Influence of the blood glucose level on the development of retinopathy of prematurity in extremely premature children

Influência do nível de glicose sanguínea no desenvolvimento de retinopatia da prematuridade em crianças extremamente prematuras

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ABSTRACT

Purpose: To investigate the influence of the blood glucose level on the development of retinopathy of prematurity (ROP) in extremely premature infants.

Methods: Sixty-four premature infants with a gestational age of less than 30 weeks and a birth weight of less than 1500 g were included in the study. Children without ROP were allocated to Group 1 (n=14, gestational age 28.6 ± 1.4 weeks, birth weight 1162 ± 322 g), and children with spontaneous regression of ROP were allocated to Group 2 (n=32, gestational age 26.5 ± 1.2 weeks, birth weight 905 ± 224 g). Children with progressive ROP who underwent laser treatment were included in Group 3 (n=18, gestational age 25.4 ± 0.7 weeks, birth weight 763 ± 138 g). The glucose level in the capillary blood of the premature infants was monitored daily during the first 3 weeks of life. A complete ophthalmological screening was performed from the age of 1 month. The nonparametric signed-rank Wilcoxon-Mann-Whitney test was used for statistical analysis.

Results: The mean blood glucose level was 7.43 ± 2.6 mmol/L in Group 1, 7.8 ± 2.7 mmol/L in Group 2, and 6.7 ± 2.6 mmol/L in Group 3. There were no significant differences in the blood glucose levels between children with and without ROP, and also between children with spontaneously regressing ROP and progressive ROP (p>0.05). Additionally, there were no significant differences in the blood glucose levels measured at the first, second, and third weeks of life (p>0.05).

Conclusion: The blood glucose level is not related to the development of ROP nor with its progression or regression. The glycemic level cannot be considered as a risk factor for ROP, but reflects the severity of newborns' somatic condition and morphofunctional immaturity.

Keywords: Hyperglycemia; Infant, premature; Retinopathy of prematurity; Gestational age; Birth weight

RESUMO

Objetivo: *Investigar a influência do nível de glicose sanguínea sobre o desenvolvimento da retinopatia da prematuridade (ROP) em prematuros extremos.*

Método: *Sessenta e quatro prematuros com idade gestacional inferior a 30 semanas e um peso de nascimento abaixo de 1.500 g foram incluídos no estudo. As crianças sem ROP foram atribuídos ao Grupo 1 (n=14, idade gestacional 28,6 ± 1,4 semanas, peso ao nascer 1.162 ± 322 g). As crianças com regressão espontânea da ROP foram atribuídos ao Grupo 2 (n=32, idade gestacional 26,5 ± 1,2 semanas, peso ao nascimento 905 ± 224 g). Crianças com ROP progressiva que se submeteram a tratamento com laser foram incluídos no Grupo 3 (n=18, idade gestacional 25,4 ± 0,7 semanas, o peso ao nascer de 763 ± 138 g). O nível de glicose de sangue capilar de prematuros foi monitorado diariamente durante as três primeiras semanas de vida. A triagem oftalmológica completa foi realizada a partir da idade de 1 mês. O teste não paramétrico de Wilcoxon-Mann-Whitney foi utilizado para análise estatística.*

Resultados: *O nível médio de glicose no sangue em crianças do Grupo 1 foi de 7,43 ± 2,6 mmol/L, o grupo 2 foi de 7,8 ± 2,7 mmol/L, e o Grupo 3 foi de 6,7 ± 2,6 mmol/L. Não houve diferenças significativas nos níveis de glicose no sangue entre crianças com e sem ROP, e também entre crianças com regressão espontânea ROP e ROP progressiva (p>0,05). Também não houve diferenças significativas nos níveis de glicose no sangue medidos na primeira, segunda e terceira semana de vida (p>0,05).*

Conclusões: *O nível de glicose no sangue não tem relação com o desenvolvimento de ROP, bem como sobre a sua progressão ou regressão. O nível glicêmico não pode ser considerado como um fator de risco para ROP, mas reflete a gravidade do estado somático de recém-nascidos e imaturidade morfofuncional.*

Descritores: *Hiperglicemia; Prematuro; Retinopatia da prematuridade; Idade gestacional; Peso ao nascer*

INTRODUCTION

Retinopathy of prematurity (ROP) is a result of abnormal growth of newly formed retinal blood vessels, with subsequent fibrovascular proliferation in premature babies. The pathogenesis of the disease is based on the defective production of vascular endothelial growth factors in the presence of chronic intrauterine hypoxia and extrauterine superoxygenation. Some authors believe that hyperglycemia in the early neonatal period is a risk factor for ROP[1-4].

Blood glucose is one of the components of the internal environment that has its own homeostasis. Hyperglycemia is defined as a fasting plasma glucose level greater than 6.5 mmol/L or a blood glucose level at any time of more than 8.9 mmol/L[1,5,6].

From the moment of birth, hypoxic infants have changes in carbohydrate metabolism, including intracellular lactic acidosis and disturbance of glucose membrane transport[7]. Hyperglycemia develops in newborns with infections, sepsis or cold stress, due to glucose tolerance. The iatrogenic causes of hyperglycemia include excessive infusion of concentrated solutions of glucose and inadequate parenteral nutrition[1,5,6].

During the first weeks of life, premature infants are at high risk of impaired glucose homeostasis associated with their immature endogenous regulatory mechanisms and critical somatic condition[2,5,6,8-10]. Extremely premature infants usually have much greater fluctuation in the range of blood glucose concentration as compared to full-term

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children. Hypoglycemia in preterm infants within the first few days is associated with a lack of glycogen. The combination of insulin resistance and relative insulin deficiency in the presence of high levels of plasma glucagon often turns hypoglycemia into hyperglycemia[8,11].

Hyperglycemia is more common in newborns compared to other metabolic disorders. In extremely premature infants, hyperglycemia is detected in 40-80% of cases during the neonatal period[1].

The aim of the present study was to investigate the influence of the blood glucose level on the development of ROP in extremely premature infants.

METHOD

Participants were recruited from the 2nd Pediatric Intensive Care Unit of the City Clinical Hospital nº 24 over 1 year (from December 2013 to December 2014). This prospective study was part of a thesis, and was approved by the Research Ethics Committee of Pirogov Russian National Research Medical University (Protocol number 113, meeting date 12/12/2011) and was performed in accordance with the ethical standards laid down in the Declaration of Helsinki. Parents or guardians of all children gave their informed consent prior to their inclusion in the study.

Sixty-four infants with a gestational age of less than 30 weeks and a birth weight of less than 1500 g were included in the study. All the children were at risk of ROP development. The glucose level in the capillary blood of the premature infants was monitored daily during the first 3 weeks of life (2688 measurements). Hyperglycemia and hypoglycemia are defined as when the glucose level in the capillary blood is more than 8.9 mmol/L and less than 2.6 mmol/L, respectively.

A complete ophthalmological screening was performed for all children from the gestational age of 30 weeks. Low transparency and opalescence of the cornea, as well as significant embryonic vascular capsule of the lens, as well as a pale, or even gray, optic disc with narrow and short retinal blood vessels, were detected often during the first examination. Ophthalmological examination was performed once every 10 days in all children at risk of ROP, once every 7 days in children with detected ROP, and once every 3-5 days in children with an aggressive disease state.

Depending on the presence of ROP, all participants were allocated to the following groups: Group 1 included children without ROP (n=14), Group 2 included children with active ROP that regressed spontaneously (n=32), and Group 3 included children with active ROP that regressed after laser coagulation of the peripheral zones of the retina (n=18).

The case histories were analyzed to evaluate the children's somatic condition.

Statistical analysis was performed using the computer package program STATISTICA 6.0 (StatSoft Inc., Tulsa, OK, USA). Results were reported as the mean ± standard deviation (SD). Differences between the groups were tested for significance using the nonparametric signed-rank Wilcoxon-Mann-Whitney test. Differences were considered statistically significant at $p<0.05$.

RESULTS

The data collected from 64 preterm infants were analyzed. The mean gestational age of children in Group 1 was 28.6 ± 1.4 weeks (range 27-30 weeks), and the mean birth weight was 1162 ± 322 g (range 840-1484 g). The mean gestational age of children in Group 2 was 26.5 ± 1.2 weeks (range 25-27 weeks), and the mean birth weight was 905 ± 224 g (range 681-1129 g). Lastly, the mean gestational age of children in Group 3 was 25.4 ± 0.7 weeks (range 24-26 weeks), and the mean birth weight was 763 ± 138 g (range 625-901 g). The mean gestational age and the mean birth weight of children in Groups 2 and 3 were statistically lower than in Group 1 ($p<0.05$).

The case history analysis showed that the severity of the newborns' condition was related to the presence of somatic and neurological diseases. All the children were in need of long-term oxygen therapy and all of the infants were diagnosed with congenital infection, pneumonia, and hypoxic brain damage. ROP was detected in children with significantly lower weight and gestational age at birth, along with severe somatic and neurological disorders and generalized inflammation. Table 1 shows the characteristics of the infants in each group.

In Group 2, all infants (100%) had active zone 3, stage 2 ROP that manifested at the postconceptional age of 37–38 weeks, which then regressed spontaneously. In Group 3, all infants had active ROP that manifested at the postconceptional age of 33–34 weeks, which then progressed and regressed only after laser coagulation of the peripheral zones of the retina. Within this group, five infants (28%) had aggressive posterior ROP (AP ROP), and 13 infants (73%) had zone 2, stage 3 ROP (plus disease).

Table 1. Characteristics of premature infants in study groups

Groups	Group 1	Group 2	Group 3
ROP	No ROP	Spontaneously regressing ROP	ROP regression after laser treatment
Number of infants	14	32	18
Mean gestational age, weeks	28.6 ± 1.4	26.5 ± 1.2	25.4 ± 0.7
Mean birth weight, g	1162 ± 322	905 ± 224	763 ± 138
Congenital pneumonia, %	100.0	100.0	100.0
Sepsis, %	-	18.7	50.0
Hypoxic brain damage, %	100.0	100.0	100.0
Purulent meningitis, %	-	9.3	27.7
Intraventricular hemorrhage			
Stage 2, %	14.2	43.7	33.3
Stage 3, %	7.1	12.5	55.5
Periventricular leukomalacia	10.0	22.0	50.0
Bronchopulmonary dysplasia, %	14.3	37.5	72.2
Necrotizing enterocolitis, %	7.0	21.8	33.3
Hemodynamically relevant patent ductus arteriosus, %	-	6.0	11.0

ROP= retinopathy of prematurity.

The mean blood glucose levels in the children in each study group are presented in table 2. The mean glucose concentration in the capillary blood was 7.43 ± 2.6 mmol/L in Group 1 (without ROP), 7.8 ± 2.7 mmol/L in Group 2 (with spontaneously regressed ROP), and 6.7 ± 2.6 mmol/L in Group 3 (with progressive ROP). There were no significant differences in the mean blood glucose levels between the study groups (p>0.05).

In addition, episodes of both hypoglycemia and hyperglycemia were registered in children in all groups. The mean duration of hyperglycemia was 1.6 ± 0.9 days in Group 1, 2.7 ± 1.3 days in Group 2, and 3.8 ± 2.3 days in Group 3. The total duration of hyperglycemia in children of Group 3 significantly differed from the duration of hyperglycemia in children of Group 1 (p=0.033).

One child in Group 3 required the administration of insulin due to prolonged elevated glucose level (above 15 mmol/L); later, this child developed AP ROP.

The mean total duration of hypoglycemia was 1 ± 0.7 day in Group 1, 2.7 ± 1.8 days in Group 2, and 5 ± 3.3 days in Group 3. There were no significant differences in the mean duration of hypoglycemia between the study groups (p>0.05).

The blood glucose levels measured in all children at the first, second, and third weeks of life were compared; the results are presented in table 3. There was a greater range of fluctuation of the blood glucose level in children in the first week of life compared to the second and third weeks of life. However, there were no significant differences in the mean blood glucose levels measured at the first, second, and third weeks of life (p>0.05).

DISCUSSION

The data presented in the literature regarding the influence of neonatal hyperglycemia on the development of ROP are ambiguous.

The available information shows that the most significant risk factors for ROP are birth weight, gestational age, oxygen therapy, patent ductus arteriosus, neonatal sepsis, intraventricular hemorrhage, and pulmonary diseases. Hyperglycemia was significant after adjustment for the other risk factors[2,12-15].

In the literature, hyperglycemia is regarded as a marker of acute critical state, reflecting its severity and insulin resistance[1,16,17]. Therefore, we are of the opinion that high concentrations of glucose in the blood should not be considered a specific risk factor for ROP, but rather, reflects the severity of the somatic condition and morphofunctional immaturity of the premature infant.

At the same time, hyperglycemia results in elevated osmotic pressure of the blood plasma[1] and increased permeability of the blood-tissue interface, including the blood-ocular barrier. Increased blood osmolarity leads to cerebral edema and intraventricular hemorrhage in newborns[1,12,18]. These pathochemical changes can promote the development of ROP and exacerbate its state.

From the literature, hyperglycemia is known to be accompanied by increased resistance of vessel walls and changes in organ blood flow[19–21]. In a previous study, we noted that the spastic, highly resistant blood flow in the ocular blood vessels was the basis of the pathogenesis of retinopathy in premature infants[22,23].

Hyperglycemia can reduce the ability of the blood to transport oxygen, thus exacerbating retinal hypoxia. However, the level and the duration of hyperglycemia are unquestionably of great importance. We agree with those researchers who suggested that permissive hyperglycemia during the first 14 days of life, which does not require insulin treatment or cause osmotic diuresis, does not increase morbidity and mortality[24].

Careful treatment of premature children in modern perinatal centers in compliance with current medical protocols enables us to avoid iatrogenic hyperglycemia and rapidly correct the critical state.

ROP progressed in morphologically less mature children with significantly lower weight and gestational age at birth and severe somatic and neurological disorders. A significantly longer duration of hyperglycemia was detected in children with severe ROP, reflecting the severity of the somatic condition of the patients. However, there were no significant differences in the mean blood glucose levels between the study groups (p>0.05).

CONCLUSION

In conclusion, there were no significant differences in the blood glucose levels between premature infants with and without ROP, and between premature infants with progressive ROP and those with spontaneously regressing ROP. High plasma glucose level cannot be considered as a risk factor for ROP, but reflects the severity of newborns' somatic condition and morphofunctional immaturity.

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Table 2. Comparison of the mean blood glucose levels of premature infants without (Group 1) and with ROP (Groups 2 and 3)

Patients	Group	Number of children	Number of glucose measurements	Mean blood glucose level, mmol/L	*p* value
Infants without ROP	Group 1	14	588	7.43 ± 2.6	
Infants with spontaneous regression of ROP	Group 2	32	1344	7.8 ± 2.7	p>0.05
Infants with ROP that regressed after laser treatment	Group 3	18	756	6.7 ± 2.6	

ROP= retinopathy of prematurity

Table 3. Mean blood glucose level in children of study groups measured during the first 3 weeks of life

Group	Group 1	Group 2	Group 3
ROP	No ROP	Spontaneously regressing ROP	ROP regression after laser treatment
1 week	7.9 ± 3.7	8.3 ± 4.0	7.29 ± 4.6
2 week	7.0 ± 1.5	7.8 ± 3.0	6.97 ± 2.2
3 week	7.8 ± 3.0	6.7 ± 2.4	6.43 ± 3.0
p value	p>0.05	p>0.05	p>0.05

ROP= retinopathy of prematurity.

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