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HYPERGLYCEMIA AS AN INDEPENDENT RISK FACTOR FOR RETINOPATHY OF PREMATURITY (ROP): A COHORT STUDY

Ophthalmology

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ABSTRACT

OBJECTIVE: Retinopathy of prematurity (ROP) is a severe morbidity that can lead to blindness in premature babies. Neonatal hyperglycemia has been related to the growth of ROP in a variety of studies. However, there aren't many observational trials to show whether hyperglycemia is linked to ROP in the absence of other comorbidities. The aim of this research was to see if hyperglycemia in premature babies is linked to ROP in a different way.

STUDY DESIGN: Premature infants (<1500 g or⩽ 32 weeks gestational age) were enrolled in a prospective longitudinal cohort study. All demographic, clinical and laboratory data were collected. Bedside whole-blood glucose concentration was measured every 8 hours daily for first 7 days of live. For any glucose reading <50 or>150 mg dl 1 serum sample was sent to the laboratory for confirmation. Hyperglycemia was defined as any blood glucose level⩾ 150 mg dl
− 1. ROP patients were compared with non-ROP patients in a bivariate analysis. Variables significantly associated with ROP were studied in a logistic regression model.

RESULT: A total of 100 patients were enrolled with gestational age <32weeks and birth weight
<1500g. Forty-eight patients (48%) were identified with hyperglycemia. On eye examination, 30 cases (30%) had ROP (19 with stage 1, 10 with stage 2 and 1 with stage 3). There were more cases of ROP in the hyperglycemia group compared with the euglycemia group (45.83% vs 15.38%, P = 0.007). Patients who developed ROP had significantly higher maximum and average glucose concentrations when compared with non-ROP patients. Multiple factors have been associated with ROP on bivariate analysis, including gestational age, exposure to oxygen, respiratory support and poor weight gain. However, in a logistic regression model including all significant variables, average blood glucose in the first week of life was the factor independently associated with ROP with an odds ratio of: 1.77 (95% confidence interval: 1.08 to 2.86), P = 0.024

CONCLUSION: In a prospective cohort study of premature infants, elevated average blood glucose concentrations in the first week of life is an independent risk factor associated with the development of ROP.

KEYWORDS

Retinopathy of prematurity, Premature, Infants., Hyperglycemia.

INTRODUCTION

In preterm children, hyperglycemia is a major risk factor for morbidity and mortality. Excess glucose intake, insulin resistance, or glucose sensitivity can occur in preterm infants due to a variety of physiological and biochemical mechanisms; the consequences of these glucose metabolism abnormalities are numerous.1,2 Hyperglycemia is linked to osmotic diuresis and dehydration, which may lead to brain bleeding and electrolyte imbalance. There are also fears that it could be linked to higher mortality and other morbidities, such as lowered immunity, elevated inflammation, slow wound healing, and skeletal and cardiac muscle failure.[3,4]

In very low birth weight babies, retinopathy of prematurity (ROP) is also a leading cause of morbidity. [5] Although supplemental oxygen is a significant risk factor, it is not the only source of ROP, as shown by a number of low-birth-weight babies who developed ROP after never consuming any oxygen.[6] Poor postnatal growth,[7,8] hypoxia[9] hypercarbia,[10] hypocarbia,[11] exposure to sustained and vigorous mechanical ventilation,[12] inotrope therapy,[6] postnatal steroids,[13,14] prolonged hyperalimentation,[15,16] blood transfusions[11,17] and vitamin E deficiency are all suggested threats for the production of ROP. [18] In addition, ROP has been linked to the existence of patent ductus arteriosus[19–22].

Hyperglycemia has recently been proposed as a potential risk factor for ROP in some retrospective trials. [27–23] Hyperglycemia is linked to a variety of complications in extremely low birth weight babies, including sepsis, candidiasis, intraventricular hemorrhage, and postnatal steroids, both of which are normal in babies that experience ROP later in life.[23]Meanwhile, it's possible that hyperglycemia causes biochemical alterations in the retina; people with poorly regulated diabetes experience a distinct neoproliferative retinopathy, which is most often seen in individuals who have had their blood sugar levels elevated for extended stretches of time. [28] The need of prospectively testing the relationship of hyperglycemia with ROP has been agreed upon[29–31].

There aren't a lot of prospective research on the correlation between hyperglycemia and Retinopathy of Prematurity, which is interesting considering the increasing interest in early and active parenteral feeding. The aim of this prospective cohort analysis is to see if high glucose levels are a separate risk factor for the production of ROP in premature babies.

METHODS

Patients

We conducted a prospective cohort study on 100 premature neonates admitted to the neonatal intensive care unit (NICU) at Nil Ratan Sircar Medical College and Hospital, Kolkata which is a teaching tertiary hospital in Eastern India. Infants were included if admitted within 24 h of life with gestational age (GA)⩽32 weeks or birth weight <1500 g. Infants with high congenital anomalies were excluded from the study. The study was approved by the ethical committee. Parental Informed with written consents were taken for all subjects. All maternal and perinatal history were collected for all the neonates. Other NICU data such as the use of oxygen, ventilation and phototherapy were documented. Data on date of start and day of full establishment of enteral feeds, type of feeding and full caloric intake were recorded.

Eye examination

The first fundus test was conducted at 4 weeks, as suggested by the American Academy of Pediatrics. 32 follow-up tests were planned based on retinal results during the NICU stay and after hospital discharge. Examinations were carried out by a single professional ophthalmologist. Binocular indirect ophthalmoscope, lid speculum, and scleral depressors were used to examine the retina. A topical

anesthetic was used to dilate the pupil before the test, accompanied by an eye drop mixture (0.2 percent cyclopentolate and 1 percent phenylephrine). According to theinternational classification of ROP, the severity stages and zones for the extent of ROP is classified (ICROP).[33,34]

Glucose measurement

Both cases underwent routine laboratory tests, including a full blood count, blood chemistry, and blood gases. A glucose concentration was also measured using a point-of-care glucometer (Optuim Xceed, Abbott, lake Forest, IL, USA). The concentration of glucose was then determined on admission and every 8 hours for the next 7 days. A serum sample was sent to the laboratory for confirmation of any glucose readings of 50 or greater than 150 mg/dl. In the analysis, only glucose concentrations in samples collected every 8 hours were used. Infants were divided into two groups based on whether their plasma glucose concentrations were ever greater than 150 mg/dl: 1) hyperglycemia and 2) euglycemia. Reduced glucose infusion was used to treat hyperglycemia in both of the participants. None of the children in the study were given insulin. Hypoglycemia was characterized as a blood glucose level of less than 50 mg/dl. [1]

STATISTICALANALYSIS

Data were coded and double entry was done to check validity. Data were analyzed using the SPSS (Statistical Package for the Social Science, Chicago, IL, USA) version 18. Data were summarized using mean, S.D. and range for continuous variables and percentage for categorical variables. Comparisons between groups were done using t-test for continuous variables and chi-squared test for categorical variables. Logistic regression model was used to test the association of hyperglycemia and ROP while controlling for confounding variables. P-values <0.05 were considered as statistically significant

RESULTS

The study was done on 100 preterm neonates admitted to the NICU in NRS Medical College and Hospital during a period of 12 months (March 2019-February 2020), out of the 100 enrolled subjects, 48 (48%) were hyperglycemic and 52(52%) were euglycemic (Fig.1). The euglycemia and hyperglycemia groups does not differ in gestational age, birth weight or mode of delivery. hyperglycemia infant group were more females, greater acuity of illness measured by using the Clinical Risk Index, with medians (ranges) of 1 (0 to 6) vs 2 (0 to 7), P = 0.001, and has received more frequent red cell transfusions (Table 1). In the hyperglycemia group, no significant difference between the mean bedside glucose and serum laboratory testing; 267.6 ± 101.2 vs 250 ± 86.4 mg /dl 1, P = 0.46.

Seventy infants (70%) had normal fundus on examination, while thirty cases (30%) had ROP. Out of the 30 ROP cases, 19 had stage-1, 10 infants had stage-2, and 1 infant had stage-3. Compared with non-ROP infants (n = 70), cases with ROP (n = 30) were significantly of younger gestational age (P<0.001), smaller birth weight (P<0.001), more likely to have respiratory distress (P = 0.001) and exposed to phototherapy (P = 0.007). Maternal and neonatal factors associated with ROP are presented in Table 2**.**

There were more cases of ROP in the hyperglycemia group compared with the euglycemia group (45.83% vs 15.38%, P = 0.007), odds ratio 4.776 (95% confidence interval (CI): 1.46 to 15.60). Figure 1 presents average daily glucose concentrations in infants with and without ROP during the first week of life. Mean, maximum and minimum values for glucose concentrations in ROP and non-ROP infants are shown in Table 3. Infants with ROP had significantly higher average and maximum glucose values. Hypoglycemia was detected in 20 (20%) of the studied population. The incidence of ROP in infants with hypoglycemia was 15%, whereas ROP in non-hypoglycemic patients was 33%; this difference was not significant (P = 0.315).

Duration of respiratory support (continuous positive airway pressure or mechanical ventilation), duration of oxygen therapy and the concentration of the administered oxygen (FiO2) during the first 3 days were all significantly higher in ROP cases (Table 4). Compared with non-ROP infants, infants who developed ROP had delayed onset to introduce enteral feeds (7.6 ± 4.5 vs 5 ± 3.4 days, P = 0.01), to reach full enteral feed (25.1 ± 6.3 vs 20.2 ± 7.8 days, P = 0.008) and gained less weight (P = 0.048) (Figure 2).

To study factors associated ROP, a forward conditional logistic regression analysis was conducted. All variables that were significantly associated with ROP on bivariate analysis, including average glucose concentration, days on oxygen, days on respiratory support and variables in Table 2 were entered into the model. Only average blood glucose was significantly associated with ROP with odds ratio 1.77 (95% CI: 1.08 to 2.86), P = 0.024. When analysis was repeated using maximum glucose concentration, results were not as significant: odds ratio 1.04 (95% CI: 1.003 to 1.084), P = 0.036. Using ROC analysis, at a cutoff point>102.5 mg/ dl[1], average blood glucose concentration was associated with ROP, with a sensitivity of 84%, specificity of 80% and odds ratio of 21.9 (95% CI: 5.2 to 91.8), Po0.001. (Figure 3).

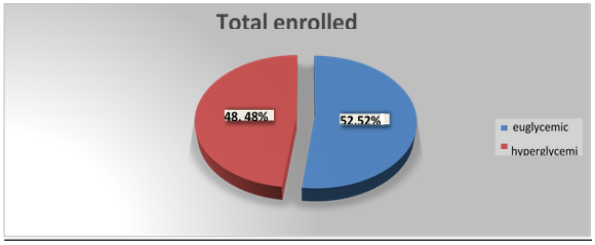

Fig.1

Table.1. Demographic and clinical characteristics of the study population (n=65)

Characteristics	Euglycemia group (n=52)	Hyperglycemia group (n=48)	P - value
Gestational Age(week	31.2+-1	30.9+-1.4	0.23
Birth weight (g)	1446+- 193	1318+-242	0.021
Sex (%of male)	29(55.76%)	13(27.08%)	0.023
LSCS	37(71.15%)	37 (77.08%)	0.58
Chorioamnionitis	0	3 (6.25%)	0.22
Maternal hypertensio	5 (9.61%)	9 (18.75%)	0.22
Phototherapy	26(50%)	22 (45.83%)	0.7
Use of breast milk	34 (65.38)	20 (41.66%)	0.07
Bronchopulmonary dysplasia	6 (11.53%)	8 (16.66%)	0.44
Intraventricular hemorrhage	8 (15.38%)	11 (22.91%)	0.31
Retinopathy prematurity	8 (15.38%)	22 (45.83%)	0.007
Death	0	6 (12.5%)	0.031

Data are presented as number (%), except for gestational age and birth weight where they are presented as mean ±s.d.

Table 2. Maternal and neonatal factors associated with ROP

Risk factor	ROP (n=30)	Non-ROP (n=70)	P-value
Maternal age (years)	30.3±3.1	28.7±2.4	0.045
Maternal hypertension	11 (36.66%)	3 (5.71%)	0.002
Premature rupture membranes	11 (36.66%)	6 (8.57%)	0.036
Gestational age (week	30±1	31.5±0.9	<0.001
Birth weight (g)	1227±204	1450±202	<0.001
Respiratory distress	26 (86.66%)	32 (45.71%)	0.001
Phototherapy	22 (73.33%)	26 (37.14%)	0.007

Abbreviation: ROP, retinopathy of prematurity. Data are presented as number (%), except for maternal age, gestational age and birth weight where they are presented as mean ± s.d.

Table 3. Relationship between glucose concentrations and ROP

Test	ROP	Non-ROP	p-value
Maximum bedside glucose concentration	280±117	161± 63	< 0.001
Average bedside glucose	119±19	97± 10	< 0.001
Minimum bedside glucose	59 ±14	56± 16	0.42
Average high serum glucose[a]	311±80	194± 59	< 0.001
Average low serum glucose[b]	49±4	45± 8	0.3

Abbreviation: ROP, retinopathy of prematurity.

Data are presented as mean ±s.d. (mg /dl)
a. Done when the bedside concentration was>150 mg /dl
b. Done when the bedside concentration waso50 mg /dl

Table 4. Respiratory management of ROP and non-ROP patients

Management	ROP	Non ROP	p-value
Days on mechanic ventilation or CPAP	10.5±7.7	8.8±14.8	0.023
FiO_2 **on day 1**	0.52±0.09	0.44±0.14	0.016
FiO_2 **on day 2**	0.52±0.09	0.39±0.17	0.003
FiO_2 **on day 3**	0.55±0.13	0.39±0.16	< 0.001
Oxygen days	26.9±10.1	18.6±18	0.001

Abbreviations: CPAP, continuous positive airway pressure. ROP, retinopathy of prematurity. Data are presented as mean ±s.

DISCUSSION

It's a prospective cohort study to see whether hyperglycemia and ROP are related in premature babies. Greater average blood glucose during the first week of life was shown to be correlated with the production of ROP in our study. While the concept of hyperglycemia is debatable,[3] elevated blood sugar is a common issue in premature babies, with research suggesting that up to 58 percent to 80 percent of extremely low birth weight of infants have hyperglycemia..[35,36] Hyperglycemia in premature infants is related to developmentally immature hepatic glucose production, inadequate pancreatic beta cell response and insulin insensitivity.[1,2] This can be worsen by stress situations such as sepsis and intraventricular hemorrhage.[3,37]Glucosuria, osmotic diuresis, and vomiting are all signs of hyperglycemia. Hyperglycemia has been linked to elevated mortality and morbidity in retrospective trials, including prolonged hospital stays, worse long-term outcomes[30,38–41,] and ROP.[23–27]

ROP is a vasoproliferative retinal condition affects children with young and premature. While it was believed to be due to increased oxygen exposure[42,] it is now considered to be multifactorial.[5] Pathophysiological similarities between ROP and diabetic retinopathy illustrate the role of hyperglycemia in the production of ROP. [43] Diabetic retinopathies, like ROP, is linked to proliferative vascular disease, which can lead to retinal detachment[28]Retinopathy is caused by elevated retinal blood pressure and shear pressures caused by hyperglycemia. [45,44] When hyperglycemia is combined with hypoxemia, which is normal in premature babies and causes extreme ROP, the effect is amplified.[46,47,48]. In diabetic rats[49], lowering blood glucose levels has been linked to increased retinal blood flow and the prevention of proliferative retinopathy.[50]Additionally, by activating protein kinase C, hyperglycemia can promote the development of vascular endothelial growth factor (VEGF),51 with evidence of increased VEGF in retinal cells in multiple animal studies.[52,53]VEGF is a therapeutic target in clinical trials to avoid ROP because it is involved in the genesis of both ROP and diabetic retinopathy. [55,54]In addition, alack of insulin-like growth factor-1 will induce glucose instability and ROP. Insulin-like growth factor-1 levels are considered to be lower in premature babies, and low serum levels have been linked to ROP[7,5]

This cohort study validates the results of previous retrospective studies associating hyperglycemia with ROP.[23–27,31,57] In our study, it was average blood glucose concentration which was more significantly related with ROP. This agrees with the findings of Chavez et al., [26] who concluded that it is not the single events of glucose⩾ 150 g/ dl but actually the time-weighted glucose concentration in the first 30 days of life that independently predicts ROP. Similarly, Studies [27] concluded that it is the duration of hyperglycemia rather than the severity that is associated with ROP. It is of interest that the cutoff point above which average blood glucose is significantly associated with development of ROP is 102.5 mg /dl, a level identified by most practitioners as normal. Similarly, in recent studies, timeweighted glucose level in the first 30 days of ⩾118 mg /dl was a indicator of severe ROP.[26] This finding raises whether we really know a good definition for hyperglycemia in premature infants. To have a direct association with outcome, a concept of hyperglycemia should most likely contain both a degree and a period.

In present study, Patients with ROP had a lower overall weight gain, had a lower gestational age, had a lower birth weight, were subject to longer cycles of increased oxygen and respiratory care, and had a lower gestational age. They also had a higher maternal age, a higher rate of maternal hypertension, premature rupture of membranes, respiratory distress syndrome, more phototherapy exposure, and less breast milk exposure. This is consistent with recent study that has identified related connections. [7,8,12,58–62] are all numbers that can be used to make a number of different None of these variables, however, remained important enough to be used in the regression model. This may be due to the fact that the sample was not large enough to investigate any of these variables. The challenge now is how to put our results into motion in the clinic. The cumulative average tolerance to elevated glucose amounts, rather than a single excessive blood glucose, is what matters, according to our research. Hyperglycemia should not be treated based on a single or multiple elevated reading, but rather on keeping glucose within a safe range throughout the first week of life. In this study, we did not use insulin to treat higher concentrations of glucose. Previous research showed no correlation between insulin use and a lower risk of ROP; in contrast, they raised questions about the efficacy of insulin use and its potential link to increased mortality.[63,64]Furthermore, insulin use was found to be a better measure of ROP than hyperglycemia on its own. [31] We can advise against using the relatively extreme insulin treatment before an evidence-based understanding of hyperglycemia is developed and a consistent clinical benefit of insulin use has been established. Finally, we performed this research at a big tertiary referral site. The infants in this sample were severely ill, which limits the applicability of the findings to the general preterm population.

CONCLUSION

The expression of ROP is linked to elevated average blood glucose concentrations in the first week of life in a cohort of premature infants. More study is required to determine the optimum blood glucose concentrations and how to sustain them without rising morbidity and mortality risks. During the first week of life, randomized trials that attempt to reduce the time of hyperglycemiarather than the peak glucose values are required, as well as their interaction with ROP. The effect of interventions that induce endogenous insulin secretion, such as early initiation of enteral feeds and more vigorous amino acid supplementation in parenteral solutions, as well as restricting lipid infusion to reduce gluconeogenesis, will also be studied.

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