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Original Article

Risk factors and clinical features of osteopenia of prematurity: Single-center experience

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ABSTRACT

Objective: Osteopenia of prematurity is an important cause of morbidity in preterm newborns. The aim of this study is to evaluate the clinical and laboratory findings and risk factors of osteopenia of prematurity in the newborns followed up in our unit.

Method: This study was a retrospective, cross-sectional study. Newborns with a gestational age of ≤ 32 weeks, a birth weight of ≤ 1500g were included in the study.

Results: The study included a total of 50 newborns. In patients with osteopenia of prematurity, invasive/noninvasive respiratory support, and duration of total parenteral nutrition (TPN) were longer, the incidence of necrotizing enterocolitis, red blood cell (RBC) transfusion rates, use of diuretics and proton pump inhibitors (PPI) were higher ($p < 0.05$). Multiple regression analysis showed that prolonged duration of TPN was the most important risk factor for osteopenia of prematurity (OR: 1.484(1.009-2.182); p: 0.045).

Conclusion: This study shows that osteopenia of prematurity remains to be an important health problem in premature newborns. Patients with prolonged TPN infusions are at risk of developing osteopenia of prematurity. Adjustment of mineral supplements in parenteral nutrition according to calcium and phosphorus levels should be started early in life, and enteral nutrition should be encouraged by reducing the duration of TPN use. Further studies are needed to increase our awareness of osteopenia of prematurity and to clarify the relationship between PPI use and RBC transfusion and osteopenia of prematurity.

Keywords: Prematurity, osteopenia of prematurity, risk factor, proton pump inhibitor, red blood cell transfusion

INTRODUCTION

Osteopenia of prematurity, also known as a metabolic bone disease of the newborn, is defined as postnatal bone mineralization lower than intrauterine bone mineral density at the same gestational age.[1,2] Many hormonal, environmental, and genetic factors have been reported to affect bone mineralization in the fetal and postnatal periods.[3] Its clinical symptoms appear 6-16 weeks after birth, and if not diagnosed in time, various short and long-term problems may occur.[2] Osteopenia of prematurity has been reported to cause bone fractures, poor respiratory outcomes, insufficient weight gain, impaired growth, and predisposition to osteoporosis in adulthood.[4-9] The diagnosis is made by measuring biochemical markers such as serum calcium, phosphorus, alkaline phosphatase, parathormone, and vitamin D and/or detecting the presence of osteopenia or fracture radiologically.[1,2] However, none of them have diagnostic value on their own.[1]

The incidence of osteopenia of prematurity is not well known due to differences in terminology and diagnostic criteria.[3] It is estimated that the incidence may have increased as the survival

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rates of premature newborns have increased as a result of the developments in neonatology in recent years.[2] There are very limited data on osteopenia of prematurity in Turkey.[10-14] There may be differences in neonatal intensive care practices between countries due to demographic structure and economic reasons. There is a need for new studies in countries such as Turkey, which have a dispersed demographic structure and health care services. This study aimed to examine the clinical and laboratory findings of osteopenia of prematurity and the affecting risk factors in the premature newborns followed up in our unit.

MATERIAL AND METHODS

The study design was a retrospective, cross-sectional design. Cases with a gestational age of ≤32 weeks and a birth weight of ≤ 1500g, followed in our neonatal intensive care unit between January 1, 2020 and May 1, 2022 were included in this study. Premature newborns with congenital malformation, genetic disease, other metabolic bone diseases (such as osteogenesis imperfecta), and missing data were excluded from the study.

The demographic data (gestational age, birth weight, gender, mode of delivery), perinatal characteristics (preeclampsia, diabetes mellitus, premature rupture of membranes, small for gestational age (SGA)), clinical outcomes (necrotizing enterocolitis (NEC), patent ductus arteriosus (PDA), bronchopulmonary dysplasia (BPD), cholestasis, hypothyroidism, duration of mechanical ventilation, duration of total oxygen requirement, red blood cell (RBC) transfusions, hospital stay), history of medication use affecting calcium metabolism (postnatal steroid, diuretic (>2 weeks), caffeine, proton pump inhibitor (PPI) use), nutritional management (duration of parenteral nutrition, the first day of enteral nutrition, use of fortifying supplements, vitamin supplementation), physical examination findings (craniotabes, enlargement of cranial sutures, fractures, etc.), laboratory analyses (serum calcium, phosphorus, alkaline phosphatase, 25-hydroxyvitamin D, parathormone, and urinary phosphorus, creatine levels in the urine taken on the postnatal 28th day of the cases) were retrospectively investigated. Renal tubular phosphorus reabsorption (TPR) was calculated (TRP: 1- [(urine phosphorus/plasma phosphorus) x (plasma creatine/urine creatine)]x100 formula was used). On the postnatal 28th day, cases with serum alkaline phosphatase of ≥500IU/L and/or phosphorus of <5.5mg/dl and TRP of >95% were diagnosed with osteopenia of prematurity.[11] The cases were divided into two groups: those with and without osteopenia of prematurity, and their data were compared.

Bronchopulmonary dysplasia (BPD) was defined as an oxygen requirement >21% for at least 28 days.[15] Cholestasis was defined as a conjugated bilirubin value of >2.0mg/dl, or a conjugated bilirubin fraction of >20% of the total. The diagnosis of NEC was made based on clinical and radiological findings. Findings such as feeding intolerance, abdominal distention, gastric residue, bile vomit, and bloody stool were considered to be associated with NEC.[16] The study was approved by the local ethics committee (No:2022/39).

Statistical Analysis

Statistical analyzes were performed using IBM SPSS (Statistical Package for Social Sciences) statistical software, version 24 (IBM Corp, Armonk, NY, USA). Categorical data were presented with n and %, and numerical data with mean ± standard deviation if normally distributed, and median (IQR) if non-normally distributed. Descriptive statistics (kurtosis and skewness), visual methods (histogram), and analytical tests (Shapiro-Wilk's test) were used to determine the normal distribution of numerical variables. In the comparison of the two groups, the student's t-test was used if the data were normally distributed, and the Mann-Whitney U test was used if the data were non-normally distributed. Chi-square tests were used for the comparison of categorical data (Fisher's exact test was used when chi-square test assumptions did not hold due to low expected cell counts). Possible factors determined by univariate analysis were analyzed by logistic regression analysis to determine independent predictors. Odds ratios (OR) (95% CI) were used in the logistic regression analysis. A p-value <0.05 was considered statistically significant.

Our unit's parenteral and enteral nutrition policy:

In our unit, total parenteral nutrition (TPN) support is administered to all premature and very low birth weight newborns on the first day of life [Aminoasid (2g/kg; Primen-%10; Baxter, S.A. Belgium), lipid solution (2g/kg; ClinOleic-%20; Baxter, S.A. Belgium), and glucose]. Amino acid/lipid doses are gradually increased to 3g/kg on the third day. Phosphate supplementation was given if serum phosphate levels were persistently lower than 4 mg/dl. Elemental phosphorus was started at 20mg/kg per day and increased to a maximum of 40mg/kg/per day. If serum calcium levels were <8mg/dl, elemental calcium was started at 20mg/kg per day and increased to a maximum of 80mg/kg per day. Enteral nutrition is usually initiated with breast milk within the first two days of life, and the premature formula is added when breast milk is insufficient. If the baby tolerates, the amount of enteral feeding is increased by 20-30 ml/kg/day, and the amount of TPN is decreased proportionally. TPN support continues until 75% of the total volume is met by enteral nutrition. When the amount of enteral feeding is more than 100ml/kg/day, 1.1g of

Eoprotein (Aptamil Milupa breast milk fortifier) is added to every 30 ml of breast milk. When the baby is on full enteral nutrition, vitamin D (800 Units/day) support is administered.

RESULTS

The study population consisted of 50 premature newborns (25 male, 25 female) with a mean gestational age of 29.3±2.2 weeks and a mean birth weight of 1198.7±266.3 g. There were 26 cases in the group with osteopenia of prematurity (Group I) and 24 cases in the group without osteopenia (Group II). Group 1 had a lower birth weight and more male gender than group 2 (1101 vs 1304, p: 0.004; 58% vs 42%, p: 0.258, respectively). Osteopenia of prematurity was detected in 9 (69.2%) of 13 newborns with a birth weight of ≤1000 g and in 17 (45.9%) of 37 newborns with a birth weight of 1000-1500 g. Maternal and neonatal demographic characteristics of the groups are shown in Table 1. The most common clinical findings in Group I cases were related to the respiratory and gastrointestinal systems. In Group I cases, invasive/noninvasive ventilation times were longer, enteral feeding initiation times were later, transition to full enteral feeding took longer and NEC incidence was higher ($p<0.05$, Table 1). No fractures or rickets were found in any of the cases. RBC transfusion rates, use of diuretics, and PPI were found to be higher in Group I cases compared to Group II ($p<0.05$, Table 1). The cases in Group I had lower serum phosphorus and vitamin D levels, and higher serum alkaline phosphatase and parathormone levels and TPR levels (Table 2). Multiple regression analysis showed that prolonged duration of TPN is the most important risk factor for osteopenia of prematurity (OR: 1.484(1.009-2.182); p: 0.045) (Table 3).

DISCUSSION

Osteopenia of prematurity is a major cause of morbidity in premature and very low birth weight newborns.[11] Determination of risk factors for osteopenia of prematurity is vital for early detection and prevention of the disease.[11] The diagnosis is made in the presence of hypophosphatemia, high alkaline phosphatase, secondary hyperparathyroidism, and high TRP (>95%).[11,17] Our results are consistent with the findings in other studies. However, there is no consensus on the cut-off values yet. Therefore, the true incidence of the disease remains unclear.[3,17] The frequency of osteopenia of prematurity has been reported to increase inversely with gestational age and birth weight and is directly proportional to postpartum diseases.[1,17] It was reported that 55% of extremely low birth weight (≤1000g) and 23% of very low birth weight newborns (1000-1500g) have osteopenia of prematurity.[2,18] In our study, osteopenia of prematurity was detected in 9 (69.2%) of 13 newborns with a birth weight of ≤1000 g and in 17 (45.9%) of 37 newborns with a birth weight of 1000-1500 g. Our rates were high compared to the literature. This may be due to the different diagnostic criteria and sample sizes used to define osteopenia of prematurity in each of the studies.

In the present study, newborns with osteopenia of prematurity had lower vitamin D levels, and the time to start vitamin D supplementation was delayed. The low levels of vitamin D in newborns with osteopenia of prematurity in our study were associated with the frequent occurrence of feeding intolerance in these cases. Vitamin D deficiency may lead to osteopenia in newborns. If newborns do not receive or make enough vitamin D, calcium and phosphorous will not be properly absorbed.[19] Our results were consistent with those of Cho et al.[20] The study of Angelika et al.[9] reported that early vitamin D supplementation increased vitamin D levels and improved bone mineralization in premature newborns. Chan et al.[6] also indicated that starting vitamin D supplementation after 14 days is an independent risk factor for osteopenia of prematurity. In our study, vitamin D supplementation was initiated after the 14th day in most cases with osteopenia of prematurity. The result of our study is significant to emphasize the importance of providing vitamin D support to premature newborns in the early period in order to prevent osteopenia of prematurity.

In the study of Chan et al.[6], gestational age below 30 weeks and use of TPN for more than 28 days were reported as the main risk factors for osteopenia of prematurity. Mutlu et al.[11] also revealed the use of anticonvulsant drugs as the most critical risk factor. The significant effect of birth weight on osteopenia of prematurity demonstrates the importance of prenatal mineralization on bone mineral density.[3] Since mineral deposition in fetal bone occurs mainly in the third trimester of pregnancy, premature newborns are born with insufficient bone mineralization. Furthermore, low birth weight may be due to a condition associated with placental insufficiency.[3] Placental insufficiency may develop due to conditions associated with chronic placental damage, such as preeclampsia.[3] Any condition that impairs placental function and thus nutritional transfer may lead to an increased risk of osteopenia of prematurity. Angelika et al.[9] also reported that they detected a relationship between premature rupture of membranes and osteopenia of prematurity. However, our study did not find a difference in the frequency of preeclampsia, premature rupture of membranes, or SGA between the groups.

Drugs such as methylxanthines, diuretics, and steroids used in the treatment of neonatal diseases have been demonstrated to increase the risk of osteopenia of prematurity.[17,21,22] Hypercalciuric drugs such as furosemide and methylxanthines have been shown to decrease bone formation by increasing

Table 1. Demographic characteristics of cases and risk factors for osteopenia of prematurity			
Variables	**Group I (n:26)**	**Group II (n: 24)**	**p**
Gestational age (week)	30.0±2.2	28.6±1.9	0.084**
≤28 week, n (%) 29-33week, n (%)	10(38.5) 16(61.5)	5(20.8) 19(79.2)	0.174*
Birthweight(g)	1101±248	1304±248	**0.004¶**
Type of delivery NVD/C/S, n (%)	2/24(7.7/92.3)	4/20(16.7/83.3)	0.409*
Gender female/male, n (%)	11/15(42.3/57.7)	14/10(58.3/41.7)	0.258*
SGA, n (%)	8(30.8)	2(8.3)	0.077*
Gravidity	2	3	0.712**
Preeclampsia/eclampsia n (%)	4(15.4)	4(16.7)	1.000*
Diabetes Mellitus, n (%)	-	2(8.3)	
Premature rupture of membranes, n (%)	5(19.2)	4(16.7)	1.000*
IMV days	3	1	**0.007****
Non-IMV days	6	2	**<0.001****
Duration of total oxygen requirement, days	8.5	3	**0.001****
BPD, n (%)	6(23.1)	1(4.2)	0.100*
Steroid use, n (%)	6(23.1)	1(4.2)	0.100*
Diuretic use, n (%)	10(38.5)	2(8.3)	**0.013***
PPI use, n (%)	12(46.2)	3(12.5)	**0.009***
Caffeine use, n (%)	23(88.5)	17(70.8)	0.164*
Eoprotein use, n (%)	16(61.5)	19(79.2)	0.174*
NEC, n (%)	12(46.2)	1(4.2)	**0.001***
Anticonvulsive drug use, n (%)	1(3.8)	1(4.2)	1.000*
Hypothyroidism, n (%)	3(11.5)	4(16.7)	0.697*
Cholestasis, n (%)	5(19.2)	1(4.2)	0.192*
PDA, n (%)	5(19.2)	1(4.2)	0.192*
Red blood cell transfusions, n (%)	10(38.5)	3(12.5)	**0.037***
First enteral feeding time (days)	4	3	**0.013****
Full enteral feeding time (days)	36	12.5	**<0.001****
TPN days	25	8	**<0.001****
Weight on the 30th days, g	1222.5	1900	**<0.001****
Vitamin D supplementation, days	30	12.5	**<0.001****
<14 days of age, n (%)	3(11.5)	13(54.2)	
≥14 days of age, n (%)	23(88.5)	11(45.8)	
Hospitalization time, days	66	34	**<0.001****

Abbreviations: SGA, small for gestational age; IMV, invasive mechanical ventilation; BPD, bronchopulmonary dysplasia; PPI, Proton pump inhibitor; NEC, necrotizing enterocolitis; PDA, patent ductus arteriosus; TPN, total parenteral nutrition. Categorical data were presentedwith n and %, and numerical data with mean ± standard deviation if normally distributed, and median (IQR) if non-normally distributed. In the comparison of 2 groups; Chi-square test*, Mann-Whitney U** test and Student's t-test¶ were used.

Table 2. Laboratory characteristics of osteopenia of prematurity

	Group I (n:26)	Group II (n: 24)	P
Serum calcium (mg/dl)	9.5±0.8	9.8±0.6	0.248*
Serum phosphate (mg/dl)	4.9	6.4	**<0.001****
Alkaline phosphatase (U/L)	569.9±204.6	343.4±60.1	**<0.001***
Parathyroid hormone (pg/mL)	85.6±51.9	82.2±63.2	0.845*
Vitamin D (ng/ml)	12.7	19.2	**0.017****
TRP (%)	96	92	**<0.001****

Abbreviations: TRP: Tubuler reabsorption of phosphate.
Numerical data were presented as mean ± standard deviation if normally distributed and median (IQR) if not normally distributed. In the comparison of 2 groups; Student's t-test* ve Mann-Whitney U test** were used.

Table 3. Risk factors of osteopenia of prematurity (multivariate analysis)

Variables	B	Wald	p	OR	%95 CI	
NEC	3.428	4.025	0.285	30.811	0.057	16574.852
PPI use	3.915	2.880	0.090	50.164	0.545	4614.347
Diuretic use	0.665	0.050	0.822	1.945	0.006	649.474
TPN days	0.395	4.025	**0.045**	1.484	1.009	2.182
Vitamin D supplementation at <14 days of age	0.517	0.138	0.710	1.677	0.110	25.523

Abbreviations: NEC, Necrotizing enterocolitis; PPI, Proton pump inhibitor, TPN, total parenteral nutrition; OR, odds ratio.
Hosmer – Lemeshow test: 0.933, **Nagelkerke R^2:** 0.718, **Cox – Snell R^2:** 0.539, **Omnibus test:** 0.001.

calcium loss, and steroids by inhibiting osteoblast growth and increasing osteoclast differentiation.[11,17] While Mutlu et al.[11] reported that caffeine and steroid use were risk factors for osteopenia of prematurity, they found no difference between the groups with regard to diuretic use. Chan et al.[6] stated that the use of aminophylline and diuretics increased the risk, but they did not find a difference with the control group in terms of steroid use. Avila-Alvarez et al.[3] also revealed that postnatal steroid use did not increase the risk of osteopenia of prematurity. Our study found that the use of diuretics was high in newborns with osteopenia of prematurity. However, we did not detect any difference between the groups with regard to caffeine and steroid use. Besides, our study did not determine a relationship between osteopenia of prematurity and BPD. However, although it was not statistically significant, we detected a higher incidence of BPD in babies with osteopenia of prematurity. Respiratory outcomes were also worse in the group with osteopenia of prematurity.

Factors such as the delay in establishing fully enteral feeding, prolonged parenteral nutrition, and the presence of NEC have been reported as risk factors in the development of osteopenia of prematurity.[17,21-23] Similarly, in our study, NEC was higher in the group with osteopenia of prematurity and the duration of TPN was longer in these cases. The present study found that prolonged TPN use was a risk factor for osteopenia of prematurity. Because the greatest need for mineral accumulation occurs during the developmental stage, calcium and phosphorus depositions in preterm neonates during the early postnatal period cannot meet the requirements of the intrauterine bone growth rate. Furthermore, the majority of premature newborns require prolonged TPN infusion due to difficulties with enteral feeding. TPN is a non-physiological route of nutrient delivery that bypasses the gastrointestinal tract and portal system. The effects of administering nutrients directly into the continuous venous blood are not fully known. Multiple factors may contribute to the development of bone disease associated with TPN. Inadequate mineral formulations, poor solubility of minerals, restricted intravenous fluid volume due to pre-existing diseases, and aluminum contamination of parenteral nutrition, frequently prevent sufficient mineral supply from TPN solutions. This seriously affects the bone health of newborns in both the short and long terms.[6,9,24,25]

Red blood cell transfusions are a crucial supportive treatment, especially in treating premature newborns. In our study, the rate of administration of RBC transfusions was higher in cases with osteopenia of prematurity. Avila-Alvarez et al.[3] also reported a

similar relationship between the development of osteopenia of prematurity and RBC transfusion. Iron overload resulting from multiple RBC transfusions in children and adults with thalassemia has been indicated to be one of the factors affecting the pathogenesis of osteoporosis.[26] Iron deposition in the bone can impair osteoid maturation and inhibit local mineralization, resulting in focal osteomalacia.[26] Premature newborns may also be exposed to iron overload caused by the destruction of transfused erythrocytes when they receive multiple RBC transfusions.[27,28] However, we did not have sufficient information on the iron levels of the cases in our study. Further studies are needed to confirm the relationship between osteopenia of prematurity and RBC transfusion.

A new and interesting finding of this study is that PPI use is higher in cases with osteopenia of prematurity. PPIs are frequently used to treat gastrointestinal diseases such as gastroesophageal reflux in newborns. In recent years, studies performed on adults and adolescents have reported a relationship between PPI use and bone fractures.[29,30] It has been reported that PPI exposure in the first year of life in children is associated with an increase in bone fractures in the first five years.[31] To our knowledge, there are no studies on this subject in premature newborns. Several hypotheses have been proposed to explain the relationship between PPI therapy and bone metabolism. One of them is that using PPIs causes hypochlorhydria, resulting in a decrease in calcium absorption from the small intestine and a decrease in bone mineral density.[32] Another hypothesis is that PPIs inhibit gastric H^+-K^+-ATPase as well as the vacuolar H^+-ATPase pump in osteoclasts. As a result, osteoclast function is impaired, and abnormal osteoclast-mediated bone resorption and osteoporosis develop.[31] The present study is pioneering in demonstrating the relationship between osteopenia of prematurity and PPI use. Physicians should be more cautious when using PPI, the lowest effective dose possible should be preferred in patients with appropriate indications, and patients using PPI should be screened for osteopenia. Due to the small number of cases in our study, PPI use may not have been determined as a risk factor for the development of osteopenia of prematurity. We think that this issue should be further investigated and the findings should be supported by larger studies.

Our study has several limitations. These include retrospective planning, a small number of cases, insufficient information about RBC transfusion (frequency, indications, iron, iron binding capacity, ferritin levels of the cases), and lack of bone imaging methods for osteopenia.

CONCLUSION

This study shows that osteopenia of prematurity remains to be an important health problem in premature newborns. Patients with prolonged TPN infusions are at risk of developing osteopenia of prematurity. Adjustment of mineral supplements in parenteral nutrition according to calcium and phosphorus levels should be started early in life, and enteral nutrition should be encouraged by reducing the duration of TPN use. Further studies are needed to increase our awareness of osteopenia of prematurity and to clarify the relationship between PPI use and RBC transfusion and osteopenia of prematurity.

Ethical approval

This study has been approved by the Kanuni Training and Research Hospital Clinical Research Ethics Committee (approval date 27/06/2022, number 2022/39). Written informed consent was obtained from the participants.

Author contribution

Surgical and Medical Practices: BSH; Concept: BSH; Design: BSH; Data Collection or Processing: BSH; Analysis or Interpretation: BSH; Literature Search: BSH; Writing: BSH. The author reviewed the results and approved the final version of the article.

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Conflict of interest

The author declares that there is no conflict of interest.

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