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IS CAFFEINE A RISK FACTOR FOR METABOLIC BONE DISEASE IN PRETERM NEONATES: AN PROSPECTIVE OBSERVATIONAL STUDY

Paediatrics

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ABSTRACT

Background: Caffeine is the most commonly consumed pharmacologically active compound in the world. In the neonatal intensive care units (NICU), it is one of the most commonly prescribed drugs to treat Apnea of prematurity. Caffeine, the most commonly used medication in Neonatal Intensive Care Units, has calciuric and osteoclastogenic effects. **Aims And Objectives:** Our study aims to determine the association between duration of therapy of caffeine and metabolic bone disease in less than 34 weeks of gestation . **Inclusion Criteria:** All preterm babies(< 34 weeks) **Exclusion Criteria:** Neonates with major congenital anomalies and congenital bone diseases, babies >34 weeks. **Methods:** To determine the association between the duration of therapy of caffeine and metabolic bone disease, a prospective observational study was conducted including premature neonates less than 34 weeks . Metabolic Bone Disease was evaluated by using Biochemical parameters like calcium ,phosphorous ,ALP, calcium : creatinine ratio at 4 weeks of postnatal period . **Results:** The prospective observational study included 35 infants. 5.7 % had metabolic bone disease. caffeine therapy showed a association with metabolic bone disease. **Conclusion:** The duration of therapy of caffeine associated with metabolic bone disease and lesser the gestational age ,requirement of caffeine for longer duration in this group of study and . Future studies are needed to confirm these findings and determine the lowest dose of caffeine needed to treat effectively apnea of prematurity.

KEYWORDS

Premature infants, Metabolic bone disease, Caffeine

INTRODUCTION AND REVIEW OF LITERATURE :

Metabolic bone disease of prematurity is a multifactorial condition characterized by a reduction in bone mineral density involving chiefly nutritional but also biochemical and hormonal factors. This is a relatively common complication among preterm infants, especially in those born before completing 28 weeks of gestation or those with extremely low birth weight (<1000 gms).These infants are prematurely deprived of calcium and phosphorus.Exact incidence of metabolic bone disease is unknown but it has estimated to effect approximately 23% of VLBW (<1500 gms)and 55% of ELBW (<1000 gms).Risk factors are prematurity, low birth weight, prolonged use of parenteral nutrition, lack of mechanical stimulation, certain drugs like diuretics and corticosteroids, caffeine, immobilization. Since much of the calcium and phosphorous accretion in utero happens during the Third trimester, preterm infants are often deprived of these elements that are needed for optimal bone health.

Caffeine is the most commonly consumed pharmacologically active compound in the world [2]. In the neonatal intensive care units (NICU), it is one of the most commonly prescribed drugs to treat Apnea of prematurity [3]. The half-life in neonates is 72–96 h (range: 40–230 hrs) and the time to peak serum concentration after oral administration ranges from 30 min to 2 h, whereas 86% of caffeine is excreted unchanged in urine [4]. The liver enzymes responsible for caffeine metabolism mature progressively with increasing Gestational age.

For treating Apnea of prematurity the recommended loading dose of caffeine citrate is 20 mg/kg, followed by a maintenance dose of 5 to 10 mg/kg/day [1]. In addition, caffeine increases minute ventilation, improves carbon dioxide sensitivity, and prevents diaphragmatic fatigue by enhancing its activity [2]. Caffeine therapy for Apnea of prematurity has also been shown to reduce the rate of bronchopulmonary dysplasia and improves the rate of survival of very low birth weight (VLBW) infants without neurodevelopmental disability at 18–21 months [3, 4].

METHODS :

This study was conducted at Rajarajeswari Medical College and hospital ,neonatal intensive care unit in Department of Paediatrics ,Banglore, Karnataka .

STUDY DESIGN AND SUBJECTS :

The study was prospective observational study in less 34 weeks of gestation preterm infants admitted to NICU to Rajarajeswari Medical and hospital -a teritary care hospital 35 preterm neonates less than 34 weeks were included in the study weeks of gestation and excludes who are having major congenital anamolies ,congenital bone diseases ,babies more than 34 weeks and parents of neonates not given consent.

METHODOLOGY AND STATISTICAL ANALYSIS:

Method of Collection of Data Cases was selected based on inclusion criteria and exclusion criteria Detailed clinical examination and physical findings will be recorded on pre designed proforma after taking informed consent.

Procedure: All eligible neonates were consecutively enrolled in the study after taking informed consent from the parents. Baseline demographics including maternal history in detail including antenatal steroids taken during pregnancy and gestational age ,birth weight ,small for gestational age, gender and perinatal characteristics including place of delivery ,mode of delivery .APGAR score at 1 and 5 ,babies requiring CPAP and ventilation ,time of initiation of feeds and time to reach full feeds and duration of caffeine ,comorbidities were collected .Birth weight was recorded by digital weighing machine .Gestational age assessed by LMP ,first trimester ultrasound and by modified new ballard scoring . Around 4 weeks of life 1 ml of Blood was collected in micro vacutainer under aseptic conditions and following investigations were done – serum Calcium, serum phosphorus, serum Alkaline phosphatase ,urine calcium : creatinine ratio. Urine sample is collected in urobag . Serum calcium and phosphorous is processed in Beckman coulter au480 . Serum alkaline phosphatase is processed by International federation of clinical chemistry. . All data was examined and entered in to Microsoft excel worksheet. Descriptive and inferential statistics was used as required .The data was analysed using Microsoft excel and SPSS (statistical package for social sciences) software.

RESULTS :

Table 1: Correlation Of Lab. Parameters With MBD

MBD		CA	P	ALP	URINE CA:CREATININE RATIO
No	Mean	9.600	4.727	351.82	.6906
	N	33	33	33	33
	Std. Deviation	.9814	.4913	154.380	.24043

Yes	Mean	8.250	3.900	466.50	.1450
	N	2	2	2	2
	Std. Deviation	.0707	.1414	14.849	.00707
Total	Mean	9.523	4.680	358.37	.6594
	N	35	35	35	35
	Std. Deviation	1.0038	.5155	152.208	.26630
P value		0.041	5.498	1.073	10.014

In present study cases with MBD had lower levels of calcium. Phosphorous, ALP and urinary calcium : creatinine ratio is with in the normal values.

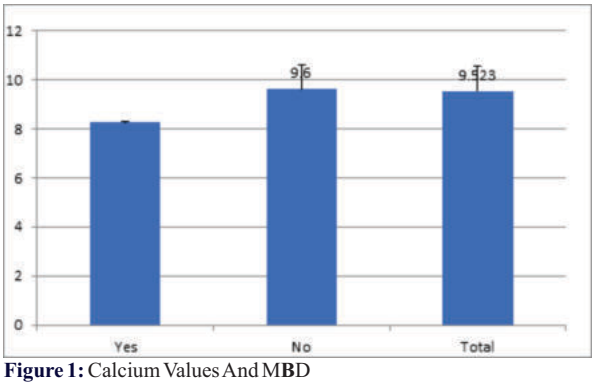

Figure 1: Calcium Values And MBD

Table 2 : Distribution Of Study Participants On MBD Incidence:

MBD	Frequency	Percent
YES	2	5.7
NO	33	94.3

In our study out of 35 neonates 2 neonates has metabolic bone disease based on the laboratory parameters .The incidence of Metabolic Bone Disease is 5.7% in our study group.

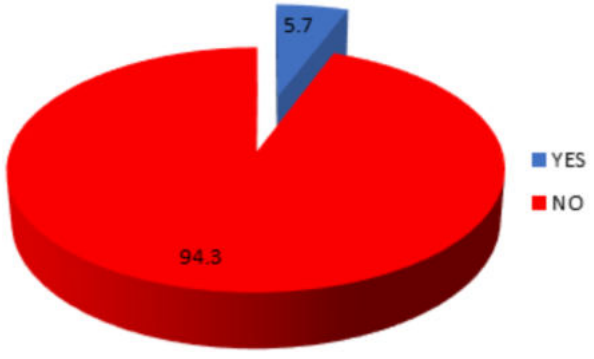

Figure 2: Distribution Of Study Participants On MBD Prevalence:

Table 3 : MBD With History Of Caffeine Usage

MBD		CAFFEINE
YES	MEAN	37.50
	N	2
	S. D	10.607
NO	MEAN	15.79
	N	29
	S. D	10.269
Total	MEAN	17.19
	N	31
	S. D	11.470
P VALUE		0.007

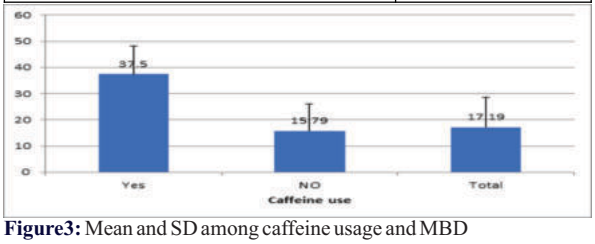

Figure3: Mean and SD among caffeine usage and MBD

Out of 35 neonates , neonates with MBD , Caffeine usage with mean duration of 37.5 days when compared to others without MBD with mean duration of 15.79 days. These differences in values are statistically significant.

Table 4 : Correlation Between Caffine And Gestational Age

GESTATIONAL AGE	CAFFEINE N	MEAN	STD. DEVIATION	P VALUE
< 28 weeks	5	28.20	15.959	0.004
28-32 weeks	19	15.33	7.063	
32-34 weeks	11	11.00	2.726	
Total	35	16.29	9.778	

The mean duration of caffeine usage was higher among neonates who were born less than 28 weeks compared to neonates who were born between 28-32 weeks and 32-34 weeks. This difference was found to be statistically significant.

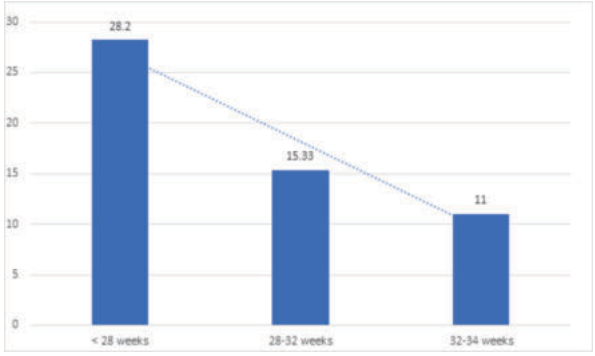

Figure -4 Mean And Sd Among Caffine And Gestational Age :

DISCUSSION:

Although the overall survival of extreme low birth weight infants has improved over the past 2 decades, these infants continue to have significant comorbidities. The incidence of metabolic bone disease in our study is reduced compared to other studies but metabolic bone disease remains a significant comorbidity in extreme low birth weight infants and puts them at increased risk for spontaneous fractures during the NICU stay. Our results are consistent with this concept, the younger and smaller the babies, the higher the incidence of metabolic bone disease. The results of this study revealed a association between caffeine treatment and the presence of metabolic bone disease. Despite caffeine's effect on treating apnea of prematurity with favorable long-term outcomes [16]. The results show that the adverse effect of caffeine is more evident in lower gestational age infants, which may be explained by the prolonged half-life of caffeine in their bodies due to diminished kidney abilities to eliminate the caffeine. Furthermore, extreme preterm infants have immature liver enzymes and are unable to catabolize caffeine leading to a prolonged effect causing calciuria and osteoclastogenesis [7, 19].

In other studies like Ebtihal Ali1 study there was a strong association between caffeine duration and dose and metabolic bone disease.

In our study we found that lesser the gestational age of the neonate ,the requirement of caffeine duration is more . Although Backström et al. suggested that serum phosphate levels lower than 1.8 mmol/L (5.5 mg/dl) may have a diagnostic sensitivity of 100% and specificity of 70% for metabolic bone disease [23], in our study, serum phosphate did not show a statistically significant correlation with metabolic bone disease.

CONCLUSION :

We conclude that caffeine has association with metabolic bone disease. Therefore despite the beneficial effect of caffeine on treating apnea of prematurity ,caffeine has its osteoclastogenic effects on bone mineral density . The effects of caffeine are more evident in less than 28 weeks gestational age neonates . The limitation of the study is the small sample size and done in a single centre .

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