Original Article

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Extrauterine Growth Restriction among Very Low Birth Weight Neonate using Intergrowth 21st in a Neonatal Intensive Care Unit: A Retrospective Study

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Abstract

Introduction: Extrauterine growth restriction (EUGR) is a universal problem but its prevalence using recent reference growth charts and morbidities associated with it are lacking. The study aims at estimating EUGR prevalence in very low birth weight (VLBW) neonates and its associated morbidities.

Methods: All VLBW neonates admitted to NICU between Jan 2018 to June 2019 were analysed. Neonatal anthropometries were recorded on Intergrowth 21st gender based postnatal growth chart. EUGR was defined by weight below 10th percentile at discharge. Demographic profile and neonatal morbidities were compared between EUGR and non-EUGR by using unpaired t test and Chi-square test. Regression was used for identification of the risk factors.

Results: Out of 148 VLBW neonates, 92 (62.1%) were male, 26 (17.56%) were below 1000 gm, 102 (68%) were EUGR at discharge. Mean (SD) birth weight and gestational age were 1202 (221) gms and 30.89 (2.77) wks respectively. Caesarean delivery, higher gestational age, lower birth weight, SGA at birth and prolonged duration to achieve full enteral feeding were significantly associated with EUGR ($P < 0.05$). Sepsis was significantly associated with EUGR (36.28% vs. 17.4%; P 0.022). EUGR babies needed longer hospital duration (24.56% vs. 16.78%; P 0.005) with a higher mean PMA at discharge (38.07 wks vs. 35.11 wks; $P < 0.001$). In regression model SGA at birth and delay in achieving full feeding were independent predictor of EUGR.

Conclusions: In VLBW neonate, prevalence of EUGR at discharge was 68%. Sepsis was significantly associated with EUGR. SGA and delay in achieving full feeding were independent predictors of EUGR.

Introduction

Survival of Very Low Birth Weight (VLBW) neonates has improved over last decades in developing countries.[1] Availability of breast milk, gradual advancement of enteral feeding, need of total parenteral nutrition, feed intolerance, necrotising enterocolitis

and high metabolic state during illness are major barrier for preterm nutrition.[2]

In addition, prematurity related morbidities are also barrier for ex-utero growth of infant resulting in extra uterine growth restriction (EUGR). EUGR is associated with long term childhood co-morbidities.[3] The nutritional status of a neonate is interpreted by longitudinal and cross sectional growth monitoring. Fenton (2013) that was widely used to monitor neonatal birth size and postnatal growth.[4] Intergrowth 21st growth chart is now more widely used in different NICUs across India for cross sectional growth monitoring.

However, there is insufficient literature on the prevalence of EUGR using this chart and morbidities associated with it. The present study was designed to estimate the prevalence of EUGR in VLBW neonates by cross sectional growth monitoring using Intergrowth 21st postnatal growth standards for preterm infants; to compare the associated factors, co-morbidities and short term outcome of EUGR with non-EUGR babies.

Methods

This retrospective study was conducted from Jan 2018 to June 2019 in a tertiary care NICU of a teaching hospital in India after obtaining approval from Institutional Ethics Committee. All VLBW neonates admitted within 48 hours of life during the study period were enrolled and followed till discharge. Neonates those who had died, left against medical advice, having lethal anomalies and babies on formula feeding were excluded from analysis. Neonatal demographic profiles (Birth weight, gestational age, gender), mode of delivery, inborn / outborn, Apgar at 5 min, maternal antenatal steroid coverage were recorded from case records. Neonatal morbidities i.e. respiratory distress syndrome (RDS), surfactant therapy, need of non–invasive and invasive mechanical ventilation, chronic lung disease (CLD), neonatal sepsis, were recorded. Duration to achieve full enteral feeding (DFF), presence of feed intolerance (FI) or necrotising enterocolitis (NEC) were assessed. Screening for intraventricular haemorrhage (IVH), retinopathy of prematurity (ROP), osteopenia of prematurity (OP) and anaemia were done as per NICU protocol. Neonatal gestational age was estimated from last menstrual period, first trimester ultrasound and new Ballard scoring. Birth weight per gestational age was interpreted as small for gestational age (SGA) and appropriate for gestational age (AGA) by using Intergrowth 21st gender and maturity based [New born size for very preterm (24 - 32 weeks) and new-born size (for ≥33 weeks)] growth charts. All neonates were managed as per NICU protocol. RDS was diagnosed by presence of respiratory distress and chest x-ray and managed as per NICU protocol.[5] Chronic lung disease was defined by need of oxygen or respiratory support at 28 days (Chronological age) and 36 weeks post menstrual age.[6]

All VLBW neonates were initiated on trophic feeding within 24 to 48 hr of life at 10 - 20 ml / kg with mother's own breast milk or pasteurised donor human milk (Neolacta, Neo Lifesciences Pvt Ltd, Bengaluru, India). Babies on formula feeding were excluded from the study. Feed increment was 10 - 20 ml / kg / day and 25 – 30 ml / kg / day for neonates with birth weight < 1000 gm and 1000 – 1500 gm respectively. Parenteral nutrition (PN) was initiated in all VLBW neonates with intravenous dextrose and 10% Aminoven (1.5 gm / kg / day), intravenous lipid added in day one to two. Aminoven 10% and intravenous lipid was gradually increased to a maximum of 3 gm / kg / day. PN was continued till achieving a full enteral feeding (120 ml / kg / day). NEC diagnosis was based on modified Bells' staging. Nutritional practice during feed intolerance was according to NICU protocol. Neonatal sepsis was diagnosed and treated as per protocol. Screening neurosonogram for diagnosing IVH and periventricular leukomalacia (PVL) was done in all between fourth to seventh day of life and before discharge. ROP screening was done as per NNF protocol.[7] Packed red blood cell transfusion for anaemia management of VLBW neonates was based on protocol. OP was diagnosed by presence of serum phosphate < 3.5 mg / dl and / or serum ALP > 800 IU / ml. Neonates were discharged as per NICU discharge policy (After 34 wk PMA, free from significant prematurity related illness, no episodes of apnoea / bradycardia over last seven days, weight gain around 15 gm / kg / day by Paladay feeding and ensuring confidence of mother in baby care at home). Kangaroo mother care was initiated in all babies as per unit protocol. Neonatal weight was measured in electronic weighing scale, head circumference was measured in tape and length was measured in infantometer. Each anthropometric entity was plotted in Intergrowth 21st postnatal growth chart (gender based) and classified as < 3rd percentile, 3rd - 10th percentile, 10th - 90th percentile and > 90th percentile. EUGR was defined as NICU discharge weight less than 10th percentile for gestational age and sex from Intergrowth 21st and severe EUGR by discharge weight less than 3rd centile (By cross sectional growth monitoring).

In this NICU about 200 VLBW neonates were admitted during last 18 months period preceding the study. In a previous study, the prevalence of EUGR among VLBW neonates admitted to NICU was 45.7%.[8] Assuming population size (For finite population correction factor or fpc) (N):200, hypothesized percentage frequency of outcome factor in the population (p): 45.7% ± 5%, confidence limits as percentage of 100 (absolute ± %) (d): 5%, the estimated sample using formula
$N = [DEFF*Np(1-p)] / [(d^2/Z^2_{1-\alpha/2}*(N-1) +p*(1-p)]$ was 132. Expecting attrition of 10% among the study population, final sample size 145 was considered. The comparison of neonatal categorical and continuous variables between EUGR and non-EUGR neonates were analysed by Chi-square test and unpaired t test respectively. The variables with $p < 0.25$ in bivariate analysis were undergone multiple regression analysis for independent predictor of EUGR. Data was analysed using STAT 1.5 version software and P value < 0.05 was considered significant.

Results

Total 206 VLBW neonates were admitted during the study period. Fifty eight neonates met exclusion criteria, and 148 VLBW neonates were analysed. The mean (SD) birth weight and gestational age were 1202 (221) gms and 30.89 (2.77) weeks respectively; 92 (62.16%) were males and 26 (17.56%) were below 1000 gm (ELBW) at birth. Majority (81.08%) were delivered inborn and Caesarean section was the mode of delivery in 79 (53.38%) neonates. Sixty-four (43.24%) babies were SGA and rest were AGA. Full feeds or enteral feeding before two weeks were achieved in only 97 (65.54%) neonates. Mean (SD) duration of hospitalisation and PMA at discharge were 43.75 (23.0) days and 37.14 (2.37) wks respectively. The prevalence of EUGR and severe-EUGR among VLBW neonates were 102 (68.9%) and 80 (54.1%) respectively. [Table 1]

Table 1. Baseline characteristics of VLBW neonate (n = 148)

Characteristics	Category	Value n (%)
Male Sex		92 (62.16)
*Gestational Age (weeks)		30.89 (2.77)
Gestational Age (weeks)		
	< 28	17 (11.49)
	28 - 32	90 (60.81)
	> 32	41 (27.70)
*Birth Weight (gms)		1202 (221)
Birth Weight (< 1000 gms)		26 (17.56)
Caesarean delivery		79(53.38)
APGAR < 7 at 5 min		22 (14.86)
Birth weight per GA		
	SGA	64 (43.24)
	AGA	84 (56.76)
Delivery inborn		120 (81.08)
Below two weeks to full enteral feeding		97 (65.54)
Use of antenatal steroid		93 (62.83)
*Hospital stay (Days)		43.75 (23.0)
*Post menstrual age at discharge (Weeks)		37.14 (2.37)
Weight at discharge (Percentile)		
	< 3rd	80 (54.10)
	3rd - 10th	22 (14.9)
	10th - 90th	46 (31.1)
	> 90th	0 (0)

Table 2 shows the comparison of different demographic parameters in EUGR and non-EUGR neonates.

Table 2. Comparison of parameters in VLBW neonates with and without EUGR in the study population (n=148)

Variable		Non EUGR (n = 46)	EUGR (n = 102)	P-value
*Gestational Age (weeks)		29.93 (1.611)	31.33 (3.068)	0.004
*Birth Weight (gms)		1300 (165)	1158 (230)	< 0.001
Gestational Age (weeks)				
	< 28	3 (6.52)	14 (13.73)	0.039
	28 - 32	40 (86.96)	50 (49.01)	
	> 32	3 (6.52)	38 (37.26)	
Birth Weight (gms)				
	< 1000	3 (6.52)	23 (22.54)	0.019
	1000 - 1500	43 (93.48)	79 (77.46)	
Caesarean delivery		14 (30.43)	65 (63.70)	< 0.001
APGAR at 5 min < 7		6 (13.04)	16 (15.68)	0.675
Male sex		28 (60.86)	64 (62.74)	0.484
Birth weight per GA				
	SGA	4 (8.60)	60 (58.80)	< 0.001
	AGA	42 (91.40)	42 (42.20)	
Place of delivery	Inborn	37 (80.43)	83 (81.37)	1.000
	Outborn	9 (19.57)	19 (18.63)	
Duration to full enteral feeding	< 2 weeks	37 (80.40)	60 (58.82)	0.015
	> 2 weeks	9 (19.60)	42 (41.18)	
Use of Antenatal steroid	Yes	26 (56.53)	67 (65.69)	0.286

Data Presented as n (%), * mean (SD). GA, gestational Age; SGA, small for gestational age; AGA, appropriate for gestational age.

Table 3. shows the comparisons of different neonatal morbidities of VLBW neonates between EUGR and non-EUGR groups.

Neonatal morbidities	Non-EUGR (n = 46)	EUGR (n = 102)	P value
Respiratory distress syndrome	25 (54.35)	54 (52.95)	0.874
Surfactant therapy	11 (23.92)	27 (26.48)	0.741
Non-invasive ventilation	12 (26.09)	25 (25.51)	0.838
Need of mechanical ventilation	21 (45.66)	38 (37.26)	0.174
Chronic lung disease	5 (10.87)	13 (12.75)	0.747
Sepsis	8 (17.40)	37 (36.28)	0.022
NEC (Bell's staging ≥II)	1 (2.20)	9 (8.83)	0.256
Anaemia requiring Blood transfusion	16 (34.79)	38 (37.26)	0.854

Data Presented as n (%). NEC, necrotising enterocolitis. Outcome of VLBW babies are compared between EUGR and

non-EUGR babies and depicted in Table 4.

Table 4. Outcome of VLBW neonate in relation to EUGR (n = 148)

Variable		Non EUGR (n = 46)	EUGR (n = 102)	P-value
*Hospital stay (days)		35.85 (16.78)	47.31 (24.56)	0.005
*Post menstrual age at discharge (wks)		35.11 (1.83)	38.07 (1.99)	< 0.001
Head Circumference at Discharge (Percentile)				
	< 3rd	04 (8.61)	72 (70.59)	< 0.001
	3rd - 10th	10 (21.73)	16 (15.69)	
	10th - 90th	31 (67.49)	14 (13.72)	
	> 90th	1 (2.17)	0(0)	
Length at discharge				
	< 3rd	2 (4.35)	73 (71.57)	< 0.001
	3rd - 10th	11 (23.91)	18 (17.65)	
	10th - 90th	33 (71.74)	11 (10.78)	
Osteopenia of prematurity		2 (4.35)	11 (10.79)	0.346
Intraventricular Haemorrhage		6 (13.05)	17 (16.67)	0.633
Retinopathy of prematurity		10 (21.74)	33 (32.36)	0.241

Data Presented as n (%), * mean (SD).

In multivariate regression model, SGA neonates (P = 0.001) and neonates requiring > two weeks for achieving full feeding (P = 0.027) were significant independent risk factors for EUGR. SGA neonates were 10.82 times more risk for EUGR compared to AGA neonates. VLBW neonates requiring > two weeks for full enteral feeding had higher OR of 3.57 times for EUGR. Though neonates born with different preterm gestational age group were not significant predictor for EUGR, neonates with gestational age < 28 weeks and more than 32 weeks groups had higher odds for EUGR (OR 4.20 and 2.51 respectively) compared to neonates born at gestational age 28 – 32 weeks. [Figure 1

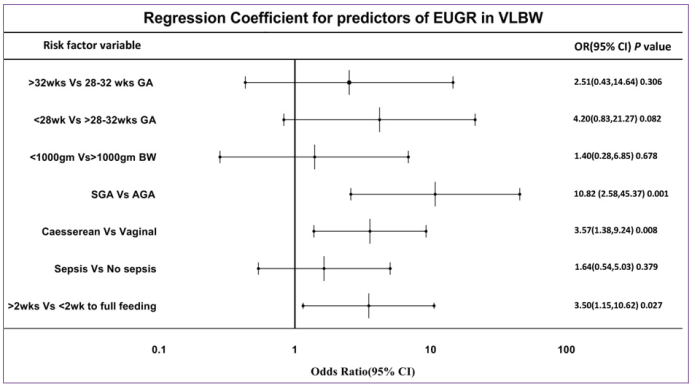

Figure 1. Regression Coefficient for predictors of EUGR in VLBW neonate

Discussion

In the present study, the prevalence of EUGR and severe EUGR among VLBW neonates using Intergrowth 21 chart were 68.9% and 54.1% respectively. Both preterm AGA and SGA were at risk of malnutrition; 50% of AGA became EUGR and 93.7% SGA failed to catch up growth during NICU stay contributing to high prevalence of EUGR at discharge. VLBW neonates requiring longer duration for full enteral feeding was an independent risk factor for EUGR, rather than associated neonatal morbidities in regression model. EUGR neonates had significantly slower brain growth and stunted at discharge compared to non-EUGR group (P < 0.001).

Postnatal growth failure is a universal problem among VLBW neonate and could be influenced by the preterm care and nutritional practices in different regions. In a multicentre study from China, the prevalence of EUGR among VLBW were 60.7% which is comparable to our results.[9] Clark et al, reported lower EUGR prevalence of 28% among preterm < 34 wk.[10] Using Fenton growth chart Vermont Oxford Network Group reported EUGR prevalence of 50% among VLBW babies.[11] In an Indian study by Kallem et al, prevalence of EUGR was 45.7% in preterm < 32 weeks using Intergrowth 21.[8] The higher prevalence of EUGR (68.9% vs. 45.7%) in our study, might be due to the higher prevalence of SGA at birth (43.24% vs. 15.1%).

Several studies reported higher prevalence of EUGR in SGA babies (68.9% - 88.6%) compared to AGA babies (17.8% - 53.7%).[3,12,13] Saluja et al. also reported reduction of approximately 1 Z-score weight in longitudinal growth monitoring for both AGA and SGA during NICU stay.[14] In the multivariate regression model, we found SGA neonate to be a significant independent risk factor for EUGR (P = 0.001). This is similar to the cross sectional study from Ethiopia reporting SGA babies to be 15 times higher risk of growth failure at hospital discharge compared to AGA neonates.[15] In a study by Khasawneh et al, the prevalence of EUGR was 80% among VLBW neonates at hospital discharge with SGA at birth, > two weeks delay in full feeding were independent predictor of EUGR along with suboptimal protein and calorie supplementation.[16]

EUGR prevalence among preterm neonates inversely proportionate to gestational age was found by Clark et al.[10] Makker et al, reported rates of EUGR in preterm < 28 weeks to be more compared to > 32 weeks (24.6% vs. 21.2%).[17] In the present study, the prevalence of EUGR among VLBW neonates born < 28 weeks were more compared to 28 – 32 weeks (82.35% vs. 50.55%). However, VLBW neonate > 32 weeks have a high prevalence of EUGR (38 / 41, 92.68%) which might be due to other associated factors.

Slower brain growth predicts lower mental developmental index and psychomotor index in Bailley III assessment; poor linear growth predicts persistent stunting in later life.[18,19] In the present study, 86.28% of EUGR neonates had HC below 10th centile vs.

30.34% in non-EUGR and 89.22% of EUGR had length below 10th percentile compared to 28.26% of non-EUGR at discharge. Longitudinal follow up of these babies are important for instituting early intervention.

Several studies reported postnatal growth failure to be associated with various neonatal morbidities i.e. need of mechanical ventilation, presence of BPD, NEC, ROP, sepsis, longer duration of total parenteral nutrition.[9,20-2] In contrast to previous studies, need of respiratory support are no more independent risk factor for postnatal growth failure which might be due to the current practice of nutrition management in this study.[10] However, neonates requiring longer duration to achieve full feeding were not surprisingly complicated with postnatal malnutrition. In this study, the average duration to full feeding among EUGR neonates was significantly longer compared to non-EUGR (15.20 ± 9.97 days vs. 10.72 ± 5.398 days, P = 0.015). Duration of full feeding ≥two weeks have a higher odd of EUGR compared to < two weeks (OR 3.5, 95% CI 1.15 - 10.62). Longer duration to full feeding (≥two weeks) was found to be independently predicting EUGR in regression model. We acknowledge the study limitations. Birth weight per gestational age is influenced by many intrauterine factors, hence the importance of maternal characteristics for prediction of extra uterine neonatal growth needs further evaluation. The parenteral and enteral nutritional intake (i.e. average calorie and individual macronutrient) per postnatal week were not analysed. The information was mono- centric with relatively small sample size on VLBW neonate group. The effect of genetics and epigenetics factor for growth retardation was beyond the scope of the study analysis. Further longitudinal growth monitoring, including composition of both parenteral and enteral nutrition for VLBW neonates need to be investigated for better prediction of postnatal growth failure.

Conclusions

In VLBW neonate, prevalence of EUGR at discharge was 68%. Sepsis was significantly associated with EUGR. EUGR babies needed significantly prolonged hospital stay with a higher mean postmenstrual age at discharge. Length and head circumference at discharge were lower in EUGR group. SGA at birth and delay in achieving full enteral feeding were independent predictor of EUGR.

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