RESEARCH PAPER

Incidence of Metabolic Bone Disease After Implementation of Bone Protective Nutritional Strategies: *A Prospective Cohort Study*

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Background: Metabolic bone disease (MBD) is a morbidity of multifactorial etiology with a high incidence in very preterm infants. We planned to study the incidence of MBD after implementation of bone health focussed nutritional strategy (BNS) in those <30 weeks gestation at birth.

Methods: This prospective cohort study including preterm newborns (<30 weeks) who received nutrition that incorporated (*a*) Early initiation of intravenous potassium phosphate; (*b*) Early enteral supplementation with multicomponent human milk fortifier at enteral feed tolerance of 40 mL/kg/day feeds itself; and (*c*) Weekly phosphorus measurements with optimization of enteral intakes. Incidence of MBD at 4 weeks of postnatal age and beyond were analyzed. Other relevant safety and clinical outcomes were measured.

Results: Of the 67 included neonates receiving BNS, 20.9% were classified as MBD. There was a low rate of hyperphosphatemia (4.5%) and hyperkalemia (2.9%). Full enteral feeds were achieved by median (IQR) of 6 (5,7) postnatal days.

Conclusion: In preterm newborns (24-30 weeks) MBD incidence was 20.9% after BNS was implemented. Intravenous potassium salt of phosphorus and early use of HMF were safe and feasible.

Keywords: *Bone health*, *Intravenous phosphorus, Outcome, Preterm nutrition*.

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Optimizing nutition in very preterm infants, right at the outset, constitutes a pivotal part of neonatal intensive care. Adequate quantities of early mineral intakes would ensure maintenance of physiological serum levels and aid in establishing normal postnatal growth [1]. Metabolic bone disease (MBD) in preterm infants result from many reasons: inadequate stores and postnatal deficiency of phosphorus, calcium, magnesium, vitamin D; use of drugs like caffeine, steroids; and lack of movement [2]. Reporting of MBD is largely inadequate with non-uniform definitions and unclear descriptions of strategies to prevent the disorder [3,4]. Diagnosis of MBD is challenging due to its indolent nature, manifesting only when severe demineralisation sets in, with clinical features like craniotabes, overt rickets, growth failure and even fractures [5].

Although phosphorus administration is recommended prophylactically from the very first hours after birth, this is standard practice only in those parts of the world where suitable formulations are available [6]. The lack thereof of literature pertaining to early phosphorus use in this part of the world is probably proof of suboptimal use [7]. We are restricted by non-availability of intravenous phosphorus formulations that can be used in immediate postnatal life. Moreover, most units across the country use enteral supplementation as multicomponent human milk fortifier (HMF) after at least 100 mL/kg/day milk feeds are safely established and tolerated [8]. In a previous study published from our own unit, we reported a high incidence of MBD (30%) in infants born between 27-32 weeks gestation despite implementing what we considered a practical and optimal nutrition policy [9]. This revelation led us to revise

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our protocols to: *i*) Supplement phosphorus early with the only available potassium salt of phosphorus as soon as safely possible; *ii*) Strict adherence to standard feed regimens (SFR) along with use of human milk and earlier initiation of oral phosphorus as HMF (when infant tolerated 40 mL/kg/day feeds); and *iii*) Weekly monitoring of serum phosphorus levels to optimize intakes as intravenous (IV) or oral formulation based on the infants' parenteral/enteral nutritional status. This study aimed to prospectively assess the incidence of MBD in those born at ≤30 weeks gestation after implemen-tation of a bone health focussed nutritional strategy (BNS).

METHODS

This prospective observational study was conducted between January, 2020 and April, 2021, in our Level IIIB teaching unit. The institute has written policies for commencing aggressive parenteral nutrition soon after birth, minimal enteral nutrition and standard feed regimens, use of mother's own milk (MOM) and pasteurized donor human milk (PDHM) [9,10].

All in-born and out-born neonates, ≤30 weeks gestation, admitted within 24 hours of age, were included. Those with congenital or acquired renal diseases, whose parents refused consent, and who did not survive or did not complete care in the unit till discharge were excluded. Written informed consent was taken from parents for data collection. Institutional ethics committee and scientific research committee approval was obtained before initiation of the study. The study protocol was registered with the Clinical Trials Registry of India.

All eligible neonates were managed as per the BNS, constituting supplementation of intraveneous potassium phosphorous, enteral phosphorous as HMF introduced earlier than conventional practice and optimisation of phosphorous supplementation by weekly monitoring of serum levels. Supplementation of intraveneous phosphorus, as a potassium phosphate salt, was initiated usually by day 2 or 3 of life, if urine output >1mL/kg/day and serum potassium <5.5 meq/dL. The amount of intraveneous phosphorus (Potphos) in parenteral nutrition was calculated to target potassium requirements (1-2 meq/kg/day) and phosphorus requirements (25-50 mg/kg/day). Intraveneous phosphorus was continued till the neonate was on parenteral nutrition (which was stopped when feeds reached atleast 100 mL/kg/day feeds). Daily serum potassium and phosphorus levels were measured while on IV supplementation. If potassium levels was noted ≥6.5 mEq/L, or phosphorus >8 mg/dL, IV phosphate was withheld till values were normal. Enteral phosphorus as HMF was initiated early once enteral feeds of 40 ml/kg/day was tolerated (at half strength, i.e., half of 1 g sachet in 25 mL expressed breast milk or PDHM) [11]. HMF was changed to the standard, full strength (1 g in 25 mL MOM/PDHM) once the neonate was on 100 mL/kg enteral feeds. Target enteral phosphorus intake targeted was 100 mg/kg/day of phosphorus, once full enteral feeds were achieved. If serum phosphorus remained <5.5 mg/dL, additional phos-phorus was supplemented as oral calcium phosphorus (syrup Ossopan D). If phosphorus levels still remained low despite optimum supplementation, vitamin D intake was optimized and phosphorus was supplemented separately using sodium-acid-phosphate granules (Addphos, Steadfast Medishield) to optimize enteral absorption [12]. We assessed the side effects in terms of proportion of neonates having hyperkalemia, hyperphosphatemia while on IV phosphorus, days to full feeds (as a measure of feed intolerance, given that early HMF was used), invasive ventilation days, bronchopulmonary dysplasia and extrauterine growth restriction (EUGR) [13,14].

Metabolic bone disease was defined as the nadir of serum phosphorous <5.5 mg/dL or the peak serum alkaline phosphatase (ALP) >800 IU/L, as measured from 4 weeks postnatal age till discharge [15]. Any clinical signs of MBD were noted. Radiological investigations were done, if indicated.

Sample size was calculated for an estimated true proportion of MBD as 0.3, with precision level of ±0.12 and a Confidence level of 0.95, to be 57 [9]. Allowing a loss of 10% (due to death or transfer out before completion of treatment), final sample size was planned to be 62. Statistical analysis was conducted using STATA version 16.

Statistical analysis: Fisher exact test was done for comparison of proportions. A value of $P<0.05$ was considered statistically significant.

RESULTS

Of 71 infants born at ≤30 weeks gestation, 67 were included (2 infants were transferred out before completion of care, 1 died and 1 had a major surgical condition). The baseline characteristics are depicted in **Table I**. The different parameters related to BNS are described in **Table II**. Half strength HMF was added when infants reached median (IQR) enteral feed tolerance of 60 (60,60) mL/kg/day.

Table I Baseline Characteristics of Preterm Newborns (< 30 weeks) Enrolled for Bone Nutritional Strategy (*N*=67)

Characteristics	*No.* (%)
Gestational age[a]	29 (27,30)
Birth weight (g)[b]	1071 (268)
Small for gestational age	20 (29)
Male sex	34 (51)
Inborn babies	65 (97)
Cesarean section	65 (97)
Antenatal steroids	
Complete coverage	35 (52)
Incomplete coverage	32 (48)
Chorioamnionitis	4 (6)
Pregnancy-induced hypertension	10 (15)
Abnormal doppler	19 (28)
PPROM	6 (9)

All values are in frequency (%), except [a]median (IQR) or [b]mean (SD). PPROM–preterm premature rupture of membrane.

Table II Parameters of Phosphorus Supplementation in Enrolled Preterm Newborns (*N*=67)

Bone protective strategy	*Median (IQR)*
Duration of parenteral nutrition (d)	5 (3,7)
Duration of IV potassium phosphate (d)	3 (2,4)
Day of life at which HMF was supplemented as full strength (at 100 mL/kg feed volume)	5 (4,6)
Total duration of HMF supplementation (d)	25 (14,28)
Duration of PDHM with HMF (d)	7 (5,8)
Cumulative IV phosphorus intake (mg/kg)	111.6 (74.4,148.8)
Cumulative phosphorus intake from HMF (mg/kg)	1019.1 (521.4,1185)
Cumulative phosphorus intakes as sum of IV and HMF (mg/kg)	1110.4 (668.5,1332.2)

HMF:Human milk fortifier, PDHM:Pasteurized donor human milk. IV-intravenous.

Parenteral nutrition was commenced within hours of birth. IV phosphorus was started after day 2, once urine output was established and serum potassium was <5.5 meq/dL. Daily serum perturbations of phosphorus levels are represented in **Web Table I**. The median (IQR) weekly serum phosphorus levels are depicted in **Fig. 1**.

Some included neonates did not have a daily monitoring of serum phosphorous levels as they were not started on parenteral nutrition based on birth weight criteria in which case they did not receive IV Potphos (*n*=12). This was according to the predefined nutrition protocol. In some neonates, potassium values were high on day 2 (>5.5 meq/dL), hence IV Potphos was delayed until safety criteria were met. IV Potphos was administered only till PN was indicated, hence the number of days of IV Potphos and daily phosphorous monitoring varied.

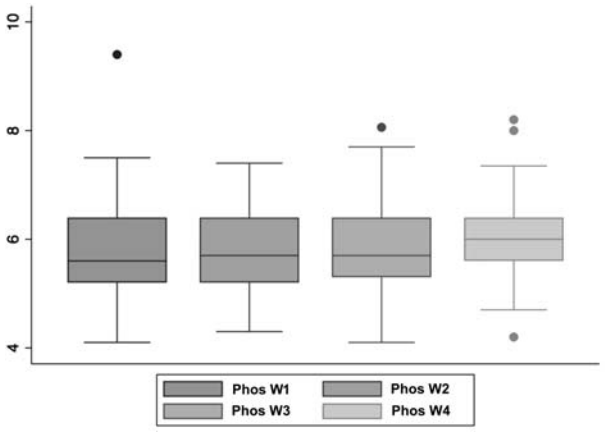

Fig. 1 Box Whisker plot showing serum phosphorus values from week 1 to week 4 of neonatal intensive care unit stay.

Not all neonates had weekly serum phosphorous sampling, it was deferred if they were on direct breast milk feeding and not receiving HMF, not warranting monitoring and optimisation as a part of BNS. In such neonates only fourth week sample was done. In some cases there were inadvertent misses of weekly sampling.

Of all included neonates with ≤30 week gestation, 14 (20.9%) developed MBD. The proportion was higher at lower gestation ages at birth: 9 (69.2%) among all those ≤26 weeks, 4 (22.2%) between 27-28 weeks and 1 (2.8%) at 28-30 weeks.

Among those diagnosed to have MBD, five babies required more than the conventional calcium phosphate supplementation: sodium acid phosphate salt in one, and activated vitamin D supplementation in four infants.

Hyperkalemia (serum level >6.5 meq/L) was noted in 3 out of 152 total samples taken for monitoring. Hyperphosphatemia was noted in 4.5%; none of them were associated with ECG changes or clinical manifestations that required therapy. Feed plan modification from standard regimens were required in 16 (23.8%), but the median (IQR) time to reach full enteral feeds was 6 (5,7) days. Other clinical outcomes are showed in **Table III**.

DISCUSSION

Our prospective observational cohort study analyzed the incidence of MBD after implementation of bone focussed nutritional strategies with best utilization of available resources.

Published literature describes the risk factors for MBD as prematurity, preeclampsia, chorioamnionitis, male gender, low birth weight and postnatally parenteral nutri-

Table III Clinically Relevant Secondary Outcomes in Preterm Neonates (≤ 30 weeks) Receiving Bone Focussed Nutritional Strategies (*N*=61)

Parameter	*No. (%)*
Weight-based EUGR	38 (56.7)
Length-based EUGR	25 (37.3)
Occipito frontal circumference (OFC) - based EUGR	1 (1.4)
Invasive ventilation (d)[a]	8 (5,15)
BPD	8 (11.9)
ROP requiring laser therapy	7 (10)
Sepsis	3 (4.4)
NEC Stage 2 or more	1 (1.7)

All values are in no. (%) or [a]median (IQR). EUGR: Extrauterine growth restriction, BPD: Bronchopulmonary dysplasia, NEC: necrotizing enterocolitis, ROP: Retinopathy of prematurity. EUGR: >1 z-score difference between birth z-score and discharge z-score.

tion, glucocorticoids, drugs like methylxanthines, NEC and BPD [2,16]. We chose a population of preterm babies born ≤30 weeks gestation, most of whom were extremely low birth weight (ELBW), as they are physiologically more vulnerable for MBD [2,16].

Studies from other units have reported high incidence of MBD among ELBW babies. While Lyon, et al. [3] described incidence of MBD as high as 50% among ELBW babies in 1987, later in 2009, Mitchell, et al. [17] described a decreased incidence to 15% among ELBW babies [3,17]. Rustico, et al. [4] described birthweight specific incidence between 16-40% among very ELBW and very low birth weight (VLBW) neonates [4]. The incidence of metabolic bone disease of prematurity in our study was less than what we published in 2019 (before BNS) [9]. We expected a higher incidence in the present study as we enrolled a cohort of smaller preterm neonates (25-30 weeks) than our previous report (27-32 weeks). The precise incidence remains elusive, partly due to lack of agreement on the definition of MBD. The biochemical criteria for identifying MBD have become more stringent in the recent times. Recent recommendations propose serum phosphorus levels of <5.5 mg/dL as most sensitive criterion for diagnosis of MBD. Serum alkaline phos-phatase levels >800-900 U/L have been used as cut off values for diagnosis of MBD. Further, the authors have questioned the utility of specific ALP in diagnostic utility, as compared to total ALP activity [18].

High amino acids protein intake without adequate phosphorus supply leads to significant tissue deficit and hypophosphatemia, due to the increased transport of phosphorus (also potassium) into the cells. This condition is named as refeeding-like syndrome in preterm neonates. This is overcome by optimizing the parenteral nutrition with optimal phosphorous supplementations [19]. Organic phosphate solutions (sodium glycerophosphate, glucose-l-phosphate) are now available in other parts of the world and substantially improved co-solubility of these compounds with calcium salts allows maintenance of in-utero accretion even postnatally [20]. Pereira-da-Silva, et al. [6], showed that high early calcium and phosphate intake by PN within first hours after birth can prevent bone strength impairment in preterm neonates. They studied neonates with a mean gestational age of 29.6 weeks and birth weight of 1262 g. Salts that are available in the country are potassium compounds that are not advised for use in the first few postnatal days when urine formation is less due to reduced glomerular filtration rates. Each mL of this formulation (Potphos, Neon pharmaceuticals) contains 4.4 meq of potassium and 93 mg of phosphorus. Phosphorus containing fluids cannot be reconstituted to supply calcium salts as it results in precipitation of calcium phosphate [21]. These issues are less often addressed during planning of parenteral nutrition in most resource restricted settings [7].

The best source of nutrition in the short and long-term is undoubtedly MOM, but unfortified human milk does not provide sufficient minerals to VLBW neonates [22]. Although use of Multicomponent HMF is practiced in NICUs all over the world, there is variability in practice. Most centres initiate fortification after the preterm neonate is on 100-150 mL/kg/day of enteral nutrition. Recent literature suggests use of HMF earlier [11]. We tried to initiate HMF once 40 mL/kg/day enteral feeds were tolerated, however in practice this ranged from 40 to 100 mL/kg/day during the study period; median being 60. Since we started HMF early, we were cautious; initially HMF was administered at half strength as described in the methodology. Earlier use of HMF was not associated with increase in feed intolerance, measured as time required to achieve full enteral feeds, as compared to our previous experience (when HMF was started at the conventional 100 mL/kg enteral feeds) [9,10]. The median (range) total duration of HMF supplementation was 25 (3-40) days.

There was a clear trend of decreasing incidence of hypophosphatemia across week one to week four with increase in median serum phosphorous values increased with ensuing postnatal age in weeks. This probably reflects the serial decrease in phosphorus loss through maturing renal tubules.

Hyperphosphatemia (>8 mg/dL) was uncommon in our study, endorsing the safety of the enteral phosphorus doses. A study published by Katharine, et al. [22] analyzed for the incidence of hyperphosphatemia among premature babies receiving the fortified human milk, they used human milk-based fortifier. In that study they concluded that incidence of hyperphosphatemia was mild and transient. We found hyperkalaemia in 2/67 (2.9%) neonates leading to withdrawal of intravenous phosphorus, although their hemodynamic status and ECG were normal and restarted after potassium values were normal. Farida, et al. [23] described the incidence of hyperkalaemia among ELBW and VLBW as 3% as compared to 2.9 % in our study .

In our study with pre-defined standard feed regimens, we could achieve 100 mL/kg/day enteral feeds on the day 6 (5,7) median (IQR). This indicates that there was no significant feed intolerance, despite early use of HMF. We attribute the success of early enteral feeding to the strict adherence to SFR and pro-active promotion of MOM. The time to full enteral feeds is comparable to other published studies. Dutta, et al. [8] published guidelines for feeding of low-birth-weight babies. The authors reported that for preterm babies <1000g, two weeks may be required to

WHAT IS ALREADY KNOWN?

- Intravenous phosphorus is recommended from day 1 of life in international guidelines, but no potassium-free salt of intravenous phosphorus is available in India.

WHAT THIS STUDY ADDS?

- Strategies with focus on phosphorus and nutrition can lead to decreased incidence of metabolic bone disease in preterm neonates.
- Intravenous potassium phosphate is safe for use in preterm neonates as part of a bone health focussed nutritional strategy.

achieve full feeds (150-180 mL/kg), while for babies 1000-1500g birth weight, one week may be enough. In an RCT published in 2010 [24], babies achieved full feeds within one week. We observed an EUGR rate of 38 (56.7%). In the study by Kim, et al. [25] including babies born <28 wks with mean (SD) birth weight of 899 (189) g, the authors observed EUGR prevalence, using the same measure of *z*-scores as definition, at about 70%. These babies were much smaller at the start.

Neonates at the thresholds of viability (22-23 wks), who would be most affected by MBD, were not included in this study as survival at this gestation in the unit is negligible. We did not plan a comparative cohort for ethical reasons. A before- and after study that compared our previous cohort might have added value, but we felt that significant differences in patient characteristics and nutrition protocols during the time epochs made the contrast less meaningful [9]. The actual days of intravenous phosphorous administration was small; hence utility cannot be determined. We did not include use of Dual energy *X*-ray absorptiometry (DEXA) as it involves exposure to ionizing radiation, not available at the bedside and entails additional costs. Measuring bone speed of sound (SOS) by quantitative ultrasound was also not planned in order to give priority to pragmatism and generalisability [5]. Still, our study had some noteworthy strengths. The population included preterm babies (≤30 weeks gestation) who are known to be at high risk for MBD. Through our prospective (BNS) nutrition study, we could demonstrate that stringent implementation of nutrition protocols is possible and beneficial. We explored the alternatives to intravenous phosphorus preparations and evaluated safety of the same; Larger studies will be required to recommend routine use. The earlier use of HMF was found to be safe. Our nutrition policies were pragmatic and applicable to units with facilities for parenteral nutrition.

Incidence of MBD in preterm neonates (≤30 wks) was 20.9% after implementation of nutritional strategies (BNS) targeted at improving bone health. Early intravenous potassium phosphate could be initiated and safely administered. Hyperkalaemia and hyperphosphatemia were uncommon. Early initiation of enteral phosphorous as HMF (after 40 mL/kg/day feed volume) and optimisation of phosphorous supplementation by weekly monitoring was possible.

Contributors: NJ,FP: conceived the study; AAK: collected data. All authors contributed to clinical care of the included neonates. AAK,FP,NJ: conducted statistical analysis; AAK,FP: wrote the manuscript and all authors approved the final draft.
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Note: Additional material related to this study is available with the online version at *www.indianpediatrics.net*

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