International Journal of Advanced Community Medicine

E-ISSN: 2616-3594
P-ISSN: 2616-3586
https://www.comedjournal.com
IJACM 2024; 7(2): 95-100
Received: 22-01-2024
Accepted: 25-02-2024

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Osteopenia of prematurity among caffeine regimen receiving babies in medical city

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DOI: https://doi.org/10.33545/comed.2024.v7.i2b.315

Abstract
Background: Due to their early delivery, preterm newborns lack bone mineralization in the third trimester, causing osteopenia of prematurity (OP). These final weeks are crucial because 80% of bone mineralization occurs and intrauterine development is fast. Study goals: to assess the effects of coffee on osteopenia of prematurity (OOP) utilizing serum alkaline phosphatase (serum-ALP) levels and radiographic findings in the 4th week of life.
Method: This prospective cohort study took place in the NICUs of three hospitals within Medical City, Baghdad, targeting neonates under 32 weeks of gestational age (GA) and a birth weight under 1500 grams. These infants, treated with caffeine for Apnea of Prematurity (AOP) until they were 28 days old, were analyzed to explore the relationship between serum alkaline phosphatase (ALP) levels and neonatal outcomes related to Osteopenia of Prematurity (OOP). Participants were categorized into high and low ALP groups, with data collected on demographics, clinical characteristics, feeding practices, and medication use. The study aimed to identify key factors influencing bone health in premature infants.
Results: The study highlights significant associations between caffeine-treated preterm infants with osteopenia and higher incidences of Respiratory Distress Syndrome (RDS), poor weight gain, and prolonged hospital stays. Increased levels of alkaline phosphatase (ALP), phosphorus, and calcium were observed in these infants, alongside a greater prevalence of grade I and II osteopenia on post-treatment X-rays. These findings emphasize the potential risks associated with caffeine therapy in the bone health of preterm infants.
Conclusion: The study reveals significant links between osteopenia in caffeine-treated preterm infants and clinical factors such as Respiratory Distress Syndrome (RDS), poor weight gain, prolonged hospital stays, and interventions like Total Parenteral Nutrition (TPN) and steroids. Elevated levels of alkaline phosphatase (ALP) and phosphorus suggest caffeine's influence on bone metabolism, underscoring the intricate relationship between neonatal medical treatments and bone health outcomes.

Keywords: Osteopenia, prematurity, caffeine, babies

Introduction
Osteopenia of prematurity (OP) is a significant clinical concern that affects the bone health of preterm infants, who are deprived of crucial bone mineralization during the third trimester of pregnancy due to their early birth. This period is critical as approximately 80% of bone mineralization occurs during these final weeks, coinciding with a rapid phase of intrauterine growth [1]. Consequently, preterm infants, who miss this vital phase, are born with substantially lower bone mineral content (BMC) and bone mineral density (BMD), predisposing them to an increased risk of bone fragility and fractures later in life [2]. The adaptation of bone to extra-uterine life involves a physiological process that enhances bone resorption, which occurs more prominently and earlier in preterm infants compared to their term counterparts. This increased bone resorption is a key factor in the development of OP, rather than a decrease in bone formation [3]. The global incidence of preterm births is substantial, with nearly 10% of all infants born prematurely, translating to over 15 million babies born too early each year. Among these infants, the risk and severity of OP are inversely related to gestational age (GA) and birth weight (BW), highlighting the vulnerability of the smallest and earliest-born infants [4]. Preterm infants also demonstrate lower weight and Ponderal indices at the corrected age of term. Additionally, assessments using computerized tomography have shown that these infants possess reduced bone strength at the distal tibia and radius compared to age and sex-matched controls in adulthood [5].

Historical data from 1989 indicated that OP affected 55% of infants weighing less than 1000 grams at birth, and 23% of those under 1500 grams. The risk of developing OP was inversely correlated with GA and directly associated with the duration of parenteral nutrition, a common practice in the neonatal intensive care settings for these vulnerable infants [6]. Pathological fractures were reported in 30% of preterm infants with osteopenia, according to a study in 2009, emphasizing the clinical severity and the long-term implications of this condition [7]. In the neonatal context, caffeine is widely used in NICUs to manage apnea of prematurity due to its stimulatory effects on the respiratory center. It has a prolonged half-life in neonates, ranging from 72 to 96 hours, with a significant proportion excreted unchanged by the kidneys [8]. The metabolism of caffeine is influenced by GA, and gender differences have also been noted, with girls showing a higher metabolic rate than boys [9]. In preterm infants, the clearance of caffeine is considerably reduced, and its volume of distribution is larger compared to term infants, with the elimination rate increasing nonlinearly until about 6 weeks postnatal [10]. The relationship between caffeine and bone health has been explored in animal models, where caffeine has been shown to induce calciuria and create a negative calcium balance. This effect is particularly pronounced in preterm rats and can lead to a compensatory increase in parathyroid hormone (PTH), which acts to normalize serum calcium levels at the expense of bone integrity [11]. Studies in mice and rats have demonstrated that caffeine can enhance osteoclastogenesis from bone marrow hematopoietic cells and increase bone resorption activity, leading to a significant reduction in BMD and calcium content in bones [12]. Aims of the study: to evaluate the effect of caffeine regimen on the development of osteopenia of prematurity (OOP), using serum alkaline phosphatase (serum-ALP) concentrations and radiological finding at the 4th week of life.

Method

This Cohort prospective study was conducted in the neonatal intensive care units (NICUs) of Baghdad Teaching Hospital, Nursing Home Hospital, and Children Welfare Teaching Hospital, all located within Medical City, Baghdad. The study population comprised neonates with a gestational age (GA) of less than 32 weeks and a birth weight of less than 1500 grams. These infants were admitted to the NICU and received caffeine therapy for Apnea of Prematurity (AOP) until they were 28 days old. The study aimed to explore the relationship between serum alkaline phosphatase (ALP) levels and various neonatal characteristics, treatment regimens, and risk factors associated with Osteopenia of Prematurity (OOP). Participants were stratified into two groups based on their serum ALP levels-high and low ALP groups. The data collected included neonatal characteristics such as gender, cause of admission, presence of Respiratory Distress Syndrome (RDS), metrics for weight gain, length of stay in days, gestational age in weeks, parity, and birth weight. Information regarding the type of feeding received (breastfeeding plus fortifier, premature formula, or mixed feeding) and medication exposure (total parenteral nutrition, steroids, phenobarbital, diuretics, and calcium and vitamin D supplementation) was also gathered for each group.

Inclusion criteria

- Neonates with a gestational age of less than 32 weeks and a birth weight under 1500 grams.
- Admittance to NICU and receiving caffeine therapy until 28 days of life for the treatment of Apnea of Prematurity.

Exclusion criteria

1. Neonates with congenital defects affecting the endocrine system, renal system, or bone mineralization/formation.
2. Neonates who died before reaching 4 weeks of age.

This approach allowed for a comprehensive evaluation of the factors influencing the development of osteopenia in preterm infants, particularly focusing on the impact of prolonged caffeine therapy and associated clinical practices in the NICU setting. Data for the study were analyzed using IBM SPSS Statistics version 29. Descriptive statistics such as frequency, percentage, mean, and standard deviation were used. Quantitative differences were assessed with the Student's t-test and Paired t-test, while qualitative differences were evaluated using the Pearson Chi-square test or Fisher Exact test as appropriate. A p-value of ≤ 0.05 was considered statistically significant. Ethical Considerations: Prior to data collection, official approvals were obtained from the Arabic Council of Medical Specialty, as well as from the Children Welfare Teaching Hospital, Nursing Home Hospital, and Baghdad Teaching Hospital within Baghdad Medical City. Verbal consent was secured from each participating caregiver following a comprehensive explanation of the study's aims and objectives. Participants were assured of data confidentiality, with questionnaires completed anonymously.

Results

As shown in table 1, there is significant association between osteopenia with caffeine and RDS, 78.4% of babies with osteopenia with caffeine have RDS as cause of admission. Also there is significant association between osteopenia with caffeine and gaining weight; only 29.7% of baby with osteopenia with caffeine have gaining weight. There is significant association between osteopenia with caffeine and Length of stay; 32.5% of baby with osteopenia with caffeine have stay in hospital 35 weeks and more. No significant association between osteopenia with caffeine and (Gender, parity, weight and gestational age).

As shown in table 2, there is significant association between osteopenia with caffeine and TPN, only 32.4% of babies with osteopenia with caffeine have TPN. Also there is significant association between osteopenia with caffeine and steroid used; only 24.3% of baby with osteopenia with caffeine have steroid used. No significant association between osteopenia with caffeine and (feeding types, Phenobarbitone used, Diuretics used, Calcium used, vitamin D used).

As show in fig 1, there is significant increase in level of mean of ALP osteopenia with caffeine than with osteopenia without caffeine. There is significant increase in level of mean of phosphorus osteopenia with caffeine than with osteopenia without caffeine. There is significant increase in level of mean of calcium osteopenia with caffeine than with osteopenia without caffeine.

Table 1: Socio demographic data of the two-group study.

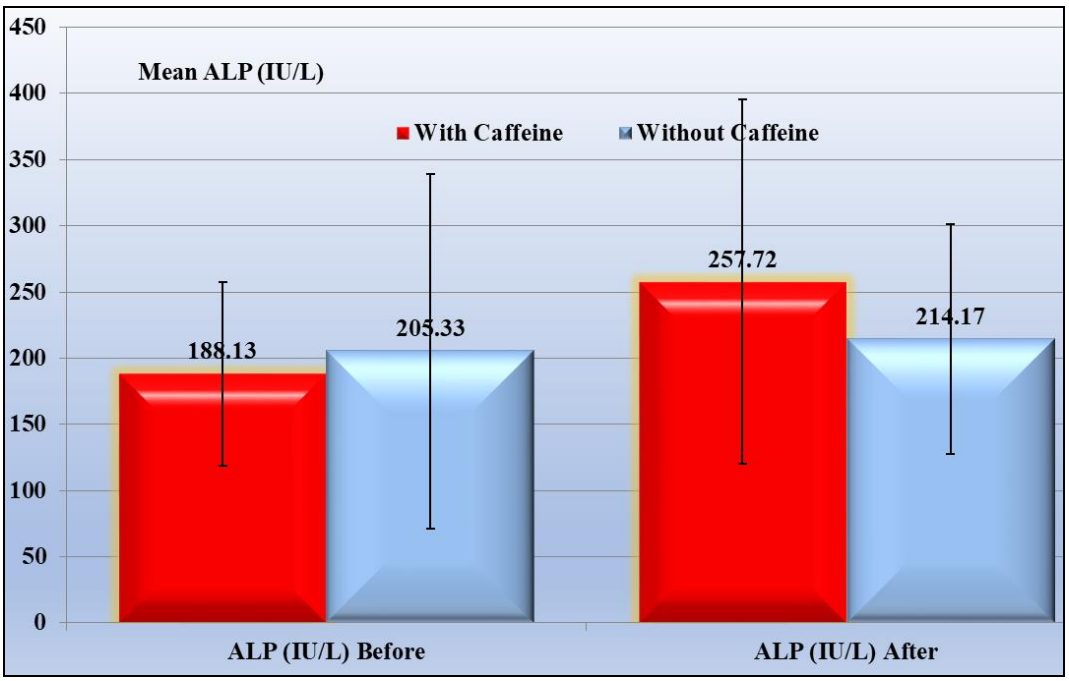
		Osteopenia With caffeine		Without caffeine		P value
		No	%	No	%	
Gender	Male	19	51.4	6	40.0	0.458
	Female	18	48.6	9	60.0	
Cause of admission						
RDS	Yes	29	78.4	7	46.7	0.025*
	No	8	21.6	8	53.3	
For gaining weight	Yes	11	29.7	9	60.0	0.042*
	No	26	70.3	6	40.0	
Length of stay (days)	14---	10	27.0	12	80.0	0.004*
	21---	9	24.3	2	13.3	
	28---	6	16.2	1	6.7	
	=>35weeks	12	32.5	-	-	
Gestational age (weeks)	<28weeks	2	5.4	-	-	0.475
	28---	9	24.3	4	26.7	
	30---	13	35.1	3	20.0	
	32---	13	35.1	8	53.3	
Parity	Low	20	54.1	7	46.7	0.526
	Middle	10	27.0	3	20.0	
	High	7	18.9	5	33.3	
Weight (Kg)	<1.0Kg	6	16.2	-	-	0.188
	1.0---	22	59.5	9	60.0	
	1.5---	9	24.3	6	40.0	

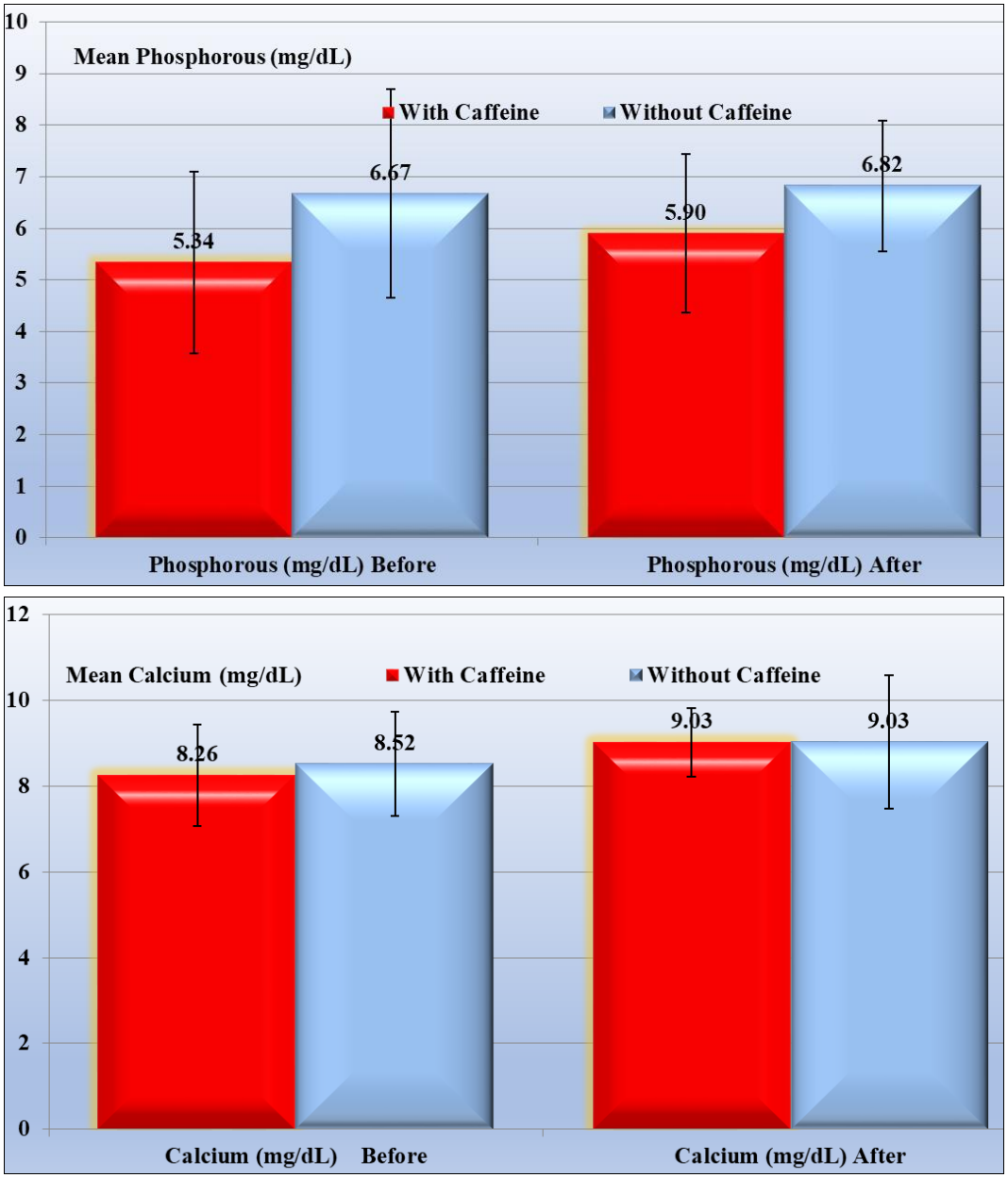
*Significant difference between percentages using Pearson Chi-square test (χ^2-test) at 0.05 level.

Table 2: Type of feeding and drugs in the two group study.

		With caffeine		Without caffeine		P value
		No	%	No	%	
Feeding	Breast feeding + Fortifier	9	24.3	2	13.3	0.646
	Premature formula	18	48.6	9	60.0	
	Mixed	10	27.0	4	26.7	
Total parenteral nutrition	Yes	12	32.4	-	-	0.012*
	No	25	67.6	15	100	
Steroids	Yes	9	24.3	-	-	0.036*
	No	28	75.7	15	100	
Phenobarbitone	Yes	4	10.8	-	-	0.185
	No	33	89.2	15	100	
Diuretics	Yes	2	5.4	-	-	0.358
	No	35	94.6	15	100	
Calcium	Yes	-	-	-	-	-
	No	37	100	15	100	
Vit D	Yes	29	78.4	13	86.7	0.492
	No	8	21.6	2	13.3	

*Significant difference between percentages using Pearson Chi-square test (χ^2-test) at 0.05 level.





Graph 1: Distribution of the two studied groups according to serum alkaline phosphatase (ALK), phosphorus, calcium levels before and after two weeks of caffeine supplementation.

As shown in table 3, there is significant increase in level of ALP and phosphorus dose (<200 mg/kg/d, 200-300 and ≥ 300 mg/kg/d), after caffeine regimen. But no significant difference in mean calcium before and after caffeine regimen.

Table 3: Caffeine cumulative dose with changes in serum levels of alkaline phosphatase, phosphorus, and calcium before and after caffeine regimen.

	Caffeine cumulative (mg/Kg/day)		
	<200 mg/Kg/d	**200---mg/Kg/d**	**≥300 mg/Kg/d**
ALP (IU/L) before	184.22±80.64 (104-371.5)	199.32±70.29 (114.9-371.4)	177.56±54.46 (104-274)
After	279.92±184.39 (104-808.1)	276.81±122.64 (104-425)	202.14±63.43 (104-311)
P value	0.002^	0.041^	0.020^
Phosph.(mg/dL) Before	5.16±1.65 (2.1-8.2)	6.09±1.52 (3.3-9.0)	4.53±1.94 (2.1-8.23)
After	6.32±1.73 (3.7-9.2)	6.07±1.38 (3.28-9.2)	5.13±1.33 (3.28-7.46)
P value	0.0001^	0.035^	0.011^
Cal. (mg/dL) Before	8.72±0.96 (7.27-10.24)	8.23±1.23 (5.4-10.12)	7.73±1.24 (6.5-10.07)
After	9.00±0.75 (7.8-10.14)	9.42±0.73 (8.6-11.3)	8.53±0.74 (7.3-9.7)
P value	0.074	0.325	0.148

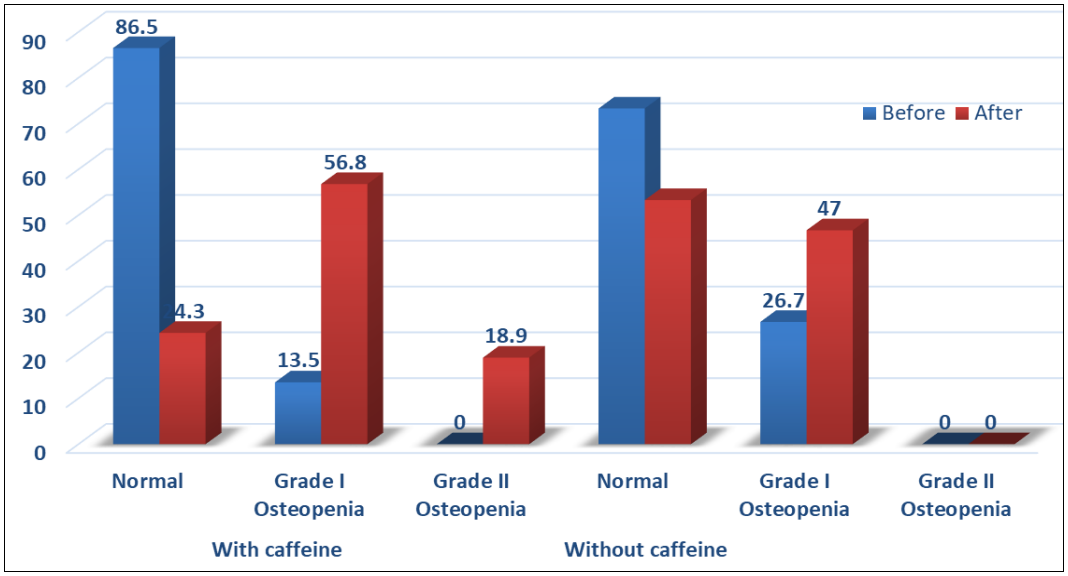
^significant difference between two dependant means using paired -t-test at 0.05 level.

As shown in table 4 and fig 2, there is significant association between x-ray after and osteopenia grade I, II in patients with caffeine regimen. 56.8% of patients have grade I osteopenia after X-ray with caffeine used increase more than in patients without caffeine used.

Table 4: Grades of osteopenia in x-ray in the two-group study before and after caffeine regimen.

		X-ray before			x-ray after			P value
		Osteopenia			Osteopenia			
		Grade 0	Grade I	Grade II	Grade 0	Grade I	Grade II	
With caffeine	No.	32	5	-	9	21	7	0.0001*
	%	86.5	13.5	-	24.3	56.8	18.9	
Without caffeine	No.	11	4	-	8	7	-	0.257
	%	73.3	26.7	-	53.3	46.7	-	

*Significant difference between percentages using Pearson Chi-square test (χ^2-test) at 0.05 level.



Graph 2: Grades of osteopenia in x-ray finding in the two-group study before and after caffeine regimen.

Discussion

The findings of this study illuminate the intricate relationships between osteopenia of prematurity and various clinical parameters in neonates treated with caffeine for Apnea of Prematurity (AOP). A striking 78.4% of infants with osteopenia who received caffeine therapy were admitted due to Respiratory Distress Syndrome (RDS), indicating a significant association between osteopenia and RDS in this cohort. This relationship suggests that the severity of RDS or its treatment may influence bone health, potentially due to prolonged periods of immobility or interventions that affect mineral metabolism [13]. In terms of growth parameters, only 29.7% of the infants with osteopenia and caffeine treatment demonstrated weight gain, underscoring a significant link between compromised bone health and poor weight gain. This finding suggests that osteopenia may either contribute to or result from inadequate nutritional intake or absorption, which is critical in the early life of preterm infants [14]. This underscores the necessity of monitoring growth and nutritional status in these infants to prevent or manage osteopenia. The study also revealed a significant association between prolonged hospital stays and osteopenia, with 32.5% of affected infants staying in the hospital for 35 weeks or more. This association likely reflects the complexity and severity of their conditions, requiring extended medical care and potentially contributing to osteopenia development through prolonged periods of minimal physical activity and ongoing medical interventions [15]. Interestingly, no significant associations were found between osteopenia with caffeine treatment and variables such as gender, parity, birth weight, and gestational age. This finding suggests that postnatal factors might be more influential in the development of osteopenia in this context than intrinsic prenatal factors [16]. Treatment-related factors also showed significant correlations, with only 32.4% of babies with osteopenia receiving total parenteral nutrition (TPN), and 24.3% treated with steroids. The use of TPN, which is crucial, can lead to deficiencies or imbalances in essential nutrients necessary for bone health, indicating a potential area for intervention. Moreover, the association with steroid use, which is known to adversely affect bone metabolism, supports this idea [17, 18]. Biochemical results demonstrated increased levels of alkaline phosphatase (ALP), phosphorus, and calcium in infants with osteopenia who received caffeine compared to those without, highlighting the metabolic impact of caffeine in this population. The known effects of caffeine on calcium metabolism could exacerbate or reveal underlying issues in bone turnover and mineralization in preterm infants [19]. Finally, radiological outcomes with a higher incidence of grade I and II osteopenia in patients under caffeine treatment post-X-ray analysis emphasize the clinical relevance of these findings. This suggests that caffeine might play a role in the progression or exacerbation of osteopenia, necessitating careful consideration of its use in the management of AOP in preterm infants [20]. Collectively, these results contribute to the growing understanding of osteopenia of prematurity, highlighting the multifactorial nature of bone health in preterm infants and identifying potential areas for targeted interventions to mitigate the risks associated with prolonged caffeine use and other related clinical practices. Further studies are needed to explore these associations and develop optimized care protocols that balance the benefits of caffeine in managing AOP with its potential risks to bone integrity [21].

Conclusion

The study indicates a significant correlation between osteopenia and various clinical interventions and outcomes in preterm infants treated with caffeine. Notably, osteopenia is strongly associated with Respiratory Distress Syndrome (RDS), inadequate weight gain, and extended hospital stays.

Additionally, significant associations were found between osteopenia and treatments like Total Parenteral Nutrition (TPN) and steroid usage. Biochemical analyses revealed elevated levels of alkaline phosphatase (ALP) and phosphorus in infants with osteopenia who received caffeine, suggesting that caffeine may influence bone metabolism and health in preterm infants. These findings highlight the complex interactions between neonatal medical interventions and bone health outcomes.

Conflict of Interest
Not available

Financial Support
Not available

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How to Cite This Article
Hussein AMZ, Ali BM, Al-Dayyeni HST Osteopenia of prematurity among caffeine regimen receiving babies in medical city. International Journal of Advanced Community Medicine. 2024; 7(2): 95-100.