Assessment of Association of Serum Lactate Level with Retinopathy of Prematurity

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ABSTRACT

Purpose: To assess the relation between serum lactate level and development and progression of retinopathy of prematurity (ROP).

Material and Methods: This retrospective study included premature newborns that received intensive medical care. Serum lactate levels that were obtained with three-day intervals during the first month after birth was noted. Patients with ROP were included in ROP group and patients without ROP were included in control group.

Results: 71 patients were included in ROP group and 35 patients included in control group. Mean gestational age 27.8 ± 1.8 weeks in ROP group and 28.7 ± 3.2 weeks in control group (p=0.061). Mean birth weight was 1150.4 ± 251.7 and 1262.3 ± 323.9 grams in ROP and control groups respectively (p<0.078). Mean serum lactate level at the first day after birth was 36.6 ± 22.3 mg/dl in ROP group and 24.9 ± 12.8 mg/dl in control group (p<0.001). Mean serum lactate level at the first month after birth was 26.6 ± 7.9 mg/dl in ROP group and 18.1 ± 6.5 mg/dl in control group (p<0.001). No significant relation was observed between lactate level at the first day and month and ROP stage and plus disease (p>0.05).

Mean serum lactate level equal or over 21.2 mg/dl at the first month predicted the development of ROP with a 76% sensitivity and 74% specificity (Area under the curve: 0.837, p<0.001).

Conclusion: Higher serum lactate levels were found associated with ROP and serum lactate level could be used to predict the development of ROP.

Keywords: Lactate, Retinopathy of prematurity, Vascular endothelial growth factor.

INTRODUCTION

Retinopathy of prematurity (ROP) is a proliferative disorder that is caused by abnormal development retinal vascularity triggered by hypoxia occurring at avascular tissue and can result in functional loss of vision.[1, 2] There are hyperoxia conditions in the early stages of ROP and factors supporting vascular development is suppressed due to increased oxygen saturation after delivery.[3, 4] The suppression of vascular development and increased oxygen demand in retina lead retinal hpoxia.[1, 4] The hypoxia occurring at retinal tissue where vascular development is very immature causes abnormal vascular development by leading excessive release of vascular endothelial growth factor (VGEF).[1, 5]

The VGEF is released from retinal pigment epithelium and glial cells under hypoxic conditions. [6, 7] Hypoxia is the most important factor that controls VGEF release at transcriptional and posttranscriptional level.[7] The transcriptional VGEF regulation is mediated by "hypoxia inducible factor 1" (HIF-1).[7-9] In addition, HIF-1 also regulates intercellular signal transduction which plays role in neovascularization.[10] In the literature, it was shown that lactate, end-product of glycolysis pathway, increases VGEF release from endothelial cells by elevating HIF level and stabilizing HIF-1. [10, 11]

In the literature, the relationship between ROP and VGEF has been investigated; however, the relationship between ROP and lactate that plays important role in VGEF regulation, hasn't been investigated. In our study, it was

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aimed to investigate relationship of ROP development and prognosis with serum lactate levels.

MATERIAL AND METHODS

This retrospective, cross-sectional study was conducted in the ophthalmology department of a tertiary hospital. The study was approved Ethics Committee of Keçiören Training and Research Hospital (approval#2102-KAK-15-1849; 27.02.2019). The study was conducted in accordance to tenets of Helsinki Declaration. The study was conducted with premature infants who treated at neonatal unit and fulfilled inclusion criteria between January, 2012 and May, 2018.

The infants with gestational age >32weeks; those with birth weight >1500 g; infants with metabolic disorder that may affect serum lactate level; those with congenital heart disease, chromosome anomaly, mitochondrial disease, liver disease; those with history of cardiac arrest, trauma or sepsis; and infants with ocular disorder other than ROP or media opacities that hamper visualization of posterior segment were excluded. The patients included were assigned into two groups: ROP group including patients with retinopathy of prematurity and control group including patients without retinopathy of prematurity. In both groups, oxygen saturation target was set as 90-95%.

All infants included were examined by a single clinician (E.U.K). After mydriasis achieved by 0.5% tropicamide and 2.5% phenylephrine drops, all patients were assessed for ROP with 360° indentation. Based on clinical presentation, the patients were followed without treatment or treated with either laser photocoagulation or intravitreal anti-VGEF injection. The follow-up was completed after achieving retinal vascularization. Serum lactate level was measured using ABL90 Flex analyzer (Radiometer Medical ApS, Brønshøj, Denmark). The assay reliability for ABL90 Flex analyzer was proven in many clinic trials and software calibration and quality control were performed in automated manner before use.[12,13] As number of lactate samples were not equal for patients included, stratified randomization was employed to prevent bias and lactate measurements on day 1 after birth and those measured by 3-days interval over first month after birth were included.

Data were analyzed using SPPS version 22.0 (SPSS, IBM Corp, Armonk, NY, USA). Normal distribution of data was assessed using Shapiro Wilks W test. Data are expressed as mean and standard deviation. Statistical difference was assessed using Independent sample t test. Sensitivity and specificity were assessed using Receiver Operating Characteristics (ROC) analysis). A p value<0.05 was considered as statistically significant.

FINDINGS

Overall, 106 patients were included into study. Table 1 presents demographic data of patients. During follow-up, 35 patients without ROP development (19 boys and 16 girls) were assigned into control group while 71 patients developed retinopathy of prematurity (37 boys and 34 girls) were assigned into ROP group. Mean gestational age was 28.7±3.2 weeks (min-max: 24-32 weeks) in the control group and 27.8±1.8 weeks (min-max: 22-31 weeks) in the ROP group. Mean birth weight was 1262.3±323.9 g in the control group and 1150±251.7 g in the ROP group. No significant difference was observed in mean gestational age and birth weight between groups (p=0.061 and p<0.078, respectively). No significant difference was observed in gender distribution between groups (p=0.833).

Table 1 presents mean serum lactate levels. Mean serum lactate level measured within first day after birth was 36.6±22.3 mg/dL in the ROP group and 24.9±12.8 mg/dL in the control group. Mean serum lactate level measured within first month after birth was 26.6±7.9 mg/dL in the ROP group and 18.1±6.5 mg/dL in the control group. Mean serum lactate levels measured within first day and first month after birth were significantly higher in ROP group (p<0.001 and p<0.001, respectively. A weak, negative correlation was observed between birth weight and mean serum lactate level (r=-0.222; p=0.024) while no significant correlation was detected between gestational age and mean serum lactate level (r=-0.184, p=0.059). No correlation was detected between mean serum lactate levels measured within first day and month and ROP stage or plus disease development (p>0.05). In ROC analysis, it

Table 1. *Demographic data and comparison of mean serum lactate levels.*

	PR group	Control group	p value
Female/Male (n)	19/16	37/34	0.833
Gestational age (wk)	27.8 ± 1.8	28.7 ± 3.2	0.061
Birth weight (gram)	1150.4 ± 251.7	1262.3 ± 323.9	0.078
Mean Serum Lactate Level (mg/dl)			
Day 1	36.6 ± 22.3	24.9 ± 12.8	<0.001
Month 1	26.6 ± 7.9	18.1 ± 6.5	<0.001

was found that mean serum lactate level within first month ≥21.2 mg/dL predicted ROP development by sensitivity of 76% and specificity of 74% (AUC= 0.837; p<0.001).

DISCUSSION

There are many risk factor leading PR development. The major risk factors are low birth weight and gestational age.[14] In addition, delayed-onset symptom, frequent blood transfusion and total number of days on oxygen supplementation have been reported as independent risk factors.[14] These factors are also associated with high mortality and morbidity in premature newborns.[15-17] It was shown that high mortality and morbidity rate are associated with elevated serum lactate levels in premature newborns.[15, 18] Given the metabolic activity of lactate, serum lactate can be used to predict ROP. This hypothesis is supported by the study of Tuten et al. who reported that serum lactate level> 4 mmol/L (36 mg/dL) on hour 1 after birth is associated with ROP development.[15] However, the relationship between serum lactate level and development and clinical course of ROP hasn't been fully understood.

In our study, serum lactate level was found to be higher in patients developing ROP when compared to those without ROP. Elevated lactate level may have induced ROP development by enhancing activity of pro-angiogenic factors.[10] In angiogenesis, there are also mediators such as HIF-1 and lactate formed as a result of hypoxia and regulates VGF release seen as primary mediator and is a target in the treatment of retinal proliferative disorders HIF-1 is a transcription factor that controls response to hypoxia.[9] In case o hypoxia, HIF-1 increases lactate level by enhancing expression of several enzyme as well as lactate dehydrogenase enzyme involved in anaerobic glycolysis pathway.[9, 19] Thus, increased lactate levels indicate hypoxia at systemic or tissue level. In addition to being energy source and transport molecule, lactate also acts as signal molecule.[20, 21] Madaan A. demonstrated that lactate increases release of pro-angiogenic mediators and induces retinal angiogenesis by direct stimulation of Muller cells via GPRS81 receptor.[22]

After birth, hyperoxia is followed by hypoxia at level of retinal issue due to suppression of vascular development.[1, 3] Systemic hypoxia may increase hypoxia at retinal level.[23] It was reported that systemic intermittent hypoxia is common within first week after premature birth, which is associated with ROP.[23] In our study, it was found that mean serum lactate level within first month ≥21.2 mg/dL predicted ROP development by sensitivity of 76% and specificity of 74% Similarly, Tuten et al. mean serum lactate level>4 mmol/L had sensitivity of 71.4% and specificity of 66.7% for prediction of ROP development.[15]

The major limitation of our study is shorter half-life of serum lactate (30-60 min). Measurements may not accurately reflect long-term course of serum lactate level and can lead bias during data collection. This makes it difficult to draw definitive conclusions about effect of serum lactate level on ROP development. Another limitation is that serum lactate level can be affected by patient-related and many other factors. Although patients with systemic factors that may have influence on serum lactate levels were excluded, there are other factors such as sample transport duration or temperature that may affect lactate levels. Due to retrospective nature of our study, it is impossible to identify and standardize factors unrelated to patient. Again, it is impossible to exclude all factors influencing on serum lactate levels in a study conducted with premature patients and sample size is inadequate to perform statistical analysis in order to assess effects of such factors. When assessing serum lactate level and ROP, patient-related factors as well as factors unrelated to patient that may affect serum lactate levels should be taken into consideration.

CONCLUSION

In our study, it was shown that serum lactate level was higher in patients developing ROP when compared to those without ROP. Based on our results, serum lactate level can be used as a predictor for ROP development. There is a need for further prospective studies with larger sample size in which serum lactate measurement will performed more frequently. .

Acknowledgments

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