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Original Article

Alkaline phosphatase levels of preterm infants under 30 weeks of gestational age and its role in the diagnosis of osteopenia of prematurity

Gulsum Kadioglu Simsek, Mehmet Buyuktiryaki, Hayriye Gozde Kanmaz Kutman, Fuat Emre Canpolat

University of Medical Sciences, Zekai Tahir Burak Health Practice and Research Center, Department of Neonatology, Ankara, Turkey

Abstract

Aim: Alkaline phosphatase is perhaps the most important biochemical marker used in the diagnosis and follow-up of metabolic bone disease or osteopenia of prematurity (OP). The aim of this study was to investigate the percentiles of alkaline phosphatase (ALP) levels in premature infants compared to gestational age and to determine cut-off values for the diagnosis of osteopenia.

Material Methods: All ALP results sent to our biochemistry laboratory between 2013-2018 were evaluated retrospectively. Of the total 2476 results, 1830 (74%) were found to belong to a separate infant born before 30 weeks of gestation. The results and demographic data of the patients whose clinical information could be reached were statistically analyzed.

Results: The mean birth weight of the infants included in the study was 995 g±254 (450-1500 g) and the mean gestational week was calculated as 27±1.7 (24-29,6 weeks). The average alkaline phosphatase level was 510±225 U/L [median: 458 IU/L (159-1554)]. In serum ALP levels; 160.8 IU/L value 5. Percentile, 203 IU/L 10. percentile, 290 U/L 25. percentile 421 IU/L 50. percentile, 583 U/L 75. Percentile, 819 U/L formed 90th percentile and 969 U/L formed 95th percentile. Separate percentiles were also calculated for each gestational week interval.

Conclusion: Although the infants included in the study were hospitalized premature infants, this is the reference range study with the largest number of patients in our country. Although the data is retrospective, these percentiles may be helpful in the evaluation and the diagnosis of osteopenia in premature infants.

Keywords: Preterm infant; alkaline phosphatase; osteopenia; phosphorus.

INTRODUCTION

Very low birth weight (VLBW) infants are at an increased risk of developing osteopenia of prematurity (OP) or named metabolic bone disease (1,2). The incidence of ostepenia in very low birth weight (VLBW, birthweight under 1500 g) was estimated at 20-30% in last decade (3). The fetus absorbs calcium (Ca) and phosphorus (P) mainly during the third trimester of pregnancy; therefore, preterm infants lose the opportunity to store such minerals (4,5). The incidence of OP has been increased correspondingly with an increase in the survival rate of very preterm infants (6-8). However, there is a lack of consensus on the definition, screening, therefore diagnosis and treatment of OP (6,10). The definition of OP varies, as patients can present with osteopenia, osteoporosis, rickets, and more dramatic as fractures (8,11). Osteopenia of prematuriy reveals, prolonged respiratory support, delayed discharge from hospital, spontaneous fractures and related morbidities. High levels of alkaline phosphatase (ALP) and low levels of P have been commonly used as serum biochemical markers for the screening of OP (6,8,12,13). There is limited data especially in VLBW infants for percentiles of ALP according to gestational age and cut off values for OP.

The aim of this study was to evaluate the mean, median and percentiles of ALP and P, the standard biochemical markers for OP screening in VLBW infants under 30 weeks of gestational age.

MATERIAL and METHODS

During the study period, biochemical laboratory results

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Corresponding Author: Gulsum Kadioglu Simsek, University of Medical Sciences NICU, Zekai Tahir Burak Health Practice and Research Center, Department of Neonatology, Ankara, Turkey **E-mail:** glsmkadioglu@gmail.com

extracted from database belonging to all neonates. Clinical records and hospital files revised for additional clinical information. Two thousand one hundred seventy-two infants were born during 6 years period under 30 gestational week. We reached 1830 of these 2172 infants detailed medical histories. Our department is a neonatal intensive care unit (NICU) with 130 beds, 100 of these are level III neonatal intensive care unit, over 17000 live births occur anually in our perinatal center which is an education and research hospital. We collect blood for Ca, P, ALP at the end of the first month for every infant under 1500 gr of birthweight. We immediately start parenteral nutrition and mother's milk as soon as possible. After reaching full enteral feeding we add human milk fortification to breastmilk (14,15). We start vitamin D after postnatal 10th day as 800 Units to all preterm infants. We analyze routinely biochemical parameters such as blood glucose, Ca, P, according to infants' clinical condition. Serum biochemistry, Ca, P, and ALP levels and blood gases were detected with a Siemens Advia 2400 automatic analyzer (Tarrytown, New York, USA).

Osteopenia of prematurity diagnosis made by clinical and biochemical findings, such as drammatic spontaneous fractures, typical bone appearance on X-ray, high levels of ALP, low levels of serum P.

There are some known risk factors for OP. The main risk factors are low gestational week and birthweight. Postnatal steroids used for bronchopulmonary dysplasia in which infant has still oxygen dependency beyond 4th weeks of life (16) and is a strong risk factor for OP. Prolonged parenteral nutrition means the delay of infants reaching full enteral feeding and it usually means more than two weeks is also another risk factor. Caffeine is another risk factor for OP (17). Additional risk factors for OP in different papers include, sedation use, prolonged intubation (intubation for more than two weeks) and/or ventilator dependency (assisted ventilation for more than two weeks), diuretics, renal and liver function impairment checked for evaluation.

Early deaths, major congenital anomalies, skeletal dysplasias, infants experienced gastrointestinal surgery and need prolonged parenteral nutrition, other bone and metabolic diseases were all excluded from analysis.

We used SPSS for Windows version 21 for data interpretation. For comparing infants with and without osteopenia through P an ALP student t test was used. We used descriptive analysis and ROC curve estimation for additional analyses. We compared ALP levels between gestational ages by One way Anova. Multinominal logistic regression analysis used for evaluating risk factors.

RESULTS

The mean birth weight of these 1830 infants included in the study was 995 g±254 (450-1500 g) and the mean gestational week was calculated as 27±1.7 (24-29.6 weeks). The average alkaline phosphatase level was 510±225 U / L [median: 458 U / L (159-1554)] in all study population. In serum ALP levels; 160.8 U / L value was 5. percentile, 203 U / L was 10. percentile, 290 U / L was 25. percentile 421 U / L was 50. percentile, 583 U / L as 75. Percentile, 819 U / L formed 90th percentile and 969 U / L formed 95th percentile. According to our results highest levels of ALP sensitivity for OP was 800 IU/L (approximately 90 percentile) which has 79% sensitivity, the lowest level for P was 2.85 mg/dl with 81% sensitivity. One hundred and twenty eight infant diagnosed as OP according to biochemical and clinical findings. Infants with OP had, lower gestational age 27.6±1.5 vs 28 ±1.3 weeks (p=0.048), lower birthweight 908 ±173 g vs 1088±219 g (p=0.001) and lower Ca, 8.9±0.7 vs 9.4 ±0.5 mg/dl (p=0.001), lower P , 3.3±0.8 vs 5.3±0.7 mg/dl (p=0.001) and finally higher ALP levels, 84±280 IU/L vs 484±198 IU/L (p=0.001).

Our results for each gestational age was also evaluated and compared which had statistical difference (With all participants with One way Anova, p=0.022, Table 1). ALP levels and serum P levels have high area under the curve measurements for developing OP, as shown in Figure 1 and Table 2. We all analysed risk factors such as caffeine usage, respiratory support, feeding intolerance etc for developing OP, but the only independent risk factor for OP was gestational age as a covariate, being under 28 weeks has an OR:2.28 (1.5-7.65 95% CI, p=0.005).

Table 1. Percentiles of serum alkaline phosphatase levels according to gestational week

		10 p	50 p	90 p
24 week	N=142	390	501	900
25 week	N=171	381	499	921
26 week	N=298	312	487	856
27 week	N=381	298	483	812
28 week	N=403	273	452	799
29 week	N=435	277	425	779

Table 2. Area Under the Curve results of P and ALP for osteopenia of prematurity

Test Result Variable(s)	Area	Std. Error[a]	Asymptotic Sig.[b]	Asymptotic 95% Confidence Interval	
				Lower Bound	Upper Bound
P	.045	.026	.000	.000	.096
ALP	.861	.026	.000	.810	.913

The test result variable(s): P, serum phosphate; ALP, alkaline phophatase has at least one tie between the positive actual state group and the negative actual state group.
[a] Under the nonparametric assumption
[b] Null hypothesis: true area = 0.5

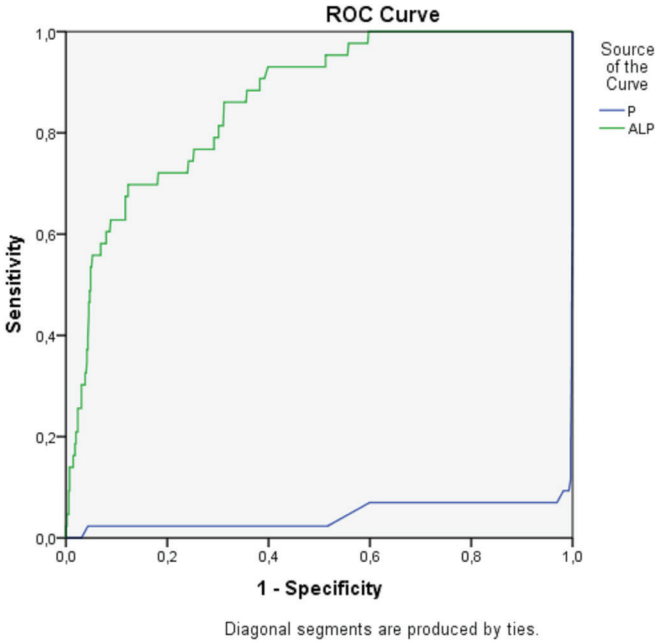

Figure 1. Receiver Operating Characteristic (ROC) curve for alkaline phophatase (ALP) and serum phosphate (P)

DISCUSSION

This study's results respresents the first percentile values of serum alkaline phospahatase and serum phosphate levels in a large retrospective cohort of preterm infants under 30 weeks of gestational age in our Country. All infants included in this study are healthy preterm newborns graduated from NICU. Medical caregivers for preterm infants in NICU should use precentiles of biochemical and other clinical parameters especially derived from their own regional study results so that our data will help for this aim.

Diagnosis of OP is sometimes difficult because of lacking radiologic tools such as dual energy X-ray absorptiometry (DEXA) and/or speed of sound (SOS) machines. Therefore biochemical and clinical findings are always useful even in low resource settings.

Elevated ALP levels are mainly related with OP but there are some other clinical conditions. Growth is another reason for ALP elevation, other bone disease such as rickets is another etiology, ALP derived from other tissues like leukocytes is also another reason.

Because preterm infants are at risk for rickets and OP, ongoing assessment in all very preterm infants should be provided throughout the birth hospitalization to detect any evidence of bone disease (18). We recommend screening with ALP, P and Ca after three weeks of life, usually we do this at the end of the first month postnatally. This typically involves routine laboratory monitoring of serum P and ALP. Because abnormal values are uncommon in the first four weeks of life in VLBW infants, initial testing is started at four weeks after birth with subsequent biweekly testing. Infants with additional risk factors for rickets, such as prolonged parenteral nutrition or inadequate enteral intake of Ca and P, are tested weekly.

We compared some variables such as BPD, steroid use, other morbidities but we could not find any difference according to ALP results. Except gestational age being under 28 week, we could not find any risk factor related to high ALP and OP.

In general, ALP values will peak at 600 to 800 international U/L and then decrease in healthy preterm infants without bone disease. Once stable values are demonstrated on full enteral feeds, (eg, once the serum ALP has peaked and is declining to less than about 500 international U/L), monitoring can be discontinued. However, ALP values greater than 800 international U/L are suggestive, but not proof, of OP or any other bone disease (19). In these patients, we obtain radiographs of the chest-wrist and/or knees to confirm the diagnosis of OP.

There are some limitations of these study. First, we do not have DEXA or speed of sound results of infants which are important tolls for the diagnosis of OP. Although these methods are accepted tools for OP daignosis are not widely used and not available in low resource settings. Another limitation of this study is being retrospective nature. Therefore we could not assess any effect of some factors such as caffeine because all infants received caffeine as soon as after birth in this study population. Additionally we do not have serial measurements of ALP and other electrolytes, we do not know the course of these parameters and detailed treatment strategies for OP, because first measurements are important for secreening and treatment and follow up is out of purpose of this study. Intercalarily we could not have serial measurements of ALP after one month as a result of restrospective nature of this data. All this maesurements are from healthy preterms, there should be further studies to show both healthy and unhealthy infants.

CONCLUSION

Early nutrition, fortification of human milk, avoiding mechanical ventilation, avoiding sedation and vitamin supplemantation are all important factors for developing OP. According to our results, every preterm infant under 1500 gram and/or 30 weeks of gestational age should be screened for OP by using ALP, P and Ca at the end of the first month or after postnatal three weeks of age. Infants with low levels of P and higher levels of ALP should be checked for osteopenia and spontaneous fractures. Biochemical results differ from one laboratory to another, results of this study should evaluated according to this variety.

Competing interests: The authors declare that they have no competing interest.

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Gulsum Kadioglu Simsek ORCID: 0000-0003-4831-8950
Mehmet Buyuktiryaki ORCID: 0000-0001-8937-4671
Hayriye Gozde Kanmaz Kutman ORCID: 0000-0002-3177-9411
Fuat Emre Canpolat ORCID: 0000-0001-9307-3003

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