Osteopenia of prematurity: Assessment of Biochemical parameters in Very low birth weight preterm neonates

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Abstract

Background: Osteopenia of prematurity, commonly called as metabolic bone disease (MBD), is mostly described in preterm babies (< 36weeks) with very low birth weight (VLBW). This condition is characterized by a reduction in bone mineral content (osteopenia), with or without rachitic changes, and is caused by several nutritional and biomechanical factors. **Objective:** To determine the incidence of osteopenia of prematurity among high risk preterm VLBW babies and also to document changes in biochemical parameters including serum calcium, serum phosphate, serum alkaline phosphate (ALP) and serum creatinine in the above cases. **Material and method:** This prospective observational study includes all the very low birth weight babies born fromNovember 2012 to July 2014. Present study comprised of 60 VLBW neonates of which 10 were <28weeks, 32 were 28-31week and 18 were 31-34weeks of gestation. Estimations of biochemical parameters were done at 2nd week of birth and again at 6th week to detect the incidence of osteopenia. **Result:** There was a significant decrease inserum calcium and serum phosphorous level where asserum ALP documented a significant increase in preterm neonates when compared to control. 14 of 60 VLBW babies developed osteopenia of prematurity at 6th week of life. **Conclusion:** As observed in the present study, gestational age, birth weight and ALP are considered to be significant risk factors and are associated with osteopenia. So early detection of this condition by monitoring of biochemical parameters in high-risk cases minimizes the development of osteopeniaand prevent future complications of osteopenia.

Keywords: Osteopenia, Very low birth weight, Alkaline phosphate, Metabolic bone disease.

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Introduction

Osteopenia, commonly known as metabolic bone disease (MBD), can be due to decreased bone mineralization or increased bone resorption [1]. Babies born prematurely (< 37th weeks of gestation or even <28th week of gestation), with very low birth weight (VLBW, <1500grams) and extremely low birth weight (ELBW, <1000grams) are at increased risk of developing the condition, called as osteopenia of prematurity [2]. This condition has drawn interest of many neonatologistsbecause of its increasing incidence over last few decades. Moreover there has been growing interest in the optimal utilization of various investigations for the assessment of an infant with suspected metabolic bone disease [3]. Accumulating

inversely associated with gestational age and body weight [1,4,5,6]. Most commonly, osteopenia occurs as a result of reduced transplacental mineral delivery in preterm, poor nutritional intake and excessive mineral loss after birth [2,4]. The etiology of MBD is multifactorial which includes degree of prematurity, low birth weight, exposure to medications that can alter mineral levels, immobilization, lack of mechanical stimulation, long term parenteral nutrition, delayed establishment of full feedand inadequate nutrients intake.[2,6,7]. This condition can remain silent or can lead to serious complications, which makes the preterm newborn more susceptible to rachitic changes and/or fracturesduring minimal invasive procedures and even with routine handling in neonatal intensive care units [8]. Several biochemical markers like calcium (Ca), phosphate (PO4), alkaline phosphatase [ALP] and osteocalcin, have been used for measurement of bone mineral densityin preterm infants to detect development

of osteopenian [3]. ALP, the sum of bone, liver and intestinal isoform, with the bone isoform contributing about 90%, represent a marker of bone mineralization and turnover.There are limitations to the use of total ALP as several studies observed conflicting results [9,10]. According to evidences, rachitic changes are more commonly associated with greater ALP levels (>800IU/L) but can also be seen at lower levels (600IU/L)[11,12]. Radiological diagnosis is likely to be imprecise because the assessment is subjective and a major loss of bone mineral content might have to occur before characteristics changes would be apparent [13,14]. Increased understanding of the pathophysiology of neonatal osteopenia has raised awareness of the need for early monitoring, prevention and treatment of the condition in high-risk neonates. Given the lack of consensus on screening, it has been recommended to weekly measure serum calcium, phosphorus and ALP for early detection of osteopenia in high-risk neonates [15]. To the best of our knowledge, there is paucity of data regarding incidence of osteopenia and status of biochemical profile in premature VLBW babies, despite being a common disease in India.With this above consideration, thepresent study is undertaken to document the incidence of osteopenia in premature VLBW neonates and to evaluate the serum biochemical markers of osteopenia so as to detect such cases at an earliest, which can reduce the prevalence and severity of the condition in preterm neonates.

Materials and Methods

The prospective observational study was conducted in department of Biochemistry, Kalinga Institute of Medical Science, Bhubaneswar, in collaboration with neonatal intensive care unit (NICU), after being approved by ethical committee of the institute. All the very low birth weight (VLBW) neonates born in our hospital from November 2012 to July 2014 were enrolled in the study for evaluation. Following exclusion criteria were kept in consideration: babies diagnosed having inborn error of metabolism and babies with multiple congenital anomalies. A total of 1020 newborn were evaluated, out of that 482 babies were admitted to NICU. 92 babies were identified as premature (<34 week) born. As per exclusion criteria cited above, total 32 babies, out of 92 premature babies, were not included in our study. Moreover few babies, who could not be followed up, were also excluded. Finally a total number of 60 VLBW babies were enrolled for the present study. A comparative data analysis was proposed with at least 20 number of control (VLBW term neonates admitted to NICU for hyperbilirubinemia). Written informed consent was taken from all parents of both VLBW neonate study participants and healthy control. Babies were constantly under observation and were followed up both clinically and biochemically for detection of osteopenia of prematurity. Anthropological parameters like weight, height, gestational age, mode of delivery, cause of premature birth, head circumference, were noted down. The demographic details, course in the hospital and nutritional supplementation were recorded as per performa prepared by us. Blood samples were collected from both the study participants for ascertaining the followings biochemical parameters: serum alkaline phosphatase (ALP), serum calcium (Ca), serum phosphate (PO4), and serum creatinine. All the investigations were taken up from 2nd week of chronological age and were repeated at 6th week. During follow up, number of babies developing osteopenia was observed and in incidence was computed. Blood samples were analyzed using Cobas-400 fully automated analyzer.

Statistical analysis of this study was performed by Microsoft excel and SPSS 16. Obtained values were expressed as mean ± SD.ANOVA analysis, student t-test and post hoc analysis were adopted to observe the percentage of outcome variables and to find the correlation of changes. A p value <0.005 is considered as statistically significant.

Table 1: Biochemical Parameters at 2 weeks of age

Parameter	<28 weeks	28-30 weeks	31-34 weeks	Term	p value
Serum Ca (mg/dl)	8.82±1.027	8.68±1.53	8.62±0.635	9.49±0.457	0.067
Serum PO4 (mg/dl)	3.2±0.679	4.46±0.763	4.85±0.615	5.58±0.477	0.0001
Serum ALP (IU/L)	678.6±161.78	585±131.26	524.35±104.98	311.75±26.34	0.0001
Serum Creatinine (mmol/L)	0.605±0.146	0.541±0.09	0.5±0.075	0.36±0.06	0.0001

Table 2: Biochemical parameters at 6weeks of age

Parameter	<28Weeks	28-30weeks	31-34weeks	p value
Serum Ca (mg/dl)	9.17±0.39	9.24±0.35	9.98±0.38	0.23
Serum PO4 (mg/dl)	3.2±0.12	4.1±0.25	4.8±0.27	0.009
Serum ALP (IU/L)	947±121.6	602±105.2	518±113	0.009

Table 3: Incidence of osteopenia based on birth weight

	Weight <1000gms	Weight 1000-1200 gms	Weight 1200-1500 gms	Total number of cases
No. of Babies in the study group	21 (35%)	21 (35%)	18 (30%)	60
No. of babies with osteopenia prematurity	11 (52%)	3 (14.28%)	0	14 (23.33%)

Table 4: Incidence of osteopenia based on gestational age

	<28 weeks	28-31 weeks	31-34 weeks	Total no. of cases
No. of babies in study group	10 (16.67%)	32 (53.33%)	18(30%)	60
No. of babies in osteopenia prematurity	6 (60%)	6 (18.75%)	2 (11.11%)	14 (23.33%)

Observation

Present study comprised of 60 preterm VLBW babies, out of which 39 were male child and 21 were female child. As per the recorded observations, there were 10 neonates (16%) less than 28weeks, 32 neonates (53.3%) within 28-32 weeks, and 18(30%) were within 31-34 weeks. In the present study, the distribution ofbabies (both cases and control) based on birth weight was like this: 28 neonates were <1000grams (35%), 28 belonged to birth weight 1000-1200grams (35%), 18 neonates belonged to 1200-1500 grams(22.5%) and 6 babies were > 1500grams(7.5%). The mean values of serum biochemical parameters at 2 weeks of age are documented in Table-1, which reveals the following data: serum Ca and PO4 levels were significantly decreased at < 28weeks, 28-30 weeks and 31-34 weeks as compared to term controls, but the decrease was insignificant when compared between 28-30weeks and 31-34weeks. Serum ALP levels were significantly increased at < 28 weeks, 28-30weeks and 31-34weeks but levels did not differ significantly when compared between 28-30 weeks and 31-34 weeks. Serum creatinine increased significantly in preterm neonates as compared to term neonates. Table-2 depicted the above parameters at 6weeks of age. As evident from the data, there was no significant difference in serum Ca level, where as serum PO4 level showed a significant decrease at < 28 weeks, in comparison to the other two groups. Serum ALP, a marker of bone turnover, was observed to be highest with < 28week babies, both at 2nd week and 6th week of life. But no significant difference was observed between 28-30weeks and 31-34 weeks. Another relevant finding of our study is the detection of osteopenia, based on birth weight and stats of biochemical markers (Table-3). Out of 60 enrolled premature babies in our study, 14 neonates (23.3%), developed biochemical parameters suggestive of osteopenia (cut off value of ALP taken as ≤800IU/L), out of which 11 number of babies (out of 21, 52%) were from <1000gms and 3 (out of 21, 14.2%) were from 1000-1200gms birth weight. There was no incidence of osteopenia observed in the category of 1200-1500gms. Table-4 revealed maximum incidence of osteopenia (60%) from the gestational age<28weeks. A total of 6 out of 32(18.7%) and only 2 out of 18(11.11%) cases were from 28-31weeks and 31-34weeks respectively.

Discussion

Prematurity is the leading cause of neonatal mortality at 25% [16]. Preterm neonates with VLBW andELBW, are most vulnerable for osteopenia of prematurity and metabolic bone disease, secondary to insufficient trans-placental mineral delivery, postnatal nutrition compromise and excessive urinary loss after birth [1,17]. Moreover, use of several medications for neonatal diseases like high dose systemic corticosteroid, diuretics, long-term methyl xanthine can impair bony growth and increase the risk of osteopenia [1,2]. Osteopenia of prematurity is reported to be 20-30% in VLBW and 60-75% in ELBW babies by several studies in this regard [18,19].

Present study aimed to determine the incidence of osteopenia of prematurity and to look into any significant difference in biochemical profile. Out of 60 enrolled preterm neonates in the current study, incidence of osteopenia of prematurity was reported to be 23.3%, based on birth weight. Our finding can be comparable to the finding of several other recent studies in this regard. Lee et al reported a high incidence of 44%, among 55 ELBW infants [19]. Another prospective study conducted in VLBW observed the prevalence of osteopenia to be 32.7% [20]. Similarly Viswanath et al confirmed 30.9% prevalence in the radiological evidence of MBD among 230 ELBW babies [21]. One more recent study also confirmed 43.9% incidence rate of osteopenia in ELBW neonates [22]. Table-4, reflects the incidence of osteopenia based on gestational age, which documented a very high incidence of osteopenia (60%) in preterm babies <28weeks. This might be due to extreme prematurity, which leads severe insufficiency in transplacental mineral delivery [17].

Moreover incidence rate of osteopenia might be associated with several factors like postnatal nutrition status, comorbidities and type of evaluation. Similar to our findings, Bass et al described an inverse relationship between MBD and gestational age [23]. With reference to the above finding, it can be concluded that birth weight <1500gm, more specifically <1000gms and gestational age <28weeks are considered as important predictor of osteopenia, apart from other factors like total parenteral nutrition for prolonged period, use of steroid and use of diuretics [2,24]. According to the result of our study, serum calcium levels at 2 weeks of age (Table-1) in babies<28weeks, 28-30weeks, 31-34weeks of age were 8.82±1.027mg/dl, 8.86±1.53mg/dl and 8.62±0.63mg/dl respectively and

there was no significant difference of results in different group. Similarly no significant difference was noted in the result of serum calcium at 6th week also. However serum calcium was reported to be significantly lower in preterm neonates when compared to term controls, which is consistent with other study in this regard [25]. Hence serum calcium has no significant importance to screen high-risk cases prone to develop osteopenia. This can be explained by the fact that neonates might be able to maintain normal serum calcium at the expense of removal from bone. Further serum Ca might get affected by hypophosphatemia, a conditionnot related to osteopenia [26].

Another observational finding in our study population was that all VLBW neonates were supplemented with calcium (100-120mg/kg/day), phosphorous (50-70mg/kg/day) and 400IU of Vitamin D after getting full enteral nutrition. Based on biochemical parameters of bone metabolic status, nutritional supplementations were modified individually, which may explain higher phosphate levels in our study population as compared to other studies [19]. Another relevant finding of our study is that, serum ALP levels, an indicator of high bone metabolism, were significantly increased at all gestational age compared to term neonates (Table-1,2).Our study evidences suggest that ALP concentration of≥800IU/L may cause osteopenia. In this study mean level of peak ALP was higher in < 28week preterm group at 6th week (947 ±121.6 IU/L). The rising trend of ALP in different preterm groups from 2nd week to 6th week, clearly suggests that biochemical tests at 6weeks of age is of more diagnostic value to detect development of osteopenia.

Similar to our finding, Mitchell et al in his cohort study concluded the association of increased ALP and higher risk of osteopenia in preterm neonates [11]. According to some data, preterm neonates having rickets register a higher ALP level compared to control (952.2+413.8 vs 524.7+158.2 IU/L) [19]. In another study, it was described that increase ALP signifies increased bone osteoblastic activity in preterm babies [27]. Also other researchers have suggested to prevent increase ALP by supplementing the preterm with appropriate minerals [28]. Moreover, there are conflicting reports on the effect of minerals on ALP level [9,10]. However it can be concluded that ALP, an indicator of high bone metabolism, rises within first few weeks of birth and increases further in mineral deficiency [20]. So it can be taken as one of the significant biochemical marker for detecting osteopenia of prematurity. In our study, serum creatinine levels were significantly increased in preterm

neonates compared to term neonates. Increased creatinine signifies lower GFR in preterm. It has been suggested that premature birth impairs final development of nephrons after birth [29]. Glomerular function shows a progression directly correlated to gestational age and postnatal age in preterm infants.

Conclusion

Prematurity is the most important risk factor for neonatal osteopenia. As described previously, there are evidences of inverse relationship of neonatal osteopenia with gestational age and birth weight. This problem is compounded by risk of pathological fracture, later on rickets. It is therefore important to detect the condition at the earliest by closely monitoring biochemical parameters in high-risk VLBW infants. So early detection, treatment and prevention of development of complications are the preferred strategies.

Limitation of the study: Our study was limited for small sample size and was limited to single center study. Since there was unavailability of DEXA scan or quantitative ultrasound in our center, we could not correlate radiological osteopenia with biochemical parameters of osteopenia of prematurity. Moreover we could not include maternal nutritional effect on neonates as in our tertiary care center, most of the mothers did not have proper antenatal check up.

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