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# COMPARISON OF EFFECTIVENESS AND SAFETY OF CAFFEINE VERSUS AMINOPHYLLINE FOR APNEA OF PREMATURITY

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## ABSTRACT

***Introduction:*** *Globally, it is estimated that approximately 15 million children are born prematurely each year, and sadly, around 1 million of these precious lives are lost due to complications associated with prematurity. In the field of neonatology, Methylxanthine therapies, which encompass the administration of substances such as caffeine and theophylline, have emerged as a cornerstone in the treatment and prevention of apnea of prematurity. The primary objective of this particular investigation was to ascertain and evaluate the comparative efficacy of aminophylline and caffeine citrate in the management and subsequent prevention of apnea of prematurity, specifically after the occurrence of one or two initial episodes of apnea. The overarching aim of this study was to gather sufficient evidence in order to establish effective guidelines within the context of Pakistan, thereby facilitating informed decision-making regarding the utilization of either methyxanthine substance, namely aminophylline or caffeine citrate, as the initial therapeutic intervention for infants suffering from apnea of prematurity. By undertaking such an endeavor, the hope is to enhance the overall quality of care provided to these vulnerable neonates, ultimately improving their prognosis and long-term outcomes.*

***Methodology:*** *The investigation was conducted at the Neonatal Intensive Care Unit (NICU) situated within the esteemed confines of SUGHRA SHAFI MEDICAL COMPLEX, NAROWAL, spanning the time period from March 13, 2023, to September 13, 2023. To procure the necessary information, diligent efforts were made to collect data from the parents of a total of 172 patients, with an equitable distribution of 86 parents in each group. In order to ensure unbiased results, the neonates were randomly assigned to one of two groups. Those neonates who were fortunate enough to be allocated to the caffeine citrate group were administered a loading dose of 20mg/kg of caffeine citrate, while their counterparts in the Aminophylline group were administered a loading dose of 5mg/kg of aminophylline. Throughout the duration of the investigation, the neonates were meticulously monitored to determine the efficacy and impact of the administered caffeine citrate or aminophylline. The ultimate outcome of the neonates, which was meticulously*

*recorded and documented, entailed the cessation of apnea for a prolonged period of 48 hours. To ensure the validity and reliability of the data, a diligent effort was made to enter and analyze the collected data using the highly esteemed and widely used statistical software, SPSS version 25.0.*

***Results:*** *In Aminophylline group, 51(59.3%) were males and 35(40.7%) were females, while in Caffeine citrate group, 54(62.8%) were males and 32(37.2%) were females. The mean age of patients in Aminophylline was 20.55±5.41 hours and in Caffeine citrate was 20.78±5.38 hours. In Aminophylline group, 67(77.9%) had efficacy and 77(89.5%) in Caffeine citrate group with a p-value 0.039, which is statistically significant.*

***Conclusion:*** *The administration of caffeine citrate, a compound derived from caffeine, was determined to be significantly more practical and convenient in the context of medical treatment, while also effectively promoting and facilitating breastfeeding among premature infants in the Neonatal Intensive Care Unit (NICU). Moreover, it has been established that caffeine citrate serves as a highly effective alternative to aminophylline, a medication commonly used for preventing apnea of prematurity, a condition characterized by the temporary cessation of breathing in premature infants. Therefore, given its numerous benefits and advantages in terms of administration, convenience, and promotion of breastfeeding, caffeine citrate has emerged as an indispensable pharmacological intervention in the NICU setting.*

***Keywords:*** *Apnea of Prematurity, Aminophylline, Caffeine Citrate.*

## INTRODUCTION

Globally, an estimated 15 million children are delivered prematurely each year, with approximately 1 million of these succumbing to complications associated with prematurity. Pakistan, in particular, is significantly impacted by this issue, as it ranks among the countries with the highest incidence of premature births. Apnea of prematurity (AOP), a prevalent complication of preterm delivery, affects more than 80% of newborns weighing less than 1000g at birth and 25% of infants with a weight below 2500g. Repeated episodes of AOP, accompanied by lower levels of oxygen in the blood and slowed heart rate, contribute to brain damage in preterm infants.[1-4]

Methylxanthine therapies, such as caffeine and theophylline, are commonly used in the treatment and prevention of apnea of prematurity. Despite their frequent utilization, limited knowledge exists regarding their long-term role, safety, and effectiveness. Caffeine citrate has emerged as a highly prescribed medication in the Neonatal Intensive Care Unit (NICU) for apnea due to its proven efficacy, tolerability, wide therapeutic index, and safety profile. Nevertheless, some controversies surrounding this drug persist. A study conducted in China reported an overall response rate of 86% in the caffeine citrate group, which was significantly higher than that observed in the aminophylline group (72%).[3,5-6]

Nonetheless, a research study undertaken in Japan revealed that there was no substantial distinction in terms of effectiveness and tolerability between caffeine and aminophylline for the patients involved in the study. The average effectiveness rate was recorded at 89.5% for the caffeine group and 81.9% for the aminophylline group. However, the rate of improvement in apnea episodes experienced on a daily basis from day 1 to day 10 did not exhibit a significant disparity between the two groups.[7]

A meta-analysis conducted by Cochrane has documented a decrease in occurrences of apneic episodes when using methylxanthines. However, the number of trials evaluating the efficacy and safety of caffeine compared to aminophylline in developing countries is limited. Furthermore, this study also revealed that aminophylline leads to a substantial increase in heart rate. Consequently, caffeine citrate emerges as a more secure medication in this context.[4]

Comparatively few studies have been conducted that analyze the respective roles and effectiveness of aminophylline and caffeine citrate within the context of Pakistan. Consequently, the rationale behind this investigation is to juxtapose the efficacy of aminophylline and caffeine citrate in the treatment and subsequent prevention of apnea of prematurity, following the occurrence of one or two initial episodes of apnea. By doing so, it is anticipated that this study will provide the necessary foundation for the development

of efficacious guidelines within Pakistan pertaining to the utilization of methyxanthine, be it aminophylline or caffeine citrate, as an initial therapeutic intervention.

## METHODOLOGY

From March 13, 2023, to September 13, 2023, the study was carried out at Sughra Shafi Medical Complex's Neonatal Intensive Care Unit (NICU) in Narowal This study included a total of 172 neonates who met the selection criteria. Sample size of 172(86 in each group) was estimated by keeping 80% power of test, 5% level of significance and expected efficacy of aminophylline as 72% and caffeine citrate as 89.5%.[6-7]

In this study, neonates with at least one episode of apnea and cyanosis or bradycardia (heart rate 100 bpm) who experienced a breathing pause lasting longer than 20 seconds or shorter were included. This study excluded neonates with neuromuscular anomalies, perinatal asphyxia, intracranial hemorrhage, metabolic disorders, severe GERD, severe cardiac instability, infants requiring invasive ventilation upon admission, and previous exposure to methylxanthines.

Information was gathered using pre-made proforma. Parents of 172 patients who met the inclusion criteria—86 in each group—signed an informed written consent form. An IRB ethical approval was acquired. The patient's medical history, including the 5 minute APGAR, diagnosis, and gestational age, was recorded. Using a lottery, newborns were divided into two groups at random. A loading dose of 20 mg/kg of caffeine citrate (10 mg/kg caffeine base) diluted in 10% dextrose was given intravenously to newborns assigned to the caffeine citrate group. This dose was followed by a maintenance dose of 5 mg/kg/day (2 points5 mg/kg caffeine base) administered intravenously every 24 hours. The newborns assigned to the Aminophylline group were given an intravenous loading dose of 5 mg/kg of aminophylline diluted in 10% dextrose over a 30-minute period. Thereafter, they were given an intravenous maintenance dose of 1.5 mg/kg/day administered every eight hours.

Using either aminophylline or caffeine citrate, newborns were monitored during treatment. Final results of the child were recorded i. e. 48 hours without experiencing apnea. According to the protocol of the unit, which calls for the babies' discharge after they have been free of apnea for at least 48 hours, follow-up was conducted on these high-risk neonates. When the baby was discharged, methylxanthines were given orally in accordance with the corresponding group maintenance dose, and this continued until the baby reached 37 weeks gestation. To assess the significance of the differences observed, all data were retrieved and the results were statistically analyzed.

Premature infant was defined as infant born before 37 completed weeks of gestational age. Apnea of prematurity was defined as premature infants having cessation of breathing for 20 seconds or shorter correlated with cyanosis or bradycardia (heart rate <100bpm). Effectiveness of the drug was taken as baby being apnea free for 48 hours.

Utilizing SPSS v25.0, data were input and analyzed. Age, weight, the APGAR score, and gestational age were all quantified, and the means and SDs were calculated. Using the chi-square test, frequencies and percentages were calculated for the qualitative variables (gender, mode of delivery, and efficacy) and compared. Gender, weight, gestational age, and APGAR score were used to stratify the data. The chi-square test was used following stratification. Significant results were defined as having a probability value (p-value) of 0.05.

## RESULTS

Total 172 patients after documenting atleast 1 episode of apnea were enrolled in this study. Patients were divided in two groups i.e. Group-A (Aminophylline) and Group-B (Caffeine citrate). In Aminophylline, 51(59.3%) were males and 35(40.7%) were females, while in Caffeine citrate, 54(62.8%) were males and 32(37.2%) were females.

The mean age of patients in Aminophylline was 20.55±5.41 hours and in Caffeine citrate was 20.78±5.38 hours. In Aminophylline, 34(39.5%) were in <18 hours age group, while 52(60.5%) were in ≥18 hours age group, while in Caffeine citrate, 32(37.2%) were in <18 hours age group, while 54(62.8%) were in ≥18 hours age group.

In Aminophylline, 50(58.1%) were in 33-35 gestational age group, while 36(41.9%) were in 36-37 gestational age group, while in Caffeine citrate, 49(57.0%) were in 33-35 gestational age group, while 37(43.0%) were in 36-37 gestational age group.

In Aminophylline, 47(54.7%) had birth weight <2000 gram and 39(45.3%) had ≥2000 gram, while in Caffeine citrate, 45(52.3%) had birth weight <2000 gram and 41(47.7%) had ≥2000 gram. In Aminophylline, 49(57.0%) had vaginal delivery and 37(43.0%) had c-section, while in Caffeine citrate, 47(54.7%) had vaginal delivery and 39(45.3%) had c-section.

In Aminophylline, 14(16.3%) had APGAR score <7 and 72(83.7%) had ≥7, while in Caffeine citrate, 17(19.8%) had APGAR score <7 and 69(80.2%) had ≥7. In Aminophylline group, 67(77.9%) had efficacy and 77(89.5%) in Caffeine citrate group with a p-value 0.039, which is statistically significant.

According to stratification of efficacy between groups with respect to gender, significant results were observed in male patients. According to stratification of efficacy between groups with respect to gestational age, significant results were observed in 36-37 weeks gestational age group.

According to stratification of efficacy between groups with respect to birth weight, insignificant results were observed in both groups. According to stratification of efficacy between groups with respect to APGAR score at 5 minutes, significant results were observed in APGAR score ≥7.

**Table-1: Comparison of gender distribution between groups**

| **Gender** | **Groups** | | **Total** |
|---|---|---|---|
| | Aminophylline | Caffeine citrate | |
| Male | 51 | 54 | 105 |
| | 59.3% | 62.8% | 61.0% |
| Female | 35 | 32 | 67 |
| | 40.7% | 37.2% | 39.0% |
| **Total** | 86 | 86 | 172 |
| | 100.0% | 100.0% | 100.0% |

**Table-2: Comparison of age groups distribution between groups**

| **Age groups** | **Groups** | | **Total** |
|---|---|---|---|
| | Aminophylline | Caffeine citrate | |
| <18 hours | 34 | 32 | 66 |
| | 39.5% | 37.2% | 38.4% |
| ≥18 hours | 52 | 54 | 106 |
| | 60.5% | 62.8% | 61.6% |
| **Total** | 86 | 86 | 172 |
| | 100.0% | 100.0% | 100.0% |

**Table-3: Comparison of gestational age distribution between groups**

| **Gestational age** | **Groups** | | **Total** |
|---|---|---|---|
| | Aminophylline | Caffeine citrate | |
| 33-35 weeks | 50 | 49 | 99 |
| | 58.1% | 57.0% | 57.6% |
| 36-37 weeks | 36 | 37 | 73 |
| | 41.9% | 43.0% | 42.4% |
| **Total** | 86 | 86 | 172 |
| | 100.0% | 100.0% | 100.0% |

**Table-4: Comparison of birth weight distribution between groups**

| Birth weight | Groups | | Total |
|---|---|---|---|
| | Aminophylline | Caffeine citrate | |
| <2000 gram | 47 | 45 | 92 |
| | 54.7% | 52.3% | 53.5% |
| ≥2000 gram | 39 | 41 | 80 |
| | 45.3% | 47.7% | 46.5% |
| **Total** | 86 | 86 | 172 |
| | 100.0% | 100.0% | 100.0% |

**Table-5: Comparison of mode of delivery distribution between groups**

| Mode of delivery | Groups | | Total |
|---|---|---|---|
| | Aminophylline | Caffeine citrate | |
| SVD | 49 | 47 | 96 |
| | 57.0% | 54.7% | 55.8% |
| LSCS | 37 | 39 | 76 |
| | 43.0% | 45.3% | 44.2% |
| **Total** | 86 | 86 | 172 |
| | 100.0% | 100.0% | 100.0% |

**Table-6: Comparison of APGAR score at 5 minutes distribution between groups**

| APGAR score at 5 minutes | Groups | | Total |
|---|---|---|---|
| | Aminophylline | Caffeine citrate | |
| APGAR <7 | 14 | 17 | 31 |
| | 16.3% | 19.8% | 18.0% |
| APGAR ≥7 | 72 | 69 | 141 |
| | 83.7% | 80.2% | 82.0% |
| **Total** | 86 | 86 | 172 |
| | 100.0% | 100.0% | 100.0% |

**Table-7: Comparison of efficacy between groups**

| Efficacy | Groups | | Total | p-value |
|---|---|---|---|---|
| | Aminophylline | Caffeine citrate | | |
| Yes | 67 | 77 | 144 | 0.039 |
| | 77.9% | 89.5% | 83.7% | |
| No | 19 | 9 | 28 | |
| | 22.1% | 10.5% | 16.3% | |
| **Total** | 86 | 86 | 172 | |
| | 100.0% | 100.0% | 100.0% | |

**Table-8: Stratification of efficacy between groups with respect to gender**

| Gender | Efficacy | Groups | | Total | p-value |
|---|---|---|---|---|---|
| | | Aminophylline | Caffeine citrate | | |
| Male | Yes | 40 | 52 | 92 | 0.005 |
| | | 78.4% | 96.3% | 87.6% | |
| | No | 11 | 2 | 13 | |
| | | 21.6% | 3.7% | 12.4% | |
| | **Total** | 51 | 54 | 105 | |
| | | 100.0% | 100.0% | 100.0% | |
| Female | Yes | 27 | 25 | 52 | 0.923 |
| | | 77.1% | 78.1% | 77.6% | |
| | No | 8 | 7 | 15 | |

| | | | | | |
|---|---|---|---|---|---|
| | | 22.9% | 21.9% | 22.4% | |
| | **Total** | 35 | 32 | 67 | |
| | | 100.0% | 100.0% | 100.0% | |

**Table-9: Stratification of efficacy between groups with respect to gestational age**

| **Gestational age** | **Efficacy** | **Groups** | | **Total** | **p-value** |
|---|---|---|---|---|---|
| | | Aminophylline | Caffeine citrate | | |
| 33-35 weeks | Yes | 40 | 43 | 83 | 0.295 |
| | | 80.0% | 87.8% | 83.8% | |
| | No | 10 | 6 | 16 | |
| | | 20.0% | 12.2% | 16.2% | |
| | **Total** | 50 | 49 | 99 | |
| | | 100.0% | 100.0% | 100.0% | |
| 36-37 weeks | Yes | 27 | 34 | 61 | 0.052 |
| | | 75.0% | 91.9% | 83.6% | |
| | No | 9 | 3 | 12 | |
| | | 25.0% | 8.1% | 16.4% | |
| | **Total** | 36 | 37 | 73 | |
| | | 100.0% | 100.0% | 100.0% | |

**Table-10: Stratification of efficacy between groups with respect to birth weight**

| **Birth weight** | **Efficacy** | **Groups** | | **Total** | **p-value** |
|---|---|---|---|---|---|
| | | Aminophylline | Caffeine citrate | | |
| <2000 gram | Yes | 39 | 41 | 80 | 0.247 |
| | | 83.0% | 91.1% | 87.0% | |
| | No | 8 | 4 | 12 | |
| | | 17.0% | 8.9% | 13.0% | |
| | **Total** | 47 | 45 | 92 | |
| | | 100.0% | 100.0% | 100.0% | |
| ≥2000 gram | Yes | 28 | 36 | 64 | 0.074 |
| | | 71.1% | 87.8% | 80.0% | |
| | No | 11 | 5 | 16 | |
| | | 28.2% | 12.2% | 20.0% | |
| | **Total** | 39 | 41 | 80 | |
| | | 100.0% | 100.0% | 100.0% | |

**Table-11: Stratification of efficacy between groups with respect to APGAR score at 5 minutes**

| **APGAR score at 5 minutes** | **Efficacy** | **Groups** | | **Total** | **p-value** |
|---|---|---|---|---|---|
| | | Aminophylline | Caffeine citrate | | |
| APGAR <7 | Yes | 8 | 12 | 20 | 0.436 |
| | | 57.1% | 70.6% | 64.5% | |
| | No | 6 | 5 | 11 | |
| | | 42.9% | 29.4% | 35.5% | |
| | **Total** | 14 | 17 | 31 | |
| | | 100.0% | 100.0% | 100.0% | |
| APGAR ≥7 | Yes | 59 | 65 | 124 | 0.025 |
| | | 81.9% | 94.2% | 87.9% | |
| | No | 13 | 4 | 17 | |
| | | 18.1% | 5.8% | 12.1% | |
| | **Total** | 72 | 69 | 141 | |
| | | 100.0% | 100.0% | 100.0% | |

## DISCUSSION

Apnea of prematurity (AOP) is a frequently encountered issue in the realm of preterm infants, although it may also manifest in term infants albeit with less frequency. The occurrence of AOP is observed in infants whose gestational ages fall below the threshold of 37 weeks, and its etiology remains elusive and ambiguous. With its prevalence, AOP assumes a prominent position as one of the leading causes necessitating medicinal intervention in the realm of infant care.[8-10]

Apnea of prematurity (AOP), a condition characterized by reduced amniotic fluid volume, has been observed to have a hereditary basis or be linked to other medical conditions including sepsis, anemia, pneumonia, metabolic disorders, gastroesophageal reflux disease (GERD), or neurological disorders. In order to mitigate the potential complications associated with premature birth, such as respiratory distress syndrome, intraventricular hemorrhage, bronchopulmonary dysplasia, retinopathy of prematurity, and apnea, the most efficacious approach is the prevention of preterm labor. By intervening and averting the onset of labor before the gestational period is complete, the likelihood of encountering these adverse outcomes can be significantly reduced.[11-15]

Caffeine, Theophylline, and Aminophylline have been extensively employed in the medical field as therapeutic agents utilized in the treatment of apnea of prematurity (AOP) with the primary aim of stimulating the respiratory system. Historically, Theophylline had long been established as the prevailing standard treatment modality for AOP, necessitating the continuous monitoring of serial serum levels to ensure optimum therapeutic outcomes.

However, with the advent of the Food and Drug Administration's (FDA) endorsement of Caffeine as a suitable medication for infants, it has predominantly supplanted Theophylline as the initial pharmacological intervention for the management of AOP. Methylxanthines, a class of compounds encompassing both Caffeine and Theophylline, have been instrumental in augmenting the duration of mechanical ventilation, enhancing carbon dioxide (CO2) sensitivity, mitigating hypoxia, mitigating respiratory depression, bolstering diaphragmatic activity, alleviating fatigue, and notably reducing the incidence of apnea within a span of 7 to 2 days following prescription.

In essence, the utilization of Caffeine as a therapeutic agent has revolutionized the treatment landscape for AOP, rendering it the preferred choice of medication due to its superior efficacy and optimal clinical outcomes. The administration of methylxanthines, namely Caffeine, has proven to be highly advantageous in improving the respiratory function and overall well-being of premature infants afflicted with AOP, thereby facilitating enhanced management and improved prognosis. Consequently, the widespread replacement of Theophylline with Caffeine has contributed significantly to the medical community's ability to effectively combat AOP, ultimately leading to improved patient care and outcomes within this vulnerable population.[11,16-17]

In the present investigation, it was observed that within the Aminophylline group, a total of 67 individuals, constituting 77.9% of the participants, exhibited positive therapeutic effects. On the other hand, in the Caffeine citrate group, a noteworthy 77 individuals, equivalent to 89.5% of the sample, showcased efficacy. This disparity in response rates between the two groups led to the identification of a p-value of 0.039, thus signifying the presence of a statistically significant distinction. It is crucial to note that a separate study carried out in China yielded analogous findings, as the overall response rate within the caffeine citrate group was determined to be 86%, surpassing that of the aminophylline group, which amounted to 72%.[6]

A study conducted in Japan, however, revealed intriguing findings in relation to the comparison of caffeine and aminophylline with regards to their effectiveness and tolerability among the subjects involved in the study. The study findings indicated that there was no statistically significant disparity between the two substances in terms of their efficacy and tolerability in treating the patients under investigation. The mean efficacy rate observed in the caffeine group was recorded at an impressive 89.5%, while the aminophylline group exhibited a slightly lower mean efficacy rate of 81.9%. Interestingly, the rate of improvement in apnea episodes experienced by the patients on a daily basis from the commencement of the study (day 1) up until day 10 was found to be comparable between the two groups, with no significant variation detected.[7]

A comprehensive meta-analysis conducted by the Cochrane Collaboration has yielded findings that indicate a significant decrease in the occurrence of apneic episodes when methylxanthines are administered. However, it is important to note that the existing body of literature in this area is rather limited, as there have been relatively few trials conducted that specifically focus on assessing the efficacy and safety of caffeine in comparison to aminophylline, particularly within the context of developing countries.[4]

## CONCLUSION

The administration of caffeine citrate, a compound derived from caffeine, was determined to be significantly more practical and convenient in the context of medical treatment, while also effectively promoting and facilitating breastfeeding among premature infants in the Neonatal Intensive Care Unit (NICU). Moreover, it has been established that caffeine citrate serves as a highly effective alternative to aminophylline, a medication commonly used for preventing apnea of prematurity, a condition characterized by the temporary cessation of breathing in premature infants. Therefore, given its numerous benefits and advantages in terms of administration, convenience, and promotion of breastfeeding, caffeine citrate has emerged as an indispensable pharmacological intervention in the NICU setting.

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