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Annals of Pediatrics & Child Health

Research Article

Impacts of the Use of Caffeine Citrate on the Ponderal Evolution of Premature Newborn in the Neonatal Intensive Care Unit of a Philanthropic Hospital in Salvador-Bahia-Brasil

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Submitted: 19 October 2021

Accepted: 13 November 2021

Published: 18 November 2021

ISSN: 2373-9312

Keywords

- Caffeine citrate
- Apnea of prematurity
- Weight gain
- Premature neonates

Abstract

Introduction: Caffeine has been commonly used for the prevention and treatment of apnea-related symptoms in preterm infants. However, exposure to caffeine can influence weight gain in this population.

Objectives: To evaluate the weight evolution of preterm newborns (NB), up to 34 weeks using caffeine citrate in a neonatal intensive care unit (NICU) of a philanthropic hospital in Salvador-Bahia-Brazil.

Materials and Methods: This is a prospective longitudinal research with a descriptive character. The study evaluated the weight evolution of preterm infants up to 34 weeks exposed to caffeine citrate at doses ranging from 5mg/kg to 10mg/kg. Preterm infants with sepsis confirmed by blood culture and premature infants with congenital anomalies of the gastrointestinal tract were excluded from the study.

Preliminary Results: Premature infants who received a maintenance dose of caffeine >5mg/kg/day had a slight reduction in weight gain. The use of caffeine associated with other factors did not have a negative impact on caloric gain. Premature infants < 32 weeks using caffeine required a higher intake of calories.

Final Considerations: Caffeine contributes positively to the treatment of apnea in prematurity, but its catabolic effect can result in less weight gain in preterm infants.

ABBREVIATIONS

AP: Apnea of Prematurity; AMP: Adenosine 3,5-monophosphate; AMPC: Adenosine 3',5'-cyclic monophosphate; CAP: Caffeine test for apnea of prematurity; CNS: National Health Council; CPAP: Continuous Positive Airway Pressure; CYP1A2: Cytochrome P450 1A2; BPD: Bronchopulmonary dysplasia; FDA: Food and Drug Administration; FM: Diet fortifier; GABA: gamma-aminobutyric acid; GI: Gestational Age; IH: Nosocomial Infection; MBP: Very low weight; PaO2: O2 partial pressure in arterial blood; PCA: Arterial Canal Persistence; NB: Newborn; RN'S: Newborns; TFIC: Informed consent form; GFR: Glomerular filtration rate; NICU: Neonatal Intensive Care Unit; VM: Mechanical ventilation; VPP: Positive pressure ventilation; VPPI: Intermittent positive pressure

INTRODUCTION

Prematurity results from multifactorial and unpredictable circumstances in all social classes and locations, requiring a better understanding of perinatal causes and outcomes. Among other comorbidities, the relationship between preterm birth and low birth weight of the newborn (NB) is evident, in addition to the prognosis of growth deficit [1].

The boundaries of fetal and neonatal viability have been expanded and, increasingly, newborns with extremely low birth weight (birth weight less than 1000g), have survived. Scientific and technological progress aimed at surfactant replacement therapy, mechanical ventilation (MV) and standardized care for the needs of preterm infants in the delivery room has increased the survival of preterm infants, greatly reducing mortality rates

in the neonatal period. This has a cost, in view of the emergence of a greater number of complications and injuries resulting from prematurity itself, as well as the prolonged hospitalization time of these NB [2].

Apnea is one of the complications that can occur exclusively due to the infant's prematurity, affecting up to 85-100% of premature NBs, and is related to the lack of complete maturity of the organs. It manifests itself by interruptions 15 to 20 seconds, accompanied by bradycardia and oxygen desaturation, which can lead to hypoxia or death. Long periods of apnea can result in childhood cyanosis or bradycardia, and newborn resuscitation is necessary when cardiopulmonary arrest occurs. These episodes can damage the baby's developing brain and disrupt the functioning of the bowel and other organs. Recurrent and long intervals result in respiratory failure, making mechanical intubation and ventilation mandatory. Apnea and hypoxemia cause electroencephalographic abnormalities and leukomalacia, leading to behavioral and neurological difficulties [3].

Preterm infants with a gestational age (GA) less than 35 weeks should be monitored for apnea, due to its high prevalence in this group of patients [4]. Its frequency has an inverse correlation with gestational age; it occurs in 7% of neonates with a gestational age of 34 to 35 weeks, 15% of neonates with a gestational age of 32 to 33 weeks, 54% of neonates with a gestational age of 30 to 31 weeks and in almost 100% of neonates with a gestational age less than 29 weeks or weighing less than 1,000 g [5].

Caffeine citrate is currently one of the most prescribed drugs in neonatal units for the treatment of apnea of prematurity. It is the first choice among all methylxanthines due to its efficacy, better tolerability and higher therapeutic index, as well as longer half-life 6]. Although the use of methylxanthines has been present for over 40 years, it has gained greater acceptance in the last decade, where the efficacy, safety and tolerability of caffeine in premature babies has been proven. With wider use, it has become one of the drugs of choice for apnea among neonatologists worldwide [6].

In addition to playing an important role in the management of this pathology, other favorable effects of caffeine were identified, such as the prevention of bronchopulmonary dysplasia (BPD), retinopathy of prematurity, reduction of extubation failure, and are currently considered a neuroprotective factor. In summary, this drug reduces the risk of apnea by up to 25%, extubation failure (27%), and the incidence of bronchopulmonary dysplasia in 10% of patients [7].

Although caffeine has respiratory benefits for premature infants, it can have adverse molecular and cellular effects on the developing brain, with the possibility of altering baseline activity in terms of brain synchrony and sleep structure, reducing the period of quiet sleep, which causes somehow deduces an interference of the brain maturation process. Its effects on metabolic rate, diuretic action, hyperglycemic property and catabolic tendency may influence short-term growth, especially considering the current practice of prolonged postnatal caffeine therapy for apnea of prematurity [8]. The increase in oxygen consumption and energy expenditure leads to less weight gain. The effects of caffeine on growth, although small, seem only temporary [6].

The main focus of this research was to show that caffeine citrate can interfere with the weight gain of preterm infants. Considering that a maintenance dose above 5m/Kg can interfere with weight gain and that premature infants < 32 weeks using caffeine require a greater intake of calories, this work is relevant for the control of NB procedures. premature, especially in Neonatal Intensive Care Units (NICU). Thus, this study points to the introduction of new nutritional support measures for newborns using caffeine in the NICU, contributing to a favorable outcome in babies with very low birth weight.

MATERIALS AND METHODS

This is a longitudinal, prospective, descriptive and exploratory research. The collection was carried out from January to October 2020. 50 premature infants up to 34 weeks who were using caffeine at doses from 5mg/Kg to 10mg/Kg were analyzed.

The research was carried out in the Neonatal ICU of a Philanthropic hospital, Hospital Português da Bahia, located in the city of Salvador, Bahia, Brazil. The hospital has 20 beds dedicated to the care of newborns. The epidemiological profile of the unit (NICU) is divided into prematurity, respiratory distress, transient tachypnea, congenital syphilis and heart disease. From January to October 2020, 181 preterm babies were born < 37 weeks, of these 53 had a gestational age of 31 – 34 weeks (Appendix A Table).

Data collection

Data collected from electronic medical records included the following variables: diagnosis, laboratory tests, gestational age, weight, caloric rate, doses used, use of diet tonic (FM), use of NPT, use of multivitamin, use of medication, use of CPAP and orotracheal tube. Preterms with sepsis proven by blood culture and those with congenital anomalies of the gastrointestinal tract (GIT).

Weight evolution was measured based on the collected weights: birth weight, weight after the 7th day of life and weight on the last day of caffeine use. The other variables throughout the research were decisive to assess whether caffeine can influence the weight gain of neonates with GA up to 34 weeks. A spreadsheet was created, using Microsoft Excel, with all the variables used to assist in the preparation of the statistical analysis (Appendix B Table).

Ethical aspects

The research was approved by the Ethics Committee for Research with Human Beings (CEP), at Hospital Português da Bahia, under protocol number 163,000/2019. The data obtained were treated confidentially, without patient identification and without intervention by the researcher.

The data used were taken from the electronic medical record that is fed daily by the entire multidisciplinary team of the unit (doctors, nurses, pharmacist, psychologist, physiotherapist, speech therapist, nursing technician and nutritionist). This excluded the need to apply the Informed Consent Term (TCLE), which is in line with resolution 466/2012 and 506/2016, of the National Health Council (CNS).

Statistical analysis

The Epi-Info v.3.5.1 program (CDC/USA) was used for data analysis. Based on the degrees of prematurity, the NB's included in this series were stratified into four groups for comparative analysis: Two groups related to the degree of prematurity: group 1 (greater severity) and group 2 (less severe) and also 2 groups related to caffeine dose; group 1 (5 mg/kg) and group 2 (> 5mg/kg).

In the construction of tables, for categorical variables (gender and outcome, for example), absolute and relative frequencies were determined. For non-categorical variables (age at birth, birth weight, etc.) the median and interquartile ranges were calculated.

Statistical probability tests were used to assess statistical significance between groups. The Mantel-Haenszel chi-square or Fisher's exact test was used to assess the statistical significance of the findings between categorical variables; Mann-Whitney tests were used to compare continuous variables. For univariate analyses, the findings were considered to be of statistical significance when the p value was <0.05.

RESULTS AND DISCUSSION

The study included a sample of 50 premature infants with up to 34 weeks of gestational age, and who were using caffeine. Table 1 describes the general characteristics of the eligible population. The number of female preterm infants was prevalent (60%) in this study. According to Bairam et al. [9], in the scientific article "Sex-based differences in apnea of prematurity", the analysis of babies diagnosed with AP showed that the chances of being diagnosed were lower in men than in women (OR 0.95; P = 0.057) , but not significant.

PA reflects an immature respiratory system, and according to Bairam et al. [9], the maturation of the respiratory system of premature babies may be faster in women than in men. Newborns with GA up to 32 weeks were highlighted in this research, with 64% of the cases analyzed, since apnea of prematurity affects a greater number at this gestational age. The average weight in grams was around 1,277.5g. There were no deaths, 96% were discharged home. Table 2 shows the main interventions performed in premature infants included in this study.

About 86% of the newborns analyzed used a multivitamin and 16% were supplemented with iron. Vitamins are essential for bone growth, wound healing, vascular integrity, immune function, cell development and differentiation [10]. With regard to children, vitamin supplementation can be especially indicated: as an aid in deficiency anemia; on restrictive and inadequate diets; in chronic illnesses/convalescence; in periods of accelerated growth; for newborns, infants and growing children; for the prevention of rickets; as an aid to the immune system [11].

Enteral iron supplementation in preterm infants is recommended to provide enough iron for growth and development without increasing the risk of iron overload [12]. Table 01 shows the main drugs used by patients during the period of this study.

There were no records of drug interactions between caffeine citrate and the drugs used in the population surveyed, as consulted in Drug interactions (Up to Date, 2021).

Table 1: General characteristics of the birth of premature infants included in this study, admitted to Hospital Português, between January and October 2020 (*n*= 50).

Characteristics	Cases (%)
Sex (*n*=50)	
Female	30 (60%)
[1]**Age at birth (weeks) (n=50)**	30 (29-32)
Degree of prematurity (n=50)	
Extreme Preterm	5 (10,0)
Very preterm	32 (64,0)
Moderate preterm	7 (14,0)
late preterm	6 (12,0)
Birth weight, in grams[1]	1.277,5 (1.015-1.510)
Ending	
Home discharge	48 (96,0)
Transfer	2 (4,0)

Source: Own collection, 2021; [1]Median (interquartile range);

The lack of scientific evidence is one of the main problems involved in the use of medication among newborns, especially those in intensive care. The limited knowledge that exists about the development of pharmacokinetics, pharmacodynamics, and dose determination in neonates, combined with the paucity of clinical trials, can make selecting the right drug and establishing doses for the treatment of neonates a complex task. Almost all medications used in the NICU are administered intravenously and, depending on gestational age and birth weight, the most used group of medications are antibiotics, followed by medications for use in the respiratory and nervous system. In Brazil, medicines are authorized by the National Health Surveillance Agency (ANVISA), but there is no specific policy for registration of pediatric or neonatal medicines [13].

Regarding ventilatory support, the average number of days of use was 6.5/days (Table 2). Due to the time of use, it does not seem to have influenced the reduction in weight gain, despite the energy expenditure. Caffeine is the drug of choice to reduce apnea rates, need for intermittent positive pressure (IPPV), ventilatory support, extubation failure, and patent ductus arteriosus ligation (PCA) in preterm infants. Schmidt et al. [14], clearly demonstrated that treatment with caffeine, in the first 10 days of life, resulted in a reduction in each of the three levels of respiratory support, need for an endotracheal tube, in any positive pressure ventilation (PPV) and supplemental oxygen.

As for the route of administration, 58% of newborns in the survey received caffeine intravenously. According to Aranda [15], gastrointestinal absorption is rapid, both in neonates and adults, and in about 30 minutes its bioavailability is complete, regardless of the administration route (oral, tube or parenteral).

A high maintenance dose of caffeine appears to be more effective in promoting lung maturation in preterm infants, being safe for the treatment of apnea. However, administering large

Table 2: Main interventions performed in premature infants included in this study, admitted to Hospital Português, between January and October 2020 (n=50).

Characteristics	Cases (%)
Corticosteroid use	4 (8,0)
Use of multivitamin	43 (86,0)
Diuretic use	4 (8,0)
Use of zinc	4 (8,0)
Use of antimicrobials	24 (48,0)
Use of ventilation (CPAP)	46 (92,0)
Use of iron	16 (32,0)
Use of invasive ventilation (orotracheal tube)	17 (34,0)
Ventilation time, days[1]	6,5 (2-12)
Type of administration route (caffeine)	
Oral/probe	21 (42,0)
Intravenous	29 (58,0)
Days of use (caffeine)[1]	22,5 (13-42)
Administered dose (caffeine, mg/kg)	
5	21 (42,0)
>5	29 (58,0)
Caloric intake, median (Kcal/day) (n=45)	159 (143-176)
Daily caloric gain estimate (n=42)	18,86 (14,6-81)
Weight in grams after seven days (caffeine use)[1]	1.162,5 (970,5-1.380)
Weight in grams on the last day of use (caffeine)[1]	1.617 (1.480-2.055)
Use of diet tonic	30 (60,0)

Source: Own collection, 2021; [1]Median (interquartile range)

Table 3: Univariate analysis of variables collected from premature infants admitted to Hospital Português, between January and October 2020, stratified by degree of prematurity (n=50).

Characteristics	Group 1** (*n* = 37)	Group 2*** (*n* = 13)	Value *p*
Sex (*n* = 50)			
Female	19 (51,4)	11 (84,6)	**0,03***
Age at birth (weeks)[1]	30 (29-30)	33 (32-34)	**0,00001**
Birth weight, in grams[1]	1.140 (1.005-1.350)	1.635 (1.475-1.970)	**0,00001**
Days of use (caffeine)[1]	28 (18-44)	8 (7-13)	**0,001**
Administered dose (caffeine, mg/kg)[1]	8 (5-10)	5 (5-8)	0,08
Caloric intake, median (Kcal/day)[1] (n=45)	160 (147-176)	93,5 (84,5-153,5)	**0,035**
Daily estimate of caloric gain[1] (n=42)	19 (14,6-85)	18 (14-60)	0,6007
Weight in grams after seven days (caffeine use)[1]	1.110 (925-1.275)	1.490 (1.300-1.710)	**0,0005**
Weight in grams on the last day of use (caffeine)[1]	1.625 (1.460-2.055)	1.610 (1.535-1.925)	1,00

* Fischer's exact test, other variables: Kruskal-Wallis test
** Group 1: Infants with degrees of prematurity 1 or 2 (More severe);
*** Group 2: Infants with degrees of prematurity 3 or 4 (Moderate);1
Source: Own collection, 2021; Median (interquartile range);

maintenance doses may increase the risk of adverse reactions. such as electrolyte disturbance, hypertension, hyperglycemia, food intolerance and restlessness [16].

The average caloric gain in most patients was 18.8 g/day and the caloric intake was 159 kcal/day (Table 2). The nutritional goal for most premature infants during hospitalization is an energy intake of 120 Kcal/kg per day (Table 2). This equates to 160 mL/kg per day of preterm formula (24 Kcal) or fortified human milk. The target volume is usually one that supports a weight gain of more than 18 g/kg per day [17].

Of the 50 patients evaluated, regarding the degree of prematurity, most had GA< 32 weeks, group 1 (Table 3). Despite being a group at higher risk due to gestational age, there were no significant differences in weight gain when compared to the 32- to 34-week group, group 2. Despite the 2 groups being heterogeneous, some results were relevant. However, regarding weight, observing the P value, caffeine did not contribute negatively, as there was no significance value between the 2 groups.

Analyzing table 3, it was possible to see an extremely important data, with a degree of significance for this study, regarding caloric intake (p= 0.035), in which group 1 preterm

infants, due to their severity, needed a greater amount of calories to reach weight. According to Barfield [18], babies born very preterm (<32 weeks' gestation), are at increased risk of death, medical complications, and neurodevelopmental and metabolic sequelae. On the other hand, late preterm babies (born between 34 weeks up to 36 weeks and 6 days), represent the largest proportion of premature babies (about 75%).

Although studies initially focused on mortality and morbidity related to very preterm births, late preterm infants have also been the focus of attention. Therefore, they may have an increased risk of respiratory complications, infections, feeding problems, hypothermia and hypoglycemia. In addition, late preterm babies are at increased risk of morbidities of long term, such as neurodevelopmental delay, cerebral palsy, chronic respiratory or metabolic diseases [19].

In table 4, the sample was divided according to the dose of caffeine used, group 1 (5mg/Kg) and group 2 (> 5mg/Kg). Currently, caffeine is the first choice for the treatment of PA. However, the maintenance dose has not been standardized.

Several studies have examined the effectiveness of different doses of caffeine for maintenance therapy in preterm infants. Charles et al. [20], reported a substantially lower extubation failure rate in a high-dose maintenance group compared to a low-dose maintenance group (17% versus 49%, P< 0.05), as well as a significant reduction in the mean time on mechanical ventilation in the high-dose group (P < 0.01). However, Mohammed et al. [21], found that a high maintenance dose of caffeine citrate was more likely to cause adverse reactions such as tachycardia. Thus, although a higher maintenance dose can improve the clinical efficiency of PA, it can also increase the frequency of adverse reactions. At present, there is no definitive evidence from systematic reviews with or without meta-analysis to support which maintenance dose is superior considering both efficacy and safety [16].

There was statistical significance for caloric intake p=0.032, in which group 1 ingested more Kcal/day compared to group 2, due to the time of use. Although the estimate of caloric gain indicates that the higher dose of caffeine had a negative effect on the weight gain in group 2 (> 5mg/kg), there was no significant result. Weight (in grams) on the last day of use was higher in group 1 (5 mg/kg) although not significant. According to Philip [8], the use of caffeine in a short period of time has a reduction in weight compared to those who used it for a longer period of time; using it for many weeks with potential catabolic effects can affect the initial weight gain in this vulnerable population.

In their original publication, Schmidt et al. [22], observed greater initial weight loss for preterm infants treated with caffeine during the first 3 weeks of life and the trend was gradually reduced in the following weeks. In a more recent study, Ting et al. [23], stated that caffeine citrate promotes slow growth, impacting the weight of premature children, also in the first 3 weeks, increasing its mechanism and basic metabolism.

Caffeine slows down cerebral and intestinal blood flow, reduces short-term weight gain, and increases heart rate, nervousness, irritability and seizures. Caffeine has been reported to have adverse molecular and cellular effects on the developing brain, especially cerebellar injury, with subsequent changes in early motor performance due to high dosage or administration time [24].

An interesting and significant finding from this study was the confirmation that very premature babies (< 32 weeks), and with doses < 5mg/Kg, had a higher caloric intake of calories to reach the necessary weight gain (Tables 3 and 4), which did not happen with the group with a dose > 5mg/Kg, which, despite the intake being higher than recommended, was below that used in group 1 (Table 4). Therefore, the need for improvement in the caloric intake of neonates, with higher doses, using caffeine citrate is evident.

Although this study did not obtain greater significance regarding the reduction of weight gain in preterm infants, it showed, in several stages, similarities with other studies in the literature, especially with regard to the impact that caffeine citrate can have on the weight evolution of infants. newborns. This research is a pioneer in the field of pharmacy, where there is a lack of studies focused on neonatology and, therefore, more studies should be carried out with a focus on this approach.

Table 4: Univariate analysis - variables collected from premature infants admitted to Hospital Português, between January and October 2020, stratified by the dose of caffeine administered (n=50).

Characteristics	Group 1** (*n* = 29)	Group 2*** (*n* = 21)	Value of *p*
Sex (*n* = 50)	10 (34,5)	10 (47,6)	0,35
Female			
Age at birth (weeks)[1]	30 (29-31)	30 (30-33)	0,13
Birth weight, in grams[1]	1.285 (1.015-1.475)	1.260 (1.010-2.990)	0,99
Days of use (caffeine) [1]	28 (17-44)	18 (11-26)	0,07
Caloric intake, median (Kcal/day)[1] (n=45)	169,5 (148-181)	147 (107-167)	**0,032**
Daily estimate of caloric gain[1] (n=42)	19 (14,5-70)	18,7 (15,8-81)	0,77
Weight in grams after seven days (caffeine use)[1]	1.150 (915-1.380)	1.170 (975-1.330)	0,72
Weight in grams on the last day of use (caffeine)[1]	1.785 (1.500-2.125)	1.590 (1.425-2.650)	0,13

* Fischer's exact test, other variables: Kruskal-Wallis test
** Group 1: Babies with 5 mg/kg of caffeine administered;
***Group 2: Babies with 6 or more mg/kg of caffeine administered;
1Source: Own collection, 2021; Median (interquartile range);

CONCLUSION

Caffeine contributes positively to the treatment of apnea in prematurity, as well as in decreasing extubation failure rates and reducing the incidence of bronchopulmonary dysplasia in preterm infants. However, it is important to evaluate its catabolic effect on weight gain, justified by its mechanism of action, in which it increases the metabolic rate and oxygen consumption, thus reducing weight gain.

Due to the small sample of this study, there was no significant evidence of a reduction in the caloric gain of the preterm infants evaluated against the use of caffeine. A larger sample of patients using caffeine, involving several health centers, would increase the probability of having more homogeneous groups. And, thus, to carry out the research using a control group x an experimental group, obtaining more significant results.

Even with a small sample, it was possible to observe that, in neonates with a higher and prolonged dose of caffeine, additional supplementation can contribute to an improvement in postnatal weight gain. This data is extremely relevant, as it requires greater attention to these patients by the multidisciplinary health team and their families, in order to increase the nutritional support of this population.

RECOGNITIONS

Hemerson Iury Ferreira Magalhães (advisor) , Aníbal de Freitas Santos Júnior (co-advisor).

CONFLICT OF INTERESTS

The authors declare that the research was carried out in the absence of any commercial or financial relationships that could be interpreted as a potential conflict of interest.

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Annexure Table 01: Medicines used during hospitalization, while using caffeine.		
Xaropea de Zinco	Palivizumabe	Vancomicina
Ampicilina	Metronidazol	Amicacina
Gentamicina	Furosemida	Micafungina
Meropenem	Dipirona	Ambisome
Cefepima	Anlodipino	Omeprazol
Teicoplanina	Apresolina	Noripurum
Vancomicina	Captopril	Dexametasona
Prednisolona	Ursacol	Paracetamol
Protovit	Neutrofer	Calnate
Source: Own collection, 2021		

Table 1: Estimated daily energy requirements for growing premature babies.

Rest energy expenditure	**50 Kcal/Kg**	**Resting metabolic rate**
Activity	15Kcal/kg	30% above rest
cold stress	10Kcal/kg	Thermoregulation
Synthetic food effect	8Kcal/kg	Dietary Thermogenesis
fecal loss	12Kcal/kg	10% of intake
Growth	25Kcal/kg	Stored calories
Total caloric requirement	120Kcal/kg	

Source: Adapted from: SINCLAIR, 1971 (Clin Obstet Gynecol 1971; 14: 840).