

## REVIEW ARTICLE

# The Relationship between Hyperglycemia and Retinopathy of Prematurity in very low birth weight infants

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### ABSTRACT

*Retinopathy of prematurity remains one of the major causes of morbidity in very low birth weight (VLBW) neonates. We evaluated the association between serum glucose level and developing ROP in VLBW infants. This case control study was performed on 60 VLBW infants admitted to neonatal intensive care unit at Ali Asghar Hospital (2012-2013). The level of blood glucose was measured at first week after birth and categorized as mild, moderate, or severe hyperglycemia. The severity of ROP was also stratified as mild or severe. Mean glucose level in neonates with ROP was  $164 \pm 42.63$  mg% and in non-ROP neonates was  $125.22 \pm 48.58$  mg% that was significantly higher in former group ( $p=0.002$ ). Using area under the ROC curve analysis showed that the measurement of blood glucose had a high value for discriminating ROP from non-ROP status (AUC (95%CI) = 0.783 (0.648 – 0.917)). The best cutoff for blood glucose for differentiating ROP from non-ROP in VLBW neonates was 145 mg% yielding a sensitivity of 82.8% and a specificity of 80.6%. Careful monitoring blood glucose levels can be helpful in the prevention of ROP in VLBW infants.*

**Key words:** Retinopathy of prematurity, Hyperglycemia, Very low birth weight, Newborn

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## INTRODUCTION

Retinopathy of prematurity (ROP) is characterized by proliferative growth of blood vessels of the retina in premature infants [1]. Despite advances in treatment of ROP, it still remains as one of the leading causes of visual loss and morbidity in children in both developing and developed countries [2, 3]. Studies have shown that supplemental oxygen is a major risk factor for the development of ROP [4]. Though it cannot be the only cause of the disease since some studies could show developing ROP in very low birth weight (VLBW) infants without ever receiving supplemental oxygen [5]. Later, more studies performed aiming on precisely controlling arterial oxygen concentration and concluded that the incidence of ROP was not decreased which explains a multifactorial disease process [6]. Other studies could identify other etiologies of ROP, including hypoxia [7], hypercarbia [8, 9], hypocarbia [10], sepsis [11], and interventricular hemorrhage (IVH) [12]. Hyperglycemia that is mostly defined as plasma glucose level higher than 150 mg/dl, can frequently occur in VLBW neonates and has been identified as a major risk factor for ROP [13]. Hyperglycemia is developed in 45% of infants weighting less than 1000 g and also in 80% of those neonates weighted lower than 750 g. There is an 18-fold increased risk for developing hyperglycemia in infants weighted lower than 1000 g compared to those who have birth weight higher than 2000 g [14]. However, a few studies have assessed the relation between serum glucose level and the development of ROP, demonstrating this association [13, 15, 16]. Furthermore, some previous studies

ignored the confounding factors affecting association between hyperglycemia and risk of occurring ROP. The present study aimed to assess whether there is a relation between serum glucose level and ROP in VLBW neonates.

## MATERIALS AND METHODS

### Study population

This cross-sectional study was performed on 60 infants were born between 2012 and 2013 in Aliasghar hospital with birth weights lower than 1500 and gestational age less than 32 weeks. Neonates with the history of receiving insulin or erythropoietin, history of seizure, intraventricular hemorrhage, sepsis (any positive culture of blood or urine or cerebrospinal fluid), patent ductus arteriosus, or necrotizing enterocolitis were excluded.

### Data collection

Demographic information including gestational age, gender, one-minute Apgar score, five-minute Apgar score, serum glucose level during the first month, and mode of delivery was extracted from patients' medical records. Ophthalmologic screening for ROP was performed for all patients. Infants were divided into either ROP (n=29) or no ROP group (n=31). Gestational age was determined on history and fetal ultrasonography. The level of blood glucose was measures at first week after birth and categorized as mild hyperglycemia (151-180 mg), moderate (181-210 mg), or severe (>210 mg). The severity of ROP was also stratified as mild (stage 1 or 2) or severe (stage 3 or 4).

### Statistical analysis:

Mean  $\pm$  standard deviation was determined to describe continuous variables and frequency (percentage) was used to describe categorical variables. In order to check the normality of distribution for numeric variables, the Kolmogorov-Smirnov test was used. If a variable was not normally distributed, median and inter-quartile range (IQR) was calculated to describe reports. The Chi-square test or Fisher's exact test was used to compare categorical variables. Independent *t* test or Mann-Whitney *u* test was used to compare quantitative variables. A receiver operating characteristics (ROC) curve analysis based on the Youden's index was performed to determine the best cutoff value of blood glucose for discriminating ROP from non-ROP status. A multivariate logistic regression analysis was used to assess relationship between level of blood glucose and ROP with the presence of confounders. Data were analyzed using SPSS software version 20.0 (Chicago, IL, USA). In order to reject the corresponding null hypothesis, a two-tailed *p*-value less than 0.05 was considered statistically significant.

## RESULTS

Table 1 describes and compares baseline characteristics between the two groups with and without ROP and. One-minute Apgar was lower and serum level of blood glucose was higher in ROP compared to non-ROP group. Nevertheless, no significant difference was found in other baseline variables including gestational age, birth weight, five-minute Apgar, rate of Cesarean-section delivery and gender of neonates. According to ROC curve analysis, increased level of blood glucose had high value for diagnosing ROP ( $p < 0.001$ ). Using area under the ROC curve analysis (figure 1), the measurement of blood glucose had a high value for discriminating ROP from non-ROP status (AUC (95%CI) = 0.783 (0.648 - 0.917)). The best cutoff for blood glucose for differentiating ROP from non-ROP in VLBW neonates was 145 mg% yielding a sensitivity of 82.8% and a specificity of 80.6%.

Multivariate logistic regression analysis (table 2) showed that high level of blood glucose could predict presence of ROP when adjusted for baseline covariates (OR: 1.024, 95% CI: 1.004 to 1.034,  $p = 0.019$ ).

Table 1: Baseline characteristics of neonates with and without ROP

Characteristics	ROP group (n=29)	Non-ROP group (n=31)	p-value
Gestational age (weeks)	29.1 $\pm$ 1.9	29.7 $\pm$ 1.8	0.231
Birthweight (g)	1141 $\pm$ 229	1225 $\pm$ 147	0.102
One minute APGAR	6.3 $\pm$ 1.6	7.1 $\pm$ 1.8	0.038
Five minute APGAR*	8 (7.5-9)	9 (8-9)	0.070
Serum glucose level	164 $\pm$ 43	125 $\pm$ 48	0.002
Male gender	19 (65.5)	14 (45.2)	0.129
C-section	23 (92)	25 (92.6)	0.936

Data are presented as mean  $\pm$  SD or number (%)

Table 2: Multivariate logistic regression analysis to determine main predictors of ROP

Item	B	S.E.	Wald	p-value	OR	95.0% CI for OR	
						Lower	Upper
Age	-0.194	0.218	0.796	0.372	0.823	0.537	1.262
Sex	1.048	0.749	1.959	0.162	2.851	0.657	12.365
Weight	0.005	0.003	1.993	0.158	1.005	0.998	1.011
Height	0.084	0.148	0.326	0.568	1.088	0.814	1.453
Apgar1	-0.011	0.314	0.001	0.973	0.989	0.535	1.830
Apgar5	0.340	0.563	0.363	0.547	1.404	0.465	4.237
Delivery	0.852	1.380	0.381	0.537	2.345	0.157	35.058
Glucose	-0.024	0.010	5.462	0.019	1.024	1.004	1.044
Constant	-4.540	8.499	0.285	0.593	0.011		

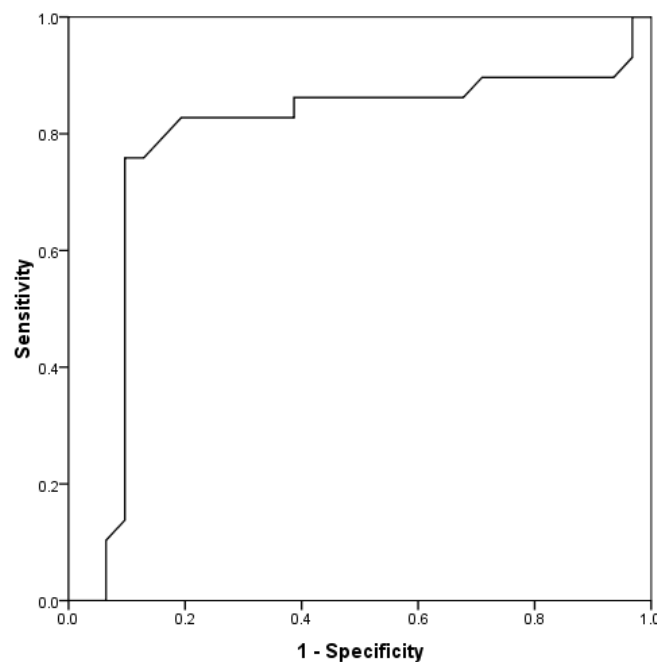


Figure 1: Area under the ROC curve for discriminating ROP from non-ROP in VLBW infants

## DISCUSSION

This study evaluates the association between serum glucose level and developing ROP in VLBW infants with gestational age less than 32 weeks. Evidences could demonstrate neonatal hyperglycemia as a significant risk factor for neonatal morbidity. One study performed by Kao et al evaluated hyperglycemia and morbidity and mortality in extremely low birth weight infants and reported a relationship between severe hyperglycemia (serum glucose > 180) and increased risk factor of death or sepsis [17]. Also, Hays et al evaluated similar issue and reported a significant association between neonatal hyperglycemia and increased risk for death or developing grade III/IV of interventricular hemorrhage [18]. Previously, there have been evidences showing hyperglycemia as a risk factor for developing ROP. Garg et al. evaluated hyperglycemia and developing stage III or IV ROP and reported that for each 10 mg/dl increase of mean serum glucose, the risk of developing ROP increases 2.7 times [13]. Mohamed et al reported an association between duration of hyperglycemia (whole blood glucose > 150) and developing ROP in premature infants less than 32 weeks gestation [19]. In this regard, we found that infants with ROP had higher daily glucose level and could show an association between serum glucose level and developing ROP. While, Garg et al. could not report an actual clinical difference in daily serum glucose level between ROP and non-ROP groups. However, in our survey, high level of blood glucose has high diagnostic value for predicting ROP. Based on ROC analysis, we determined a cutoff point of 145 mg/dl for glucose level which is a new cutoff point for this biomarker for discriminating ROP from non-ROP state. Previous studies reported the cutoff point of 150 mg/dl [20]. Besides, Garg et al. reported an increasing daily trend of blood glucose level and developing ROP. They also showed a lower glucose tolerance among ROP group

[13]. Mohamed et al. also indicated an association between duration of hyperglycemia and developing ROP. Yet, similar to present study, they could not conclude a causative relation between hyperglycemia and the development of ROP might be due to the retrospective design of both studies [19].

As the potential limitation, our study is a retrospective study and thus we could not show a causative relation between hyperglycemia and developing ROP. Thus, it still remains ambiguous whether hyperglycemia is a causal risk factor for developing ROP. Further prospective studies could be conducted to clarify the causative relation.

## CONCLUSION

We finally conclude a significant association between hyperglycemia and developing ROP in VLBW infants. Based on our analysis, a cutoff value of 145 mg% for blood glucose level can effectively predict ROP in these infants.

## CONFLICT OF INTEREST STATEMENT

Authors declare no conflict of interest.

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