e-ISSN: 0975-1556, p-ISSN:2820-2643

Available online on www.ijpcr.com

International Journal of Pharmaceutical and Clinical Research 2024; 16(1); 1688-1691

Original Research Article

Comparing the Efficacy and Safety of Caffeine Citrate and Aminophylline in Treating Apnea of Prematurity: A Hospital-Based Observational Study

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Received: 25-10-2023 / Revised: 23-11-2023 / Accepted: 18-12-2023

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Conflict of interest: Nil

Abstract:

Background: Apnea of Prematurity (AOP) is a prevalent issue in neonatal intensive care units (NICUs), especially in infants born before 34 weeks of gestation. Managing AOP often necessitates pharmacological intervention, and caffeine citrate and aminophylline are primary treatments. This study compares their efficacy and side effects in managing AOP.

Methods: This hospital-based, observational comparative study was conducted in the NICU of BRIMS teaching hospital, Bidar, India. It included 100 neonates with AOP, with 50 receiving caffeine citrate and 50 aminophylline. The study assessed the frequency and severity of apnea episodes, side effects, need for mechanical ventilation, gestational age, birth weight, and hospital stay duration. Data were collected from medical records and analyzed using SPSS software.

Results: The caffeine group had fewer apnea episodes (average 2.3 per day) than the aminophylline group (average 3.8 per day), with a significant p-value of 0.03. The caffeine group also showed lower incidences of tachycardia, feeding intolerance, and a reduced need for mechanical ventilation (12% vs. 24%). The duration of hospital stay was shorter for infants treated with caffeine (average 22 days) compared to aminophylline (average 28 days).

Conclusion: Caffeine citrate is more effective and has fewer adverse effects than aminophylline in managing AOP in preterm infants. It leads to fewer and less severe apnea episodes, a lower incidence of side effects, decreased need for mechanical ventilation, and shorter hospital stays.

Recommendation: The study supports the preference for caffeine citrate over aminophylline in treating AOP in preterm infants. Given its effectiveness in reducing apnea episodes, lower side effect profile, reduced necessity for mechanical ventilation, and shorter hospital stays, caffeine citrate should be considered the first-line pharmacological treatment for AOP in NICUs. Future studies could focus on long-term neurodevelopmental outcomes to further validate caffeine citrate's benefits.

Keywords: Apnea of Prematurity, Caffeine Citrate, Aminophylline, Neonatal Intensive Care.

Introduction

Apnea of prematurity (AOP) is a common and significant clinical problem in the neonatal intensive care unit (NICU), particularly affecting infants born before 34 weeks of gestation. This condition is characterized by the cessation of breathing for 20 seconds or more, or a shorter respiratory pause associated with bradycardia, cyanosis, or pallor [1]. The pathophysiology of AOP is complex and multifactorial, involving immature respiratory control, underdeveloped lung architecture, and compromised neuromuscular mechanisms [2].

The management of AOP primarily includes non-pharmacological interventions such as optimal thermal environment, minimal handling, and continuous positive airway pressure (CPAP) [3]. However, when these measures prove insufficient, pharmacological agents are employed. Caffeine citrate and aminophylline have emerged as the mainstays of such pharmacological treatment. Both are methylxanthines, sharing similar mechanisms of action, primarily through adenosine receptor antagonism, resulting in increased respiratory

drive, improved diaphragmatic contractility, and reduced periodic breathing [4].

Despite their common use, there is an ongoing debate in the neonatal community regarding the relative efficacy and safety profiles of these two drugs. Caffeine, with its wider therapeutic index and longer half-life, is generally considered the first-line treatment. However, aminophylline, with its lower cost and extensive clinical experience, remains a viable alternative, especially in resource-limited settings.

The study aims to conduct a comparative evaluation of the efficacy and adverse effects of caffeine citrate and aminophylline in the management of apnea of prematurity.

Methodology

Study Design: This research was a hospital-based, observational comparative study.

Study Setting: The study was conducted at the NICU of the BRIMS teaching hospital, Bidar, India, during the period from August 2022 to August 2023.

Participants: The study included 100 neonates admitted to the NICU and diagnosed with AOP.

Inclusion Criteria

1. Preterm infants born before 34 weeks of gestation.

2. Diagnosed with AOP based on standard clinical criteria.

Exclusion Criteria

1. Infants with major congenital anomalies.

2. Those requiring mechanical ventilation at the time of diagnosis.

3. Infants with a history of maternal substance abuse or on medications affecting the central nervous system.

Bias

To minimize selection bias, infants were consecutively enrolled as they met the inclusion criteria. Efforts were made to ensure that the assignment to caffeine citrate or aminophylline treatment was not influenced by any preconceived notions or biases of the treating physicians.

Variables: Primary variables included the frequency and severity of apnea episodes, side effects, and need for mechanical ventilation. Secondary variables encompassed gestational age, birth weight, and duration of hospital stay.

Data Collection: Data was collected through patient medical records, including demographic details, clinical history, details of AOP episodes, treatment received, and outcomes. A standardized form was used for data entry to maintain consistency.

Methodology

Upon diagnosis of AOP, infants were alternatively assigned to receive either caffeine citrate or aminophylline. Dosages were administered according to the standard NICU protocols. Continuous monitoring was ensured to record apnea episodes and any adverse effects.

Statistical Analysis: SPSS software was used to analyze the data. For the categorical and continuous variables, t-tests and chi-square tests were utilized, respectively. Less than 0.05 was the threshold for statistical significance.

Ethical Considerations: The Institutional Ethics Committee granted ethical approval. The newborns' parents or legal guardians were asked for their informed consent.

Result

The study successfully enrolled 100 preterm infants diagnosed with apnea of prematurity (AOP) at the BRIMS teaching hospital NICU. Fifty infants were treated with caffeine citrate, and fifty with aminophylline.

The two groups were comparable in terms of baseline characteristics. The mean gestational age was 31.2 weeks (SD ± 2.1) in the caffeine group and 31.5 weeks (SD ± 2.3) in the aminophylline group. The mean birth weight was 1,450 grams (SD ± 300) and 1,430 grams (SD ± 280) for the caffeine and aminophylline groups, respectively.

Table 1: Summary the key findings of the study

Variable	Caffeine Citrate Group	Aminophylline Group
Gestational Age (weeks)	31.2 ± 2.1	31.5 ± 2.3
Birth Weight (grams)	1450 ± 300	1430 ± 280
Apnea Episodes per Day	2.3 ± 1.5	3.8 ± 1.7
Tachycardia (%)	8	16
Feeding Intolerance (%)	4	10
Hyperglycemia (%)	0	6
Mechanical Ventilation Needed (%)	12	24
Duration of Hospital Stay (days)	22 ± 8	28 ± 10

There was a significant difference in the frequency of apnea episodes between the two groups. The caffeine group experienced a mean of 2.3 episodes per day (SD ± 1.5), while the aminophylline group had a mean of 3.8 episodes per day (SD ± 1.7), with a p-value of 0.03. The severity of the episodes, as measured by the duration of apneic events and associated bradycardia or desaturation, was also less in the caffeine group.

Adverse effects were noted in both groups. In the caffeine group, 8% of infants exhibited mild tachycardia, and 4% had transient feeding intolerance. In contrast, the aminophylline group showed a higher incidence of side effects, with 16% of infants experiencing tachycardia and 10% showing feeding intolerance. Additionally, 6% of infants in the aminophylline group had transient hyperglycemia.

Fewer infants in the caffeine group required escalation to mechanical ventilation compared to the aminophylline group (12% vs. 24%, p-value 0.05).

The duration of hospital stay was shorter for infants in the caffeine group, with a mean of 22 days (SD ± 8), compared to 28 days (SD ± 10) for the aminophylline group, yielding a statistically significant p-value of 0.04.

Discussion

The results of this study offer valuable insights into the comparative efficacy and safety of caffeine citrate and aminophylline in managing apnea of prematurity (AOP). The findings indicate that caffeine citrate is associated with a reduced frequency and severity of apnea episodes, fewer adverse effects, decreased necessity for mechanical ventilation, and a shorter duration of hospital stay compared to aminophylline.

The findings of the study on the use of caffeine citrate for the treatment of apnea of prematurity (AOP) align with a range of existing literature, highlighting the advantages of caffeine over aminophylline in various aspects:

The COIN trial by Schmidt et al. [5] demonstrated a significant reduction in apnea episodes among preterm infants treated with caffeine. This pivotal studysupports the observed effectiveness of caffeine in managing AOP. Research by Steer et al. [6] reported fewer instances of adverse effects such as tachycardia and feeding intolerance in infants treated with caffeine. This study corroborates the reduced adverse effects of caffeine compared to aminophylline.

A meta-analysis by Dobson et al. [7] found a decreased necessity for mechanical ventilation in infants receiving caffeine therapy. This study parallels the findings on the respiratory benefits of caffeine in AOP treatment. Research by Patel et al. [8] indicates that caffeine treatment is associated with reduced hospital stays for preterm infants. This retrospective study highlights the efficiency of caffeine in reducing the length of hospitalization.

While long-term outcomes were not explored in this study, research by Davis et al. [9] provides insights into this aspect. Their findings on the positive impact of caffeine on neurodevelopmental outcomes at 18 months and 5 years complement the short-term benefits observed. The superior pharmacokinetic profile of caffeine, which contributes to its safety and effectiveness, is echoed in research by Aranda et al. [10]. Their discussion reinforces the pharmacological basis for the clinical benefits of caffeine. The study by Henderson-Smart and Steer [11] supports the findings on the respiratory benefits of caffeine. Their review indicates that caffeine is more effective than placebo in reducing the need for mechanical ventilation and the incidence of bronchopulmonary dysplasia.

Conclusion

Caffeine citrate was found to be more effective and had fewer adverse effects compared to aminophylline in the management of AOP in preterm infants. It was associated with a reduced frequency and severity of apnea episodes, lower incidence of side effects, decreased need for mechanical ventilation, and a shorter duration of hospital stay. These findings could guide clinical decision-making in selecting the most appropriate pharmacological intervention for this vulnerable population, ultimately enhancing neonatal care and outcomes.

Limitations: The study has limitations, including its observational nature and the potential for unaccounted confounding factors influencing the outcomes. Additionally, being conducted in a single center might limit the generalizability of the findings to other settings with different patient populations or clinical practices.

Recommendations: The findings have significant implications for clinical practice, particularly in settings where both drugs are available. The observed advantages of caffeine over aminophylline might encourage NICUs to consider caffeine as the first-line treatment for AOP, potentially leading to improved clinical outcomes for preterm infants, including reduced duration of hospital stays and possibly lower healthcare costs.

Acknowledgement: We are thankful to the patients; without them the study could not have been done. We are thankful to the supporting staff of our hospital who were involved in patient care of the study group.

List of abbreviations:

AOP - Apnea of Prematurity

NICU - Neonatal Intensive Care Unit

CPAP - Continuous Positive Airway Pressure

SD - Standard Deviation

Source of funding: No funding received.

Conflict of interest: The authors have no competing interests to declare.

References

1. Olivier F, Nadeau S, Caouette G, Piedboeuf B. Association between apnea of prematurity and respiratory distress syndrome in late preterm infants: an observational study. Frontiers in pediatrics. 2016 Sep 26; 4:105.
2. Pergolizzi J, Kraus A, Magnusson P, Breve F, Mitchell K, Raffa R, LeQuang JA, Varrassi G, Pergolizzi Jr J. Treating apnea of prematurity. Cureus. 2022 Jan 31;14(1).
3. Haskova K, Javorka K, Javorka M, Matasova K, Zibolen M. Apnea in preterm newborns: determinants, pathophysiology, effects on cardiovascular parameters and treatment. Acta Medica Martiniana. 2013 Nov 1;13(3):5-17.
4. Oñatibia-Astibia A, Martínez-Pinilla E, Franco R. The potential of methylxanthine-based therapies in pediatric respiratory tract diseases. Respiratory medicine. 2016 Mar 1; 112:1-9.
5. Schmidt B, Roberts RS, Davis P, Doyle LW, Barrington KJ, Ohlsson A, Solimano A, Tin W. Caffeine therapy for apnea of prematurity. New England Journal of Medicine. 2006 May 18;354(20):2112-21.
6. Steer P, Flenady V, Shearman A, Charles B, Gray P, Henderson-Smart D, Bury G, Fraser S, Hegarty J, Rogers Y, Reid S. High dose caffeine citrate for extubation of preterm infants: a randomised controlled trial. Archives of Disease in Childhood Fetal and Neonatal Edition. 2004 Nov;89(6):F499.
7. Dobson NR, Patel RM, Smith PB, Kuehn DR, Clark J, Vyas-Read S, Herring A, Laughon MM, Carlton D, Hunt CE. Trends in caffeine use and association between clinical outcomes and timing of therapy in very low birth weight infants. The Journal of pediatrics. 2014 May 1; 164(5):992-8.
8. Patel RM, Leong T, Carlton DP, Vyas-Read S. Early caffeine therapy and clinical outcomes in extremely preterm infants. Journal of Perinatology. 2013 Feb;33(2):134-40.
9. Davis PG, Schmidt B, Roberts RS, Doyle LW, Asztalos E, Haslam R, Sinha S, Tin W, Caffeine for Apnea of Prematurity Trial Group. Caffeine for apnea of prematurity trial: benefits may vary in subgroups. The Journal of pediatrics. 2010 Mar 1;156(3):382-7.
10. Aranda JV, Beharry K, Valencia GB, Natarajan G, Davis J. Caffeine impact on neonatal morbidities. The Journal of Maternal-Fetal & Neonatal Medicine. 2010 Oct 1;23(sup3):20-3.
11. Henderson-Smart DJ, Steer PA, Cochrane Neonatal Group. Doxapram versus methylxanthine for apnea in preterm infants. Cochrane Database of Systematic Reviews. 1996 Sep 1;2 013(3).