# Comparing the Effect of Caffeine and Aminophylline on the Osteopenia of Prematurity in Neonates

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## ABSTRACT

**BACKGROUND:** Methylxanthines produce renal effects such as diuresis and natriuresis. Premature neonates have increased urinary calcium excretion following treatment with methylxanthines for apnea. We compared the effect of two commonly used methylxanthines, caffeine and aminophylline, in the development of osteopenia of prematurity and phosphorus and alkaline phosphatase levels.

**METHODS:** In a randomized clinical trial, 125 preterm infants with gestation age 32 weeks or less and birth weight less than 1500 grams with an indication for methyxanthine therapy were enrolled in the study. Group A (N=60) received aminophylline and group C (N=65) received caffeine. These drugs were started from the second day of birth until neonate was apnea free for 1 week or reached corrected gestation age of 34 weeks. Serum phosphorus and alkaline phosphatase levels were measured at 45 days of life as surrogate biomarkers for the osteopenia of prematurity.

**RESULTS:** The mean gestation age and birth weight were 28.7±1.8 weeks and 1090±144 grams in group A and 28.7±2.0 weeks and 1042±170 grams in group C (P>0.05). Osteopenia of prematurity was diagnosed in 65 neonates (52%) of which 29 neonates (48.3%) were in aminophylline group and 36 patients (55.3%) in caffeine group (P=0.27). Bronchopulmonary dysplasia was detected in 53 neonates (42%) of which 21 (35%) were in group A and 32 (49.2%) were in group C (P= 0.07).

**CONCLUSION:** In our study, aminophylline and caffeine were similar with respect to the risk of osteopenia of prematurity in preterm infants.

Keywords: Premature Infant; Methylxanthine; Aminophylline; Caffeine; Osteopenia of Prematurity

## INTRODUCTION

Methylxanthines (such as caffeine and aminophylline) are among the most commonly used drugs in the neonatal intensive care units (NICU) [1]. The most frequent indication for methylxanthine prescription is for the treatment of apnea of prematurity and to facilitate extubation [2]. Methylxanthines increase central inspiratory drive, increase minute ventilation, improve $CO_2$ sensitivity, enhance diaphragmatic activity and prevent diaphragmatic fatigue. These drugs have some well-defined acute adverse effects including tachycardia, cardiac dysrhythmia, feeding intolerance and seizure. Methylxanthines produce renal effects such as diuresis and natriuresis [3, 4]. Caffeine induced diuresis increases calcium loss [5, 6]. Caffeine induced urinary calcium loss is due to a reduction in renal reabsorption without significant effect on creatinine clearance [7].

Caffeine consumption is associated with low bone mineral density and high fracture risk in post-menopausal women, likely due to increase urinary and intestinal calcium excretion [6-8]. With methyxanthines therapy, diuresis and

urinary loss of sodium and calcium have been reported in neonates [4, 9, 10]. For example, a 10-fold urinary calcium excretion in ten premature neonates following 5 days of caffeine was reported by Zanardo [9].

The urinary loss of calcium can contribute to the development of osteopenia of prematurity (metabolic bone disease) in preterm infants [11]. Osteopenia of prematurity is a significant decrease in bone mineral content in an infant compared to that seen in the normal fetal skeleton [12]. The incidence of osteopenia of prematurity in very low birth weight infants (VLBW; i.e., less than 1500 g) is 30-55% [13, 14]. Serum alkaline phosphatase activity, serum phosphorus and calcium have traditionally been used to screen for metabolic bone disease in preterm infants. Alkaline phosphatase levels greater than five times the reference value for normal adults have been used in clinical practice as biochemical indicator of metabolic bone disease in preterm infants [15]. Serum calcium can have normal or low levels, serum phosphorus is low and alkaline phosphatase increased [15, 16]. Metabolic bone disease may be secondary to loss of calcium, or inadequate supplementation of essential vitamins or minerals.

The main risk factor for development of osteopenia of prematurity include preterm labor, prolonged (>3-4 weeks) use of parenteral nutrition, immobilization, and medication use (e.g. corticosteroids, loop diuretics, methyxanthines and antiepileptics) [12]. Despite widespread use of methylxanthines, considerable uncertainty exists regarding their role in the development of osteopenia of prematurity. This study was conducted to compare the effect of two commonly used methylxanthines, caffeine and aminophylline, in the development of osteopenia of prematurity through measuring surrogate markers of bone metabolism (serum calcium, phosphorus and alkaline phosphatase).

## METHODS

This was a randomized controlled clinical trial conducted from 1 March 2013 to 30 March 2014 in a tertiary care teaching hospital. Ethics committee of Tabriz University of Medical Sciences approved the study. Preterm newborn infants with gestation age 32 weeks or less and birth weight less than 1500gm were enrolled in the study. Preterm infants with neuromuscular disorders, neonatal cholestasis, patients who were exposed to prenatal or postnatal phenobarbital or corticosteroids, and infants with Apgar score less than 4 at 5 minutes of birth were excluded from the study. Written informed consent was obtained from parents. One hundred fifty one patients met the inclusion criteria. The enrolled preterm infants admitted to the NICU who needed methylxanthines for treatment or prevention of apnea or to facilitate weaning from respiratory support were randomly allocated into two groups. Neonates in group A received loading dose of aminophylline 5 mg/kg followed by maintenance dose of 1-2 mg/kg every 8 hours. Group C received loading dose of caffeine citrate 20 mg/kg intravenously followed by 10 mg/kg daily maintenance dose. Patients were followed till 45 days of life for evidence of osteopenia of prematurity by measurement of serum concentration of calcium, phosphorus and alkaline phosphatase. We considered the diagnosis of osteopenia of prematurity when serum phosphorus was 5 mg/dl or less and alkaline phosphate above 900 IU/ L. Wrist radiograph was obtained at the same time from all enrolled infants and reported by a pediatric radiologist who was blinded to laboratory tests and patients' group. Radiographs were classified using Koo scoring method; grade 0 to infants with normal bone, grade 1 to those with mineral rarefaction, grade 2 to those with fraying and cupping of the metaphysis and grade 3 to infants who had fractures [17].

Bronchopulmonary dysplasia was defined as requiring supplemental oxygen therapy beyond 28 days of life and categorized as mild when oxygen therapy was discontinued before 36 weeks corrected gestation age and moderate or severe as continued need for oxygen beyond 36 weeks. A nurse, who was not involved in the management plan of patient, completed the questionnaire. During parenteral nutrition, calcium, phosphate and multivitamins with trace minerals were added to parenteral nutrition appropriately. Breast milk feeding is routine in our hospital and it is fortified when the feeding volume reaches 100-120 ml/kg/day.

Statistical analyses were performed using the statistical package for social sciences version 15.0 (SPSS, Chicago. IL, USA). Quantitative data were presented as mean ± standard deviation (SD) and qualitative data as frequency and percent. Independent t- test was used for testing continuous scale data and chi square or Fisher exact test for categorical data. A *p. value* less than 0.05 was considered statistically significant.

## RESULTS

A total of 151 preterm infants were enrolled during the study period. Twenty six infants were excluded because of death or discharge at < 4 weeks of life. Finally, 125 preterm infants completed the study; 60 neonates in group A and 65 neonates in group C; total of 68 (54.4%) boys and 57 (45.6%) girls. The mean gestation age of studied patients was 28.7±1.9 weeks and birth weight was 1065±159 grams (Table 1).

Maternal risk factors for preterm labor were determined in 51 cases (40.8%) including maternal hypertension and eclampsia in 30 patients (58.8%), placenta previa in 4 mothers (7.8%) and maternal diabetes in 2 cases (3.9%).

Most (74 cases (59.2%)) neonates were nourished by fortified breast milk, 24 neonates (19.2%) by preterm formula and 36 neonates (28.8%) received both fortified breast milk and preterm formula. Osteopenia of prematurity was diagnosed in 65 neonates (52%); 29 (48.3%) were in aminophylline group and 36 (55.3%) in caffeine group, $p$=0.27. Bronchopulmonary dysplasia was detected in 53 neonates (42%); 21 (35%) were in aminophylline group and 32 (49.2%) in caffeine group, $p$= 0.07. The mean duration of oxygen supplementation was 16.8± 2.5 in aminophylline group and 16.9±2.8 in caffeine group, $p$=0.98. The mean concentrations of biochemical markers of osteopenia of prematurity are shown in table 2. Radiographic evaluation showed osteopenia in 50 neonates (40%), that it was stage 2 in 20 neonates and none had fracture. The mean alkaline phosphatase levels in patients with radiologic evidence of osteopenia of prematurity were 1421.3±401.4 IU/L and in neonates without radiologic findings it was 979.2±471.8 IU/L, $p$<0.001. The mean serum phosphorous levels were significantly lower in neonates with radiographic findings (3.56±1.21 vs. 4.84 ±1.29 mg/dl, $p$<0.001). The mean duration of oxygen therapy was not different among neonates with or without radiographic findings (18.80± 2.94 vs. 15.63± 2.50 days, p=0.42.

## DISCUSSION

In our study, osteopenia of prematurity was present in 52% of the preterm infants. The incidence of osteopenia of prematurity varies among different studies, This may be due to variation in study design, population, or serum

**Table 1:** Demographic characteristics of patients

| | Aminophylline group (n=60) | Caffeine group (n=65) | P value |
|---|---|---|---|
| Gestation age, weeks | 28.72±1.85 | 28.71±2.03 | 0.98 |
| Birth weight, gr | 1090±144 | 1042±170 | 0.08 |
| Weight at 45 days, gr | 1579±417 | 1458±373 | 0.70 |
| Maternal age, years | 28.58±5.05 | 28.22±5.73 | 0.39 |
| gravidity | 1.64±0.92 | 1.80±1.07 | 0.32 |
| Apgar score<br>1 min<br>5 min | <br>6.68±1.73<br>7.86±1.40 | <br>6.38±1.73<br>8.20±1.10 | <br>0.13<br>0.09 |
| Age of breast milk feeding initiation | 4.78±2.51 | 4.62±2.57 | 0.72 |
| Age of full enteral feeding | 15.68±8.38 | 18.09±14.42 | 0.26 |

**Table 2:** Biomarkers of osteopenia of prematurity in two groups

| | Aminophylline group (n=60) | Caffeine group (n=65) | P value |
|---|---|---|---|
| Calcium, mg/dl | 9.26±0.63 | 9.32±0.77 | 0.63 |
| Phosphorus, mg/dl | 4.56±1.35 | 4.12±1.43 | 0.08 |
| Alkaline phosphatase , IU/L | 1133.62±541.74 | 1176.75±448.15 | 0.62 |
| Positive radiographic evaluation, n (%) | 23 (38.3) | 27 (41.5%) | 0.85 |

phosphorus and alkaline phosphatase concentration threshold used for detection of osteopenia of prematurity. The metabolic bone disease was reported in 50% of extremely low birth weight (ELBW) infants and fracture in 17% of them in the 1980s [18, 19]. In a study in Korea, metabolic bone diseases were detected in 43.9% of ELBW infants and 13% had fractures [19]. In one study, 18-23% of preterm neonates had elevated alkaline phosphatase and 4-10% had radiographic evidence for osteopenia of prematurity [20]. In a study in USA, 50% of neonates with birth weight (BW) less than 600 grams, 14% of neonate with BW 600-800 grams and at least 4% of infants with BW 800-1000 grams developed radiographic rickets. They had radiographic evaluation for osteopenia when infants had alkaline phosphatase higher than 800 IU/L, received total parenteral nutrition for more than 3-4 weeks or were clinically suspected to have osteopenia of prematurity [21]. Serum alkaline phosphatase activity, serum phosphorous and calcium have been used to screen for metabolic bone disease in preterm infants. Alkaline phosphatase >900 IU/L have a sensitivity 88% and specificity 71% to detect radiologic osteopenia of prematurity and along with a serum phosphorus concentration less than 5.5 mg/dl, can be used for screening of osteopenia of prematurity [22].

There are few studies to compare different doses of caffeine on alkaline phosphatase level and osteopenia of prematurity. In a retrospective descriptive study, 152 extremely low BW infants were enrolled in the study. Patients were divided into high and low dose caffeine groups based on the maximum daily dose of caffeine citrate received. There were no significant differences between groups in radiographic evidence of osteopenia of prematurity, fracture or median maximum alkaline phosphatase level [20].

In this study we compared the effect of caffeine and aminophylline in the development of osteopenia of prematurity. We have not found any significant difference in serum concentration of calcium, phosphorus or alkaline phosphatase between groups.

## CONCLUSION

In our study, the bronchopulmonary dysplsia and osteopenia of prematurity were found in neonates treated by aminophylline or caffeine without significant difference. There is no superiority among these two drugs with respect to osteopenia of prematurity in preterm infants.

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