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Insulin, Hyperglycemia, and Severe Retinopathy of Prematurity in Extremely-low-birth-weight Infants

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Abstract

Objective—To determine the association between hyperglycemia, insulin therapy, and severe retinopathy of prematurity (ROP) in extremely-low-birth-weight (ELBW) infants.

Study design—In this retrospective database study, we included all ELBW infants who were ≤32 weeks gestational age (GA). We excluded infants without any ophthalmology evaluation and who died before 28 days of life. A multivariable model was constructed to determine the association between hyperglycemia, insulin use, and severe ROP. We defined hyperglycemia as blood glucose (BG) >180 mg/dL. Covariates were GA, small for GA status, discharge year, sex, Apgar score at 5 minutes, mechanical ventilation, oxygen use, bacteremia, and postnatal steroid exposure. We defined severe ROP as ROP requiring bevacizumab, cryotherapy, laser therapy, or vitrectomy. Sensitivity analysis using BG >150 mg/dL and >200 mg/dL was performed.

Results—24,548 infants were included; 2547(10%) had severe ROP. Hyperglycemia alone was not associated with severe ROP (odds ratio [OR]=0.88 [95% CI: 0.66–1.17]). Hyperglycemia and insulin use were not associated with severe ROP (OR=1.43 [0.91–2.23]). BG >150 mg/dL and insulin use were associated with severe ROP (OR=1.34 [1.02–1.76]).

Conclusions—Hyperglycemia alone was not associated with severe ROP in ELBW infants. However, we did observe a possible trend between the use of insulin and severe ROP.

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Conflicts of interest
The authors declare that they have no potential conflicts to report.

Keywords

hyperglycemia; retinopathy of prematurity; extremely low birth weight; infants

Retinopathy of prematurity (ROP) is one of the main causes of preventable childhood blindness and accounts for up to 20% of childhood blindness in developed countries.[1,2] Low birth weight (BW) and prematurity are the main risk factors for ROP, with up to 75% of infants born ≤25 weeks gestational age (GA) developing some degree of ROP. Severe ROP, without intervention, leads to blindness[3] and is also associated with increased risk of poor neurodevelopmental outcomes.[4]

Hyperglycemia is common in premature infants and has been associated with increased mortality and morbidity.[5–7] The prevalence of hyperglycemia in very-low-birth-weight (VLBW) infants has been reported to be as high as 50%.[5,7] Small, single-center retrospective studies have demonstrated a link between hyperglycemia and early and severe ROP.[8–11] Hyperglycemia was associated with a 3- to 4-fold increased risk of ROP in VLBW infants.[9,10] Although insulin therapy is associated with better control of glucose levels, it predisposes infants to increased risk of hypoglycemia and may increase mortality.[12–14] The association between the use of insulin and development of ROP is conflicting.[15,16]

It is critical that risk factors be identified to help reduce the risk for severe ROP. To investigate the association between abnormal glucose homeostasis, insulin therapy, and severe ROP in extremely-low-birth-weight (ELBW, <1000 g birth weight) infants, we conducted a study using a large, multicenter administrative database. We hypothesized that hyperglycemia and insulin therapy are associated with increased risk of severe ROP in ELBW infants.

Methods

Data

We used an administrative database that prospectively captures information from daily progress notes generated by clinicians on all infants cared for by the Pediatrix Medical Group. Data on multiple aspects of care are entered into the system to generate admission notes, daily progress notes, and discharge summaries. Information is collected regarding maternal history, demographics, medications, laboratory results, diagnoses, and procedures.

Study cohort

We included infants <1000 g birth weight (BW) and ≤32 weeks GA discharged between 2001 and 2010 from 1 of 305 neonatal intensive care units (NICUs). We included infants admitted to the NICU on the day of birth who had at least 1 retinal examination prior to discharge. Retinal examinations were done according to the standard of care at the respective NICU. We excluded infants who did not have any retinal examination and all infants who died prior to day of life 28, as they could not develop ROP.

We collected data on all days of hospitalization prior to the diagnosis of severe ROP. The primary outcome was severe ROP, defined as ROP requiring cryotherapy, laser therapy,

vitrectomy, or intravitreal injection of bevacizumab. Infants who received surgical interventions for severe ROP that were not specifically identified as 1 of the interventions above were considered to have severe ROP that required "surgical interventions not further classified." We defined the start day of severe ROP as the first day of 1 of these interventions. Each infant with severe ROP was thus only analyzed once.

Definitions

We categorized each infant-day based on the presence of hyperglycemia and insulin use. Daily insulin use was considered a binary variable. We defined hyperglycemia as blood glucose >180 mg/dL.[7] We considered the highest value of glucose reported on each day to define the presence of hyperglycemia for that particular day. Our classification resulted in 4 categories for each infant-day of hospitalization: hyperglycemia without insulin use, hyperglycemia with insulin use, no hyperglycemia without insulin use, and no hyperglycemia with insulin use. To take into account the difference in the length of stay prior to the diagnosis of severe ROP for each infant, we then divided the total number of days in each of the 4 categories for each infant by the number of days prior to the diagnosis of severe ROP. For infants without a diagnosis of severe ROP, we divided the number of days in each category by 84, which corresponded to the mean day of diagnosis of severe ROP in our cohort. The 4 categories of infant-days described above in percentages were then transformed into deciles for each infant. Thus, at the infant level, data for these infant-days were considered at the decile level (Figure 1).

We defined supplementation of oxygen as the need for fraction of inspired oxygen (F_iO_2) >21%. We defined mechanical ventilation as the need for conventional or high-frequency mechanical ventilation. We reported infant-days with any F_iO_2 >21% or need for mechanical ventilation as percentages for each infant, as described above. Steroid use was defined as any exposure to dexamethasone. We defined bacteremia as the presence of a positive blood culture. We considered steroid use and bacteremia to be present if they occurred prior to the diagnosis of severe ROP or prior to day of life 84 for the infants with and without severe ROP, respectively.

Statistical analysis

We summarized categorical variables as percentages and continuous variables as medians and interquartile ranges. Comparisons between categorical and continuous variables were performed using the chi-square and Wilcoxon rank sum tests, respectively. We performed univariable logistic regression with clustering by center to examine risk factors for severe ROP. In this analysis, we evaluated GA, small for gestational age status, and Apgar score at 5 minutes as categorical variables; steroid use, exposure to insulin, need for mechanical ventilation, oxygen supplementation, bacteremia, and presence of abnormal glucose readings were evaluated as binary variables.

We used multivariable analysis with clustering by center to evaluate the association between the percent of hospital days (prior to the diagnosis of severe ROP for infants with severe ROP or day of life 84 for infants without severe ROP) that an infant spent in 1 of 3 categories of days: 1) days with hyperglycemia and insulin exposure; 2) days with

hyperglycemia without insulin exposure; and 3) days without hyperglycemia and with insulin exposure. The category of normoglycemia without insulin exposure was not included in the model to avoid collinearity with the other 3 variables and because it represents a state without impaired glucose homeostasis or insulin effect. The model yielded 3 adjusted odds ratios (ORs) representing the change in odds of developing severe ROP with each 10% increase in proportion of hospital days prior to ROP diagnosis or median time to diagnosis spent in 1 of the 3 categories for each infant. All models were adjusted for the following covariates: GA, small for gestational age status, year of discharge, sex, Apgar score at 5 minutes, need for mechanical ventilation, oxygen supplementation, steroid use, insulin use, bacteremia, and hyperglycemia. We excluded BW from all our analysis due to collinearity with GA.

For both univariable and multivariable analysis, we analyzed the association of risk factors and severe ROP at the infant level. As part of a sensitivity analysis, we used a Cox proportional hazard model to calculate the hazard ratio (HR) of the various risk factors for severe ROP. We analyzed the data with STATA 12 (College Station, TX) and considered a $p < 0.05$ statistically significant. This analysis was approved by the Duke University Institutional Review Board without the need for written informed consent as the data were collected without patient identifiers.

Results

We identified 24,548 infants who met our inclusion/exclusion criteria. The median BW was 795 g (interquartile range: 680, 900), and the median GA was 26 weeks (25, 27). Of the 24,548 infants, 2547 (10%) infants were diagnosed with severe ROP (Table 1). The median BWs of infants with and without severe ROP were 680 g (589, 780) and 810 g (695, 910), respectively ($p < 0.001$). The median GAs of infants with and without severe ROP were 25 weeks (24, 26) and 26 weeks (25, 28), respectively ($p < 0.001$). The median age of diagnosis of severe ROP was 81 days (65, 100).

Of the 2547 infants diagnosed with severe ROP, 1949 (77%) underwent laser surgery, 8 (0.3%) cryotherapy, 10 (0.4%) vitrectomy, and 574 (23%) infants had surgical interventions not further classified. Ten (0.4%) infants received intravitreal bevacizumab. There was no difference between the median gestational age of infants who underwent laser surgery and “surgical interventions not further classified” (25 weeks [24, 26] vs. 25 weeks [24, 25], $p = 0.360$).

Hyperglycemia was present in 1102 (43%) and 5764 (26%) infants with and without severe ROP ($p < 0.001$). The median number of days from first episode of hyperglycemia and severe ROP was 72 (59, 84). We included a total of 1,792,003 infant-days in our analysis (Table 2). Hyperglycemia was present in 14,016 (0.8 %) infant-days. Insulin use was documented on 25,121 (1.4%) infant-days. Within the 14,016 infant-days with documented hyperglycemia, 3447 (25%) infant-days had recorded insulin use.

Risk Factors

Risk factors for severe ROP identified in unadjusted analysis were GA, male sex, oxygen supplementation, mechanical ventilation, steroid exposure, bacteremia, hyperglycemia, and insulin use (Table 3). Risk factors identified in adjusted analysis included GA, oxygen supplementation, mechanical ventilation, steroids, and bacteremia. Hyperglycemia by itself was not a risk factor on adjusted analysis. Hyperglycemia in the presence of insulin use was also not associated with an increased risk of severe ROP. For each 10% increase in days that an infant had hyperglycemia in the presence of insulin use, there was 1.43 (95% confidence interval [CI]: 0.91–2.23) increase in the odds of severe ROP (Table 3). As part of a sensitivity analysis, we used different thresholds of hyperglycemia (blood glucose [BG] >150 mg/dL and BG >200 mg/dL) and repeated our analysis of the multivariable model. In these new models, we did not find that hyperglycemia alone was a significant risk factor (Table 4). The presence of hyperglycemia in the presence of insulin use was associated with increased risk of severe ROP for BG >150 mg/dL (OR 1.34 [95% CI: 1.02–1.76]). In our sensitivity analysis using the Cox proportional hazard model, hyperglycemia (HR: 1.57 [95% CI: 0.70–3.51]) and insulin use (HR: 0.49 [95% CI: 0.20–1.19]) were not associated with severe ROP.

Discussion

In a large cohort of ELBW infants, we found that the use of insulin in the setting of hyperglycemia was not associated with severe ROP. We also did not find any association between hyperglycemia and severe ROP.

Hyperglycemia alone has been reported as a risk factor for ROP. Two retrospective studies of VLBW infants demonstrated that hyperglycemia was associated with a 3- to 4-fold increased risk of ROP.[9,10] A more recent and larger study of nearly 600 infants <32 weeks GA also showed an increased risk of ROP with hyperglycemia (OR=1.073 [1.004–1.146]).[11] None of the 3 studies described whether insulin was used in their cohort. In our unadjusted analysis, there was a difference in the proportion of infants with hyperglycemia in infants with severe ROP compared to those without (43% vs. 26%, p <0.001). However, after adjusted for important clinical covariates, we did not find this association to be significant. The lack of association between hyperglycemia alone and severe ROP in our study is in contrast to findings from these previous studies. All these studies use a blood sugar threshold of >150 mg/dL in their definition of hyperglycemia; we used 180 mg/dL as the threshold for our main model. We considered alternative definitions of hyperglycemia in our sensitivity analysis but did not find any association between hyperglycemia (using different thresholds of 150 mg/dL and 200 mg/dL) alone and severe ROP. Furthermore, all 3 studies examined the presence of hyperglycemia as a categorical variable and did not take into account the number of days with hyperglycemia in their analysis. The ROP variable was defined differently in our study compared with the previous studies. We only considered ROP that required surgical intervention or intravitreal bevacizumab. In contrast, 2 of the previous studies[10,11] considered the most severe stage of ROP as determined by the ophthalmologist and another considered any stage of ROP.[9]

Clinical evidence of the association of insulin use to ROP is also conflicting. Infants <30 weeks GA with ROP (stage 3 and 4) had more days of insulin use compared with those without ROP.[15] However, another study of ELBW infants did not observe that exposure to insulin affected the development of ROP.[16] We observed a plausible trend between insulin use and development of ROP requiring treatment. Our data further suggest that this association is modified by the level of blood glucose during the use of insulin. The adjusted odds ratio for insulin use during days when BG was >180 mg/dL was higher than when BG was <180 mg/dL (OR=1.43 [0.91–2.23] vs. 1.05 [0.95–1.15], respectively). Furthermore, when we used a glucose threshold of 150 mg/dL, hyperglycemia and insulin use was significantly associated with severe ROP (OR: 1.34 [95% CI: 1.02–1.76]).

Defining the biologic basis for the association between hyperglycemia requiring insulin infusion and higher likelihood of severe ROP is challenging. The early postnatal vascular arrest/obliteration period, when insulin-like growth factor (IGF)-1 levels are low, is when most hyperglycemia and use of insulin occurs, so associations between hyperglycemia and insulin and simultaneous IGF-1 levels could be informative. A pilot study of routine, continuous insulin infusion in VLBW infants led to higher IGF-1 bioactivity levels early in life compared with the standard clinical approach of infusing insulin only with hyperglycemia.[17] The higher IGF-1 levels could be helpful in reducing risk of ROP[18]; however, when this intervention was tested in larger multicenter trial, it was not efficacious (more deaths in the first 28 days, and no improvement in ROP outcomes for the continuous infusion group).[15] Thus, the relationship between insulin and IGF-1 is more complex and may involve other factors.[19]

We acknowledged that our cohort definition of infants <1000 g BW and ≤32 weeks GA may result in an oversampling of small-for-gestational age infants; we did not include all infants who satisfied either criteria because we wanted to concentrate on the impact of hyperglycemia and insulin use on high-risk infants. We used aggregated data from a large administrative database to determine the association between insulin use and ROP requiring treatment. Classification of ROP based on the International Grading criteria for ROP is not collected consistently across all sites in the database.[20] As such, we chose to define severe ROP as those that required interventions. In addition, the indications for all these interventions are not the same across centers within the Pediatrix Medical Group. There is also no standardized protocol for checking blood glucose levels and indication for starting of insulin infusion across all centers. Because we used data from over a 10-year period, there may have been unmeasured changes in clinical practice with regard to ventilator management strategies and oxygenation saturation targets, both of which may have modified the effect of glucose homeostasis and insulin therapy on ROP. Our decision to use a cut-point for hyperglycemia limited our analysis to examine effects of extreme ranges of glucose levels. Finally, the dose of insulin was not available for this analysis.

In contrast to data obtained from a randomized controlled trial, our observational study limits us from making any causal inference between hyperglycemia and severe ROP. In addition, we were unable to investigate the association of weight gain following insulin therapy with the development of severe ROP. We were also unable to examine the impact of

the lack of acute reduction in glucose level in response to insulin use because the time of day of insulin administration or glucose measurement was not available in the database.

Our findings suggest that insulin use may be associated with increased risk of ROP requiring treatment, but we lack evidence of a plausible biological mechanism to explain this association. Given the potential long-term consequences of ROP requiring treatment, effects associated with hypoglycemia, and little proven benefit of elective insulin therapy, clinicians should be cautious with the use of tight glycemic control when using insulin in premature infants.

The incidence of severe ROP in developed countries has declined over the past decade.[21,22] This is likely due to a combination of evidence-based management strategies in NICUs. Interestingly, the impact of management of hyperglycemia in ROP has not been investigated in research studies or as a quality improvement initiative. Future studies that aim to prospectively investigate the effects of tight glucose control in premature infants should include ROP as a clinical outcome to better ascertain the role of glycemic control with insulin.

Conclusion

We observed no association between hyperglycemia alone with severe ROP in ELBW infants. However, we did observe a possible trend between the use of insulin and severe ROP.

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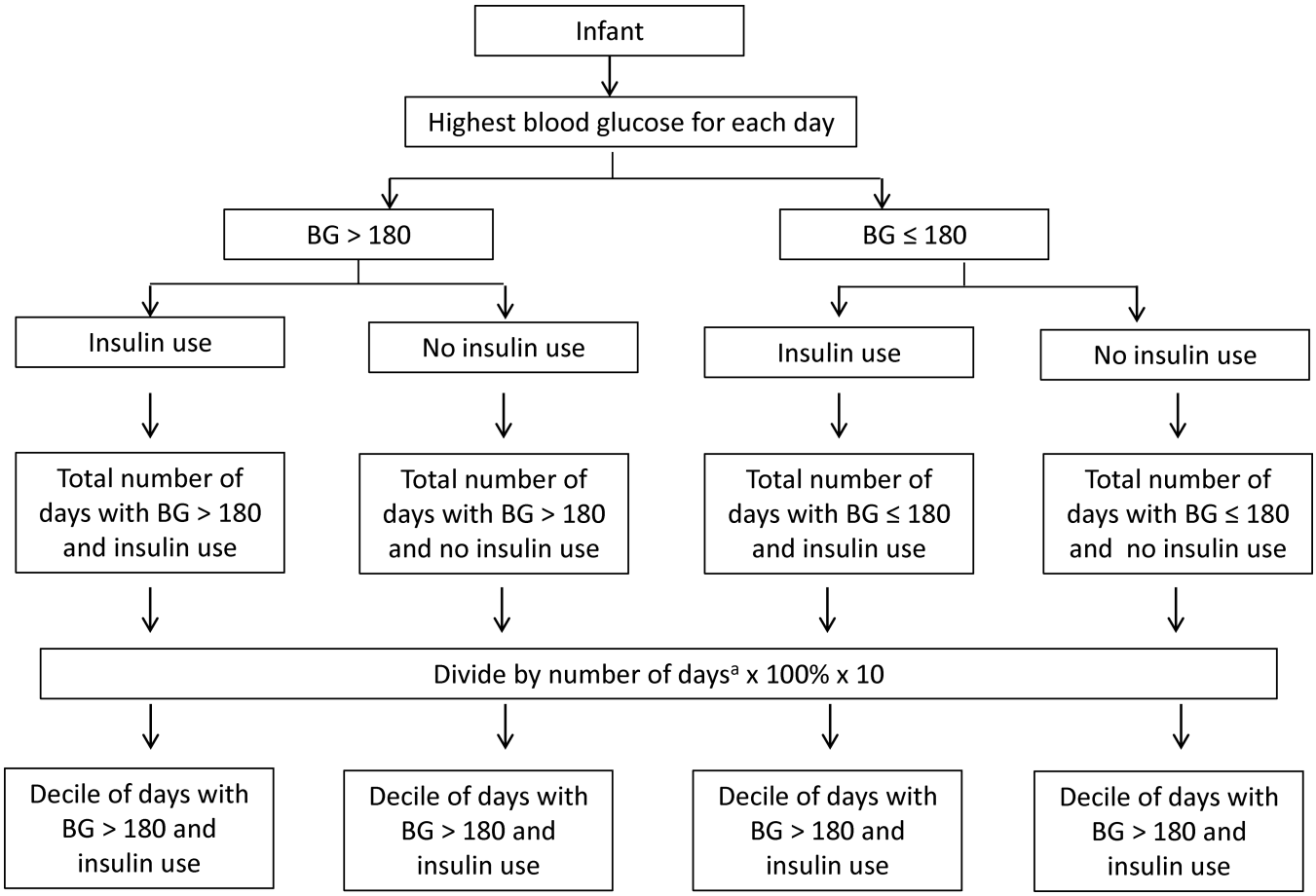

Fig. 1.

Classification and transformation of days based on glucose level and insulin use into deciles for each individual infant.

[a] Denominator is number of days prior to diagnosis of severe ROP for infants with severe ROP or 84 for infants without diagnosis of severe ROP.

Table 1

Baseline Characteristics of Infants by Presence of Severe Retinopathy of Prematurity

	Severe ROP, n (%) (N=2547)	No severe ROP, n (%) (N=22,001)
Gestational age (weeks)		
≤25	1852 (73)	7666 (35)
26–28	643 (25)	11,443 (52)
29–32	52 (2)	2902 (13)
Birth weight (g)		
<750	1738 (68)	7835 (36)
750–1000	809 (32)	14,166 (64)
Small for gestational age	606 (24)	5880 (27)
Cesarean section	1685 (67)	16,502 (76)
Male	1405 (55)	10,367 (47)
Race/ethnicity		
White	1180 (48)	9561 (45)
Black	494 (20)	6790 (32)
Hispanic	615 (25)	3876 (18)
Other	165 (7)	1103 (5)
Apgar score at 5 minutes		
0–3	229 (9)	1093 (5)
4–6	807 (33)	4823 (22)
7–10	1444 (58)	15,645 (73)
Hyperglycemic	1102 (43)	5764 (26)
Received mechanical ventilation	2488 (98)	19,614 (89)
Received supplementation oxygen	2520 (99)	20,957 (95)
Steroids	1059 (42)	4492 (20)
Received insulin	770 (30)	3106 (14)
Bacteremia	913 (36)	4857 (22)
Year of discharge		
2001	115 (5)	909 (4)
2002	194 (8)	1348 (6)
2003	237 (9)	1564 (7)
2004	291 (11)	1893 (9)
2005	264 (10)	2260 (10)
2006	271 (11)	2500 (11)
2007	317 (12)	2807 (13)
2008	310 (12)	2877 (13)
2009	297 (12)	2887 (13)
2010	251 (10)	2956 (13)

ROP, retinopathy of prematurity.

Table 2

Distribution of Infant-days Classified According to Presence of Hyperglycemia and Exposure to Insulin

	Severe ROP, n (%) (N=200,033)	No severe ROP, n (%) (N=1,591,970)
Hyperglycemia without insulin use	1951 (1.0)	8618 (0.5)
Hyperglycemia with insulin use	1001 (0.5)	2446 (0.2)
BG ≤180 without insulin use	193,179 (96.6)	1,564,134 (98.3)
BG ≤180 with insulin use	4902 (2.5)	16,772 (1.1)

BG, blood glucose; ROP, retinopathy of prematurity.

For each day an infant stays in the neonatal intensive care unit, he/she contributes an infant-day. Hyperglycemia and insulin exposure were considered as binary outcomes for each infant-day. Hyperglycemia defined as blood glucose > 180 mg/dL.

Table 3

Risk Factors for Severe Retinopathy of Prematurity

		Unadjusted odds ratio (95% CI)	Adjusted odds ratio (95% CI)*
Gestational age (weeks)			
	≤25	13.48 (9.89–18.38)	5.43 (3.56 – 8.27)
	26–28	3.14 (2.38–4.14)	2.22 (1.59–3.11)
	29–32	Reference	Reference
Small for gestational age		0.86 (0.75, 0.97)	1.40 (1.22–1.61)
Apgar at 5 minutes			
	0–3	2.27 (1.92–2.69)	1.17 (0.97–1.41)
	4–6	1.81 (1.62–2.03)	1.20 (1.06–1.36)
	7–10	Reference	Reference
Male		1.38 (1.26–1.51)	1.15 (1.04–1.26)
Supplemental oxygen[a]		1.03 (1.02–1.03)	1.01 (1.00–1.01)
Mechanical ventilation		1.03 (1.02–1.03)	1.02 (1.01–1.02)
Bacteremia		1.97 (1.72–2.26)	1.23 (1.06–1.42)
Steroids		2.77 (2.37–3.25)	1.36 (1.14–1.61)
BG ≤180 without insulin use		0.70 (0.64 – 0.77)	Omitted due to collinearity
BG ≤180 with insulin use		1.40 (1.27–1.54)	1.05 (0.95–1.15)
Hyperglycemia without insulin use		1.90 (1.20–3.01)	0.88 (0.66–1.17)
Hyperglycemia with insulin use		5.21 (2.84–9.54)	1.43 (0.91–2.23)

BG, blood glucose; CI, confidence interval.

*Adjusted for gestational age, small for gestational age status, male sex, Apgar score, percent oxygen days, percent mechanical ventilation days, steroid use, bacteremia, center and discharge year.

Hyperglycemia defined as blood glucose > 180 mg/dL.

[a]Sensitivity analysis using supplemental oxygen threshold of 40% did not demonstrate that oxygen is an independent risk factor for severe ROP. The adjusted odds ratio for supplemental oxygen at this threshold was 1.10 (95% CI: 0.79–1.52).

Table 4

Adjusted Odds Ratio for Severe ROP Using Different Glucose Thresholds

	Adjusted odds ratio (95 % CI)		
	Threshold 150	**Threshold 180**	**Threshold 200**
BG ≤ threshold with insulin use	1.03 (0.94–1.13)	1.05 (0.95–1.15)	1.08 (0.98–1.17)
BG > threshold without insulin use	0.98 (0.81–1.20)	0.88 (0.66–1.17)	0.85 (0.57–1.26)
BG > threshold with insulin use	1.34 (1.02–1.76)	1.43 (0.91–2.23)	1.26 (0.77–2.06)

BG, blood glucose; CI, confidence interval; ROP, retinopathy of prematurity.

Adjusted for gestational age, small for gestational age, male sex, Apgar score, percent oxygen days, percent mechanical ventilation days, steroid use, bacteremia, center and discharge year.