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Bone fracture in severe small-for-gestational-age, extremely low birth weight infants: A single-center analysis

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ABSTRACT

Introduction: Bone fracture is a complication of extremely low birth weight infants (ELBWIs). This study aimed to analyze risk factors for bone fracture in a population of severe small-for-gestational-age (SGA) ELBWIs.
Methods: We retrospectively studied data from ELBWIs with a birth weight <1000 g and <−2 standard deviations (SDs) born at the National Center for Child Health and Development, Japan, from 2013 to 2015. Infants were divided into fracture and control groups. Serum calcium (Ca) and phosphorus (P) levels, perinatal factors, and previously reported risk factors were analyzed.
Results: Of 25 cases of severe SGA ELBWIs, 5 cases of bone fracture were identified. Gestational age was 27.7 ± 2.2, 29.1 ± 2.6 weeks (mean difference [MD] −1.4, 95% confidence interval [CI]: −4.0, −1.2, p = 0.280), birth weight (BW) 448 ± 105, 673 ± 216 g (MD −225, 95% CI: −433, −17, p = 0.036) and BW-SD −4.1 ± 0.1, −3.4 ± 0.8 (MD −0.8, 95% CI: −1.5, −0.02, p = 0.045) in the fracture and control groups, respectively. Minimums of serum Ca and P were 6.6 ± 1.4, 8.1 ± 0.8 mg/dl (MD −1.5, 95% CI: −2.5, −0.6), p = 0.003) and 2.3 ± 0.6, 3.5 ± 1.1 mg/dl (MD −1.2, 95% CI: −2.2, −0.1, p = 0.027) in the fracture and control groups, respectively.
Conclusion: Lower BW and BW-SD were possible risk factors for bone fracture. Hypocalcemia and hypophosphatemia may also contribute to the condition.

1. Introduction

Metabolic bone disease (MBD) is often observed in extremely low birth weight infants (ELBWIs) [1,2], and is associated with an increased risk of rickets, fractures and growth disorder [3,4]. Fractures occur in 7% of ELBWIs [5]. Known risk factors for fractures include chronic lung disease (CLD), usage of diuretics and nutritional disorder [6,7]. Small-for-gestational-age (SGA) infants commonly have low bone mass due to poor intrauterine nutrition [8] as well as nutritional disorder caused by cholestasis after birth, leading to a higher risk for bone fractures [9]. Despite knowledge of these risk factors, it is often difficult to achieve ideal nutritional support in severe SGA ELBW infants.

Calcium (Ca) and phosphorus (P) are important minerals for bone formation [10]. Dual energy X-ray absorptiometry (DEXA) is the "gold standard" for assessing MBD [11]. However, DEXA cannot be used in the acute phase after birth. Previous studies have shown that assessing serum levels in P and alkaline phosphatase (ALP) can be useful to predict MBD [12,13]. However, few studies have explored the trends of these factors. As the treatment of ELBWIs is always progressing and changing, information on Ca and P trends may be important to predict MBD. In this study, we aimed to analyze the Ca and P levels, perinatal factors, and previously reported risk factors in severe SGA ELBWIs.

2. Methods

Extremely low birth weight infants with a birth weight (BW) <1000 g and <−2 standard deviations (SD) who were born at the National Center for Child Health and Development, Japan, between January 2013 and December 2015 were included in this analysis. Infants with complications such as chromosomal abnormalities, multiple anomalies, congenital infections, diseases with a poor prognosis, or infants who were discharged before the 56th day of life [2], were excluded.

At our neonatal intensive care unit (NICU), we start total parenteral nutrition at day 1 with the administration of amino acids (0.5 g/kg/day) and lipids (0.5 g/kg/day). We gradually increase both amino acids and lipids up to 2–3 g/kg/day. If available, breast milk is given from day 0. We increase the rate of breast milk by 10–20 ml/kg/day if there are no problems with digestion. We do not use donor breast milk. If breast milk is not enough, we use fortified milk. Breast milk is fortified when the amount reaches 100 ml/kg/day.

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2.1. Confounding factors

We collected data for the following confounding factors: maternal age, primiparity, singleton, diabetes mellitus (DM), pregnancy-induced hypertension (PIH), clinical chorioamnionitis (CAM), magnesium use, antenatal corticosteroid use, cesarean section (C/S), sex, gestational age (GA), BW, birth length, birth head circumference, Apgar score at 1 and 5 min, duration of mechanical ventilation, CLD, patent ductus arteriosus (PDA), day of establishment of enteral feeding, necrotizing enterocolitis (NEC), use of diuretics, vitamin D, postnatal steroid, cholestasis, abdominal surgery, sepsis, intraventricular hemorrhage (IVH) and retinopathy of prematurity (ROP) [14–17]. Weight growth velocity (WGV) from birth to the 56th day of life was also calculated using an exponential model [18]. When no weight data was available for day 56, we used data from days 57 or 58. CAM was defined by clinical findings, for example, fever, leukocytosis, or local pain during pregnancy, labor or delivery [19]. Antenatal corticosteroid use means the administration of corticosteroids at least once to the mother before delivery. GA was calculated using findings from an early prenatal ultrasound, the date of the last menstrual period, and a physical assessment of the infant at birth. BW-SD was calculated based on the standard BW for GA as published by the Japan Pediatric Society [20]. CLD was defined as requiring oxygen at 36 weeks (corrected age). PDA was defined as receiving indomethacin treatment or surgery. The day of establishment of enteral feeding was the day when the enteral feeding amount was over 100 ml/kg/day. NEC was defined by a Bell classification of stage II or greater [21]. Cholestasis was diagnosed with direct bilirubin over 2 mg/dl [22]. Sepsis was diagnosed by blood culture. The severity of IVH was diagnosed by cranial echography and classified according to the Papile grading system [23]. ROP was defined as being treated with laser coagulation.

Fractures were found by chance when an X-ray was taken. In the acute phase, chest-abdominal X-rays were taken almost every day, however in the chronic phase, X-rays were performed only a few times per month. Radiologists assessed all X-rays. We divided the evaluated cases into two groups: fracture and control. In the fracture group, data were collected up until the day the fracture was found. In the control group, data were collected at day 100. Collected data included levels of Ca, P, creatinine (Cr) and ALP in serum and Ca, P and Cr in urine.

2.2. Analysis

We compared data between the two groups. Continuous data are expressed below as means ± standard deviations (SDs) and were compared using Student's *t*-test. Binary or categorical data are expressed as frequencies and percentages, and were compared using Fisher's exact test. In addition, risk ratios (RRs), mean differences (MD), 95% confidence intervals (CIs), and p-values were calculated.

We analyzed the trend of serum Ca, P, ALP, urine-Ca/urine-Cr and the percentage of tubular reabsorption of phosphate (%TRP).

All statistical analyses were performed using JMP 10.0.0 software (SAS Institute, Cary, NC, USA), with p-values <0.05 indicating statistical significance. The present study protocol was approved by the Ethics Review Committee of the National Center for Child Health and Development.

3. Results

Over a 3-year period from 2013 to 2015, 65 ELBWIs were born at our hospital. Of these, 33 were severe SGA with a birth weight <1000 g and <− 2SD. Data from 25 of these 33 infants were included in the analysis. The remaining 8 cases were excluded for reasons including trisomy 18 (n = 1), parvovirus infection (n = 1), multiple anomalies (n = 1), mitochondrial disease (n = 1) and discharge before day 56 (n = 4). All 25 infants survived to discharge.

Five cases of bone fracture were identified: left humerus (n = 2), left femur (n = 1), and multiple long bone fractures (n = 2). We found that fractures occurred between days 73 and 100. Radiological evidence for MBD was found in all five infants: four infants showed evidence of rickets and one showed osteopenia. In the fracture and control groups, the number of males, gestational age, BW and BW-SD were 4 (80%) and 7 (35%) (risk ratio (RR) 2.3, 95% confidence interval (CI): 1.1, 4.8, p = 0.133); 27.7 ± 2.2 weeks and 29.1 ± 2.6 weeks (mean difference (MD) −1.4, 95% CI: −4.0, 1.2, p = 0.280); 448 ± 105 g and 673 ± 216 g (MD −225, 95% CI: −433, −17, p = 0.036), and −4.1 ± 0.1 and −3.4 ± 0.8 (MD −0.8, 95% CI: −1.5, −0.02, p = 0.045), respectively (Table 1).

DM and PIH were 0 (0%), 1 (5%), (RR 0, p = 1.000) and 1 (20%), 11 (55%), (RR 0.4, 95% CI: 0.06, 2.2, p = 0.322) in the fracture and control groups, respectively.

Singleton and cholestasis were 5 (100%), 15 (75%), (RR 1.3, 95% CI: 1.04, 1.7, p = 0.544) and 4 (80%), 7 (35%), (RR 2.3, 95% CI: 1.1, 4.8, p = 0.133) in the fracture and control groups, respectively. Maternal age, primiparity, singleton, CAM, magnesium, antenatal corticosteroid, C/S, duration of mechanical ventilation, PDA, NEC, vitamin D, postnatal steroid, abdominal surgery, sepsis, IVH 3–4 and ROP showed no significant difference.

Minimum levels of serum Ca and P, and a maximum level of serum ALP were 6.6 ± 1.4 mg/dl, 8.1 ± 0.8 mg/dl (MD −1.5, 95% CI: −2.5, −0.6, p = 0.003), 2.3 ± 0.6 mg/dl, 3.5 ± 1.1 mg/dl (MD −1.2, 95% CI: −2.2, −0.1, p = 0.027), 3664 ± 1440 U/l, 2469 ± 694 U/l (MD 1196, 95% CI: 295, 2097, p = 0.012) in the fracture and control group, respectively. These factors had significant differences.

Trends of serum Ca, P and ALP are shown in Fig. 1. ALP rose rapidly just before the fracture was found. Serum Ca, P and ALP fluctuated during the first 2 months, and the data was analyzed after day 56 (Table 2). In addition to the minimum levels of Ca and P, and the maximum of ALP, we found significant differences in the maximum of Ca and P, and the minimum of ALP.

Trends of urine-Ca/urine-Cr and %TRP are also shown in Fig. 1. The urine-Ca/urine-Cr appeared to be slightly high and the %TRP slightly low. However, as we did not have enough data for each infant, we could not conclude if the urine-Ca/urine-Cr was high or the %TRP was low in the fracture group.

Multivariate logistic regression analysis was not performed due to the small sample size of this study.

4. Discussion

In this study, we determined that low Ca, low P and high ALP were associated with bone fracture, especially after day 56. Trends of Ca and P showed that levels of Ca and P decreased after day 56, and that the difference in Ca and P levels increased between the fracture and control groups. Previous research has shown that peak ALP was higher in ELBWIs with rickets compared to the control, and that both the lowest Ca and P were not significant [1]. Another study found that serum P at 1–8 weeks was lower and ALP at 5–8 weeks was higher in the MBD groups, although no difference was observed for serum Ca [2]. It is possible that in the chronic phase, infants in the fracture group may have experienced low mineral absorption from the intestine and/or high mineral loss from stools and urine. As a result, bone resorption could no longer compensate for hypocalcemia and hypophosphatemia. As well, bones were likely to be of very low volume and increased fragility, increasing the risk for bone fracture.

Our findings showed that serum ALP rose rapidly in the days prior to the identification of a fracture. This increase may pinpoint the occurrence of the fracture, however, prior to this rise, ALP was already high in the fracture group. As cases of rickets generally have a higher level of ALP than that of control cases [1], this could indicate that bone formation was excessively stimulated in our sample.

We could not clarify if urine-Ca/urine-Cr was high and %TRP was low in the fracture group, even though serum Ca and P were low. Increased