

Studies comparing the neurodevelopmental outcomes of preterm SGA and AGA babies showed inconsistent results in the literature. Studies in which the intellectual abilities of SGA infants were assessed by standardized IQ tests found a lower IQ in the SGA group.^{20,21} More specific analyses of the cognitive development showed difficulties in language and social skills.²¹⁻²³ Several studies done by Sung et al, Mc Carton CM et al, Feldman R et al, Frauz A R et al, Guellec I et al and Morsing E et al had shown that among children whose birth weight was in the lowest decile for gestational age, tend to be at increased risk of cognitive limitations.^{7,24-28} On the contrary study by Kan E et al found no association between fetal growth restriction and cognitive limitations.²⁹ Studies by Guellec I et al and Morsing E et al have identified magnitude of the growth restriction and sex of the child as factors that influence growth restriction and development in children born at a low gestational age.^{27,28} According to the study by Iris G. Streimish et al, only severe growth restriction is associated with delayed development. They also concluded that the neurosensory limitations appeared to obscure increased risks of low Mental Development Index in girls with severe growth restriction, and low Psychomotor Development Index in boys with even less severe growth restriction.³⁰

Apart from severe neurological impairment, 32 – 44 % of all preterm children with birth weights < 1500 g showed mental developmental deficits when tested at the age of 5 years.³¹

METHODS

This is a prospective observational study conducted in the Neonatal Intensive Care Unit, Government Medical College, Kozhikode.

Sample Size

Study conducted by Streimish et al at 14 institutions in the United States²⁸ showed that the neurodevelopmental delay for preterm SGA infants is 37 % and that for preterm AGA infants is 18 %. Sample size determination for estimating difference between proportions

$$n = \frac{(Z\alpha + Z\beta)^2 pq \times 2}{d^2}$$

Considering a dropout of 10 %, minimum sample size is calculated as 190 preterm babies with 95 babies in each group.

Duration of the Study

6 months for recruitment of subjects. Follow up at 1 year from the day of recruitment.

Inclusion Criteria

SGA Group

Babies born between 30 and 34 weeks admitted in NICU with birth weight <10th percentile for the gestational age

AGA Group

Babies born between 30 and 34 weeks admitted in NICU with birth weight $\geq 10^{\text{th}}$ and < 90th percentile for gestational age

Exclusion Criteria

Out born babies, babies born to mothers with no record of expected date of confinement and babies having HIE (Hypoxic Ischemic Encephalopathy), major congenital anomalies and genetic abnormalities.

Study subjects will be recruited over a 6-month period. Gestational age is calculated from the expected date of confinement and New Ballard Score. Babies will be grouped into AGA and SGA. Anthropometry will be calculated at birth. Length is measured using infantometer with an accuracy of 0.1 cm. Head circumference measurement using non-stretchable tape. Infants were observed for the following neonatal complications.

1. Respiratory Distress Syndrome (RDS) - Clinical features include tachypnoea, retractions, flaring of the nasal alae, grunting, and cyanosis. The classic radiographic appearance is of low-volume lungs with a diffuse reticulogranular pattern and air bronchograms.
2. Hypoglycaemia - For infant with abnormal signs or symptoms <45 mg / dL.
3. Neonatal Hyperbilirubinaemia - Total bilirubin ≥ 12 mg / dL.
4. Sepsis - Infection was diagnosed either by a positive blood culture or an abnormal white blood cell count and differential, positive CRP in the presence of obvious clinical signs of infection.
5. Disseminated Intravascular Coagulation (DIC) - Detection will be based on clinical and laboratory findings.
6. Thrombocytopenia - Platelet count below 100,000.
7. Hypocalcaemia - Total serum calcium concentration of < 7 mg / dL or an ionized calcium concentration of < 4 mg / dL (1 mmol / L).
8. Polycythaemia - Venous haematocrit of at least 65 %.
9. Necrotizing Enterocolitis - Diagnosis is based on clinical characteristics, radiological and laboratory findings.
10. Patent Ductus Arteriosus - Clinical identification of murmur with confirmation by echocardiography.
11. Intraventricular Haemorrhage - Cranial ultrasonography, performed by ultrasonologist.
12. Apnoea - Pathological apnoea is when absent airflow is prolonged (usually 20 seconds or more) or accompanied by bradycardia (heart rate < 100 beats / minute) or

hypoxaemia that is detected clinically (cyanosis) or by oxygen saturation monitoring.

13. Retinopathy of Prematurity (ROP) - By indirect ophthalmoscopy by experienced ophthalmologist.

14. Developmental Assessment - Performed at 1 year of post-natal age using Bayley scales of infant and toddler development III. Test results will be summarized as scores.

Statistical Analysis

Data were entered in to excel worksheet and analysed using SPSS statistical program. There were 133 AGA babies and 80 SGA babies. They were compared for neonatal complications. 23 babies expired during the NICU stay. Follow-up study was conducted at 1 year of age. 6 babies expired before 1 year and 37 were lost to follow up.

Statistical analysis was done using the software Statistical Package for Social Studies (SPSS) version 16.0. Data was described as mean and standard deviation for normally distributed quantitative variables and as counts and percentages for qualitative variables. Chi square test and Fischer's exact test was done to find the association between categorical variables. P value < 0.05 was taken as significant.

RESULTS

Of 213 preterm babies, 133 belonged to AGA and 80 belonged to SGA group. The study population had 113 male babies and 100 female babies. Male babies were more in both the groups (SGA – 52.5 %, AGA – 53.4 %).

Figure 1. Distribution of SGA and AGA Based on Gestational Age

Ponderal Index was calculated and found that 71 (88.8 %) SGA babies had a PI of < 2 and 9 (11.2 %) SGA with PI ≥ 2 . Hence, it is analysed that 88.8 % of SGA babies were having asymmetrical IUGR and rest of them with symmetrical IUGR.

While 55 % of SGA babies developed hypoglycaemia, only 20.3 % of AGA babies developed hypoglycaemia. The difference is statistically significant. But symptomatic hypoglycaemia occurred in 9 % of AGA babies while it is only 5 % in SGA babies.

2 SGA and 8 AGA babies had PDA. However, comparison between the groups does not assume statistical significance (p = 0.326). 4 babies required medical closure. None of them needed surgical intervention.

10 % of SGA and 11.3 % of AGA babies constituted total of 23 babies expired during the neonatal period. The difference is not statistically significant ($p = 0.824$).

Of the 213 babies follow up study was done in 148 infants. 23 babies expired during the neonatal period. 36 infants lost to follow up and 6 infants expired after their discharge from NICU. Study population who came for follow up include 92 AGA infants and 56 SGA infants.

	SGA (n = 80)		AGA (n = 133)		'P' Value
	Frequency	Percentage	Frequency	Percentage	
Hypoglycaemia	44	55	17	20.3	0.000
Hypocalcaemia	13	16.2	5	3.8	0.002
NEC	16	20	13	9.8	0.035
ROP	21	26.3	16	11.3	0.004

Table 1. Neonatal Complications: SGA vs. AGA with Significant Difference

	SGA (n = 80)		AGA (n = 133)		'P' Value
	Frequency	Percentage	Frequency	Percentage	
RDS	37	46.3	62	46.6	0.841
Hyperbilirubinaemia	46	57.5	68	51.1	0.367
Sepsis	20	35	24	18.1	0.471
Thrombocytopenia	17	21.3	18	13.5	0.332
Polycythaemia	4	5	9	6.8	0.771
PDA	2	2.5	8	6	0.326
Pulmonary Haemorrhage	9	11.2	12	9	0.597
Intra Ventricular Haemorrhage	6	7.5	10	7.5	0.996
Apnoeic Spells	9	21.2	12	15	0.246

Table 2. Neonatal Complications: SGA vs. AGA without Significant Difference

Figure 2. Comparison of Developmental Delay in SGA vs. AGA

Domain of Development	SGA (n = 56)	AGA (n = 92)	P Value
Cognitive Developmental Delay	26 (46.4 %)	14 (16.2 %)	< 0.001
Language Developmental Delay	34 (60.7 %)	15 (16.3 %)	< 0.001
Motor Developmental Delay	36 (64.3 %)	19 (20.7 %)	< 0.001

Table 3. Domain Specific Developmental Delay - SGA vs. AGA

DISCUSSION

We found that the differences in cognitive, language, and motor development, between preterm SGA and AGA preterm infants at the age of 1 year were marked, indicating that there is significant additional risk of neurodevelopmental delay for children born preterm and small for gestational age. Remarkably, we found a higher number of intraventricular haemorrhage and significantly higher occurrence of hypoglycaemia in SGA than in AGA preterm infants, which could possibly explain the outcome. However, the number of

babies with intraventricular haemorrhage is low which limits the possibility of association.

Studies done by Fernandez-Carrocer et al and Figueras et al found that children with IUGR had higher rates of neuromotor and neurologic abnormalities than controls at 1 year.^{32,33} Fernandez-Carrocer et al also found that children with IUGR scored significantly lower than controls on the Bayley Scales of Infant Development, version II (Bayley-II).³² Another study conducted by Padilla et al also concluded that, there is no significant difference in neurodevelopmental assessment at 1 year between preterm SGA and AGA.³⁴ This may be due to the fact that Padilla et al didn't employ Bayley scales, instead they applied the Hammersmith Infant Neurologic Examination. Of the 5 studies which assessed neurodevelopment of preterm SGA from 1 - 2 years, 4 indicate that these children are at increased risk for delay.^{30,34-38}

The Bayley scales represent a well-established tool to assess the mental development in toddlers and preschool infants.³⁹ Standardized developmental testing of SGA children at later ages could reveal in more detail difficulties in attention, language tasks and social skills as recently suggested by Strauss RS and others.⁴⁰ Most studies on differences in developmental outcome between SGA and AGA; children involved with SGA showed developmental changes at the age of 5 years and older.⁴¹

In our study proportion of preterm SGA infants developing hypoglycaemia, hypocalcaemia and NEC is significantly higher compared to that of AGA group. It is believed that redistribution of blood flow in intra uterine growth restriction leads to a brain sparing effect at the expense of other organs and tissues, such as kidneys, muscles, or intestines.⁴² Studies by Ree IM et al showed similar results.⁴³ This may explain the significantly higher occurrence of NEC in the SGA group. The concept of accelerated lung maturation in response to stress has been supported by some studies.³ However, in this study, we did not find any difference in the incidence of RDS between the SGA and AGA groups. However, the need for surfactant therapy in RDS is more for preterm AGA infants than SGA infants, but fails to assume statistical significance. Consistent with our results, several previous studies found no differences in the incidence of RDS between the two groups¹² and studies by Thompson PJ et al even showed an increased incidence and severity of RDS in premature SGA infants.¹⁴ The concept of intrauterine growth retardation on accelerating lung maturation and improving outcome was not supported by Tyson et al¹³ in their study comparing SGA and AGA with the same gestational age, sex, and race.

Development of thrombocytopenia, neonatal hyperbilirubinaemia, sepsis, DIC, apnoea and pulmonary haemorrhage is observed more with SGA infants than AGA infants but lacks statistical significance. 6 % of AGA infants had PDA while for SGA it was 2.5 %. No significant difference was noticed in the occurrence of polycythaemia and IVH among the groups. Concerning the neonatal complications of the SGA infants, controversial findings exist about the fact whether intraventricular haemorrhage occurs more often in SGA preterm infants.¹² Ortigosa Rocha C et al found that IUGR with a gestational age of more than 33 weeks was shown to be associated with an increased risk for intraventricular haemorrhages.⁴⁴ Our results show no evidence that SGA is associated with increased risks of IVH. Similarly, most previous studies found no differences in the incidence of IVH between SGA and AGA preterm neonates.^{10,11} However,

because several other studies contradict these findings further research is needed to explore this issue.

It is noteworthy to note that the occurrence of ROP was found to be significantly higher in SGA. Similar observation was made by Garite et al.¹⁰

The present study didn't find any significant difference in mortality among the groups. Previous studies have shown that the mortality of infants with a birth weight below the 10th percentile was higher than that of AGA neonates at all gestational ages up to 36 weeks.⁴ In the study conducted by Tyson JE et al, it was suggested that there is high mortality in SGA infants with low birth weights.¹⁵ The lack of difference in our study can be due to low proportion of SGA babies in the study. Bardin et al did not observe any significant difference in mortality between the SGA and AGA groups.¹² Lackman et al also showed in a larger population-based study, that the risk of perinatal death attributed to being born preterm SGA increased significantly only with a birth weight below the third percentile, but no differences were observed in the SGA infants whose birth weights were between the 3rd and the 10th percentiles.⁴⁵

What This Study Adds

Cognitive, language and motor developmental delay is significantly more in preterm SGA compared to AGA at 1 year of age.

Limitations of the Study

Sample size is not comparable between the two groups. Follow up was limited to 1 year. Statistical significance cannot be established in subcategories owing to inadequate number in each.

CONCLUSIONS

Being born small for gestational age is significantly associated with neurodevelopmental delay for preterm babies at the age of 1 year. There is no statistically significant difference in mortality between preterm SGA and preterm AGA in 30 - 34 weeks' gestation. NEC and metabolic complications like hypoglycaemia and hypocalcaemia are significantly increased in preterm SGA babies when compared to preterm AGA babies. Occurrence of ROP is also significantly high in SGA babies. Several other neonatal complications except for RDS are also more common among preterm SGA infants although they lack statistical significance.

Data sharing statement provided by the authors is available with the full text of this article at jemds.com.

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