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The Use of Caffeine Citrate in the Management of Neonatal Apnea in Low- and Middle-Income Countries: A Rapid Systematic Review

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ABSTRACT

Background and Aims: Caffeine citrate is an example of a methylxanthine approved for managing apnea of prematurity (AOP). However, there is limited evidence of its use in low- and middle-income countries (LMICs). This rapid systematic review aims to appraise the literature on using caffeine citrate in managing neonatal apnea in LMICs.

Methods: A comprehensive search was conducted on literature reporting the treatment of AOP in LMICs. The search was based on a population, intervention, comparison, and outcome format using medical subject heading terms. The PRISMA and PRISMA extension for scoping reviews guidelines were meticulously followed. PubMed, Science Direct, and Scopus were among the bibliographic databases searched. Initially, 2638 articles were identified based on the keywords used. However, after eliminating duplicates and implementing advanced options (only full-text, language, and year), the articles were further screened by abstract and title, ensuring a rigorous selection process.

Results: The evaluation of 10 studies involving 1010 preterm infants provided compelling evidence. Our findings demonstrated that caffeine citrate, compared to aminophylline, had fewer adverse effects. The adverse effects, including feeding intolerance, tachycardia, central nervous system derailment, and hyperglycemia, were significantly reduced with caffeine citrate. Furthermore, data from the included studies revealed that caffeine citrate had a lower risk of recurrent apnea and was less likely to fall out of the recommended therapeutic range than aminophylline. These results unequivocally establish caffeine citrate's safety, efficacy, and cost-effectiveness in treating prematurity apnea in LMICs, providing a reliable and beneficial intervention for neonatal care in these regions.

Conclusion: Caffeine may be a preferred option in managing AOP in LMICs. However, high drug prices and lack of availability of caffeine may be factors limiting its use in these settings.

1 | Introduction

1.1 | Background

Apnea in neonates can be defined as a cessation of breathing for 20 s or more or a short respiratory pause associated with oxygen desaturation and/or bradycardia. Apnea is commonly found in preterm and low-birth-weight neonates because of their undeveloped respiratory system. Often, neonates with gestational age less than 37 weeks have a high risk of developing episodes of apnea, as well as hypoxemia and bradycardia. Signs of acute apnea of prematurity (AOP) include oxygen saturation

(SpO_2) of less than 80% for more than 4 s, a heart rate that is lower than 67% from baseline for more than 4 s, and a breathing pause that lasts for more than 15 s [1]. The frequency of apneic episodes in neonates is influenced by birth weight and gestational age. According to Zhao et al., the incidence of AOP is higher in neonates born between 30 and 31 weeks of gestation than in those born between 32 and 33 or 34 and 35 weeks of gestation [2]. Pharmacotherapeutic interventions are often used to lower the frequency of apneic episodes [3]. Prolonged apnea, bradycardia, and reduced cerebral blood flow have the potential to induce hypoxic-ischemic damage to the developing brain of an infant [4]. As such, neonatal apnea, if untreated for an extended period, can lead to organ impairment or even death [5].

Apnea is known to occur in nearly 50% of neonates between 33 and 34 weeks of gestation and is likely to occur in almost every neonate born before 28 weeks of gestation [6]. There is a low likelihood of apnea occurring in late preterm neonates (34–36 weeks of gestation) ranging from 4% to 7% [7]. The pathophysiology of AOP is multifaceted, and it involves components important for controlling respiratory function and developing the lungs. AOP is almost always caused by immaturity of the respiratory system, which is one of the key contributing factors. Preterm infants do not have a completely formed respiratory control center responsible for regulating breathing in the brain. This immaturity can lead to occasional pauses in breathing which can lead to hypoxemia, hypercapnia, and acidosis [8]. Premature neonates typically have underdeveloped lungs that produce insufficient surfactant, which can cause the airways to collapse during expiration. Furthermore, this can lead to the accumulation of air and hyperinflation, both of which can cause respiratory distress and apneas [9]. Anemia, temperature instability, gastric reflux, and medicines are maternal variables that can also contribute to AOP [10]. Indeed, neonatal apnea contributes significantly to infant mortality in resource-poor countries [11].

Management of neonatal apnea requires continuous monitoring and, in some cases, pharmacological interventions. The cornerstone in the pharmacological management of neonatal apnea is using methylxanthines. Methylxanthines are central nervous system stimulants that work as nonspecific adenosine receptor antagonists [12]. They increase respiratory rate, reduce hypercapnia sensitivity, and increase diaphragm contractility [13]. Caffeine, aminophylline, and theophylline are methylxanthines used to manage neonatal apnea [14]. Caffeine and theophylline are substrates for the enzyme cytochrome P450 (CYP) 1A2. According to Carrillo and Benitez [15], the liver is mainly responsible for N-demethylation of caffeine, producing paraxanthine, theobromine, and theophylline.

Aminophylline has been historically used as a treatment for prematurity apnea. However, its use has declined in favor of caffeine due to the latter's superior safety profile and effectiveness. Studies comparing aminophylline and caffeine have shown that caffeine is associated with fewer side effects and better neurodevelopmental outcomes in preterm infants [16, 17]. Caffeine or 1,3,7-trimethylxanthine is a stable alkaloid with mild central nervous system stimulant effects. Caffeine citrate, made up of caffeine and citric acid, is approved for the management of AOP. It can be administered intravenously as a 20 mg/kg loading dose. This is followed by a maintenance dose of 5 mg/kg/day [18]. Caffeine and theophylline, despite having similar chemical structures, have slightly different clinical efficacies in managing and preventing acute obstructive pulmonary diseases.

Caffeine blocks adenosine at the A1 and A2 receptors while stimulating catecholamine release. As a result of this, there is a general improvement in an individual's well-being, as well as in their ability to concentrate and energy levels. In addition, research suggests that caffeine can improve the performance of specific mental tasks [19]. When taken in large doses, caffeine inhibits phosphodiesterase. This, in turn, leads to an increase in intracellular cyclic adenosine monophosphate, a rise in adrenoceptor activity, and eventually bronchodilation [20, 21]. Anti-inflammatory effects have also been reported with caffeine because it inhibits the release of tumor necrosis factor-alpha [22, 23].

Caffeine's efficacy in treating AOP has been extensively studied, with significant findings highlighted in seminal works. Schmidt et al. conducted a landmark randomized controlled trial demonstrating that caffeine reduces the incidence of bronchopulmonary dysplasia in preterm infants [24]. Subsequent follow-up studies by the same group revealed that caffeine therapy not only improved survival rates without neurodevelopmental disability at 18–21 months but also had lasting positive effects on academic performance, motor function, and behavior at 11 years of age [17, 24, 25]. Some studies have reported using caffeine citrate as a treatment for prematurity apnea in high-income countries [26]. Although caffeine has been approved for use in neonatal apnea management, there appears to be a paucity of data on its use in low- and middle-income countries (LMICs). LMICs are defined as countries belonging to low-income countries, LMICs, and upper-middle-income countries [27].

This rapid systematic review sought to assess caffeine citrate's efficacy, safety, and/or cost-effectiveness in LMICs. The review focused on studies published between 2000 and 2023. This period was selected to capture the most recent and relevant data on caffeine use for prematurity apnea, as significant changes in clinical practice and guidelines have occurred over the past two decades. However, this limitation in date range may exclude earlier seminal works and studies that established caffeine's initial efficacy and safety for this condition. To mitigate this, the review also references earlier studies that have shaped current understanding and practices [16, 24]. This review also identified gaps in using caffeine citrate in LMICs. This study's findings will aid the medical community, the general public, and policymakers in their efforts to improve neonatal care.

2 | Methods

2.1 | Study Design, Participants, Intervention, Comparator, and Approach

A rapid systematic review was conducted using interventional and observational studies on caffeine citrate as therapy for AOP

TABLE 1 | Population intervention comparator outcome (PICO) on the use of caffeine citrate in neonatal apnea management in low-middle income countries.

Population	Studies reporting the treatment of neonatal apnea in low- and middle-income countries
Intervention	The administration of caffeine citrate to treat apnea of prematurity
Comparator	The administration of aminophylline to treat apnea of prematurity
Outcome	The efficacy, safety, and cost-effectiveness of caffeine citrate in the management of neonatal apnea in low- and middle-income countries

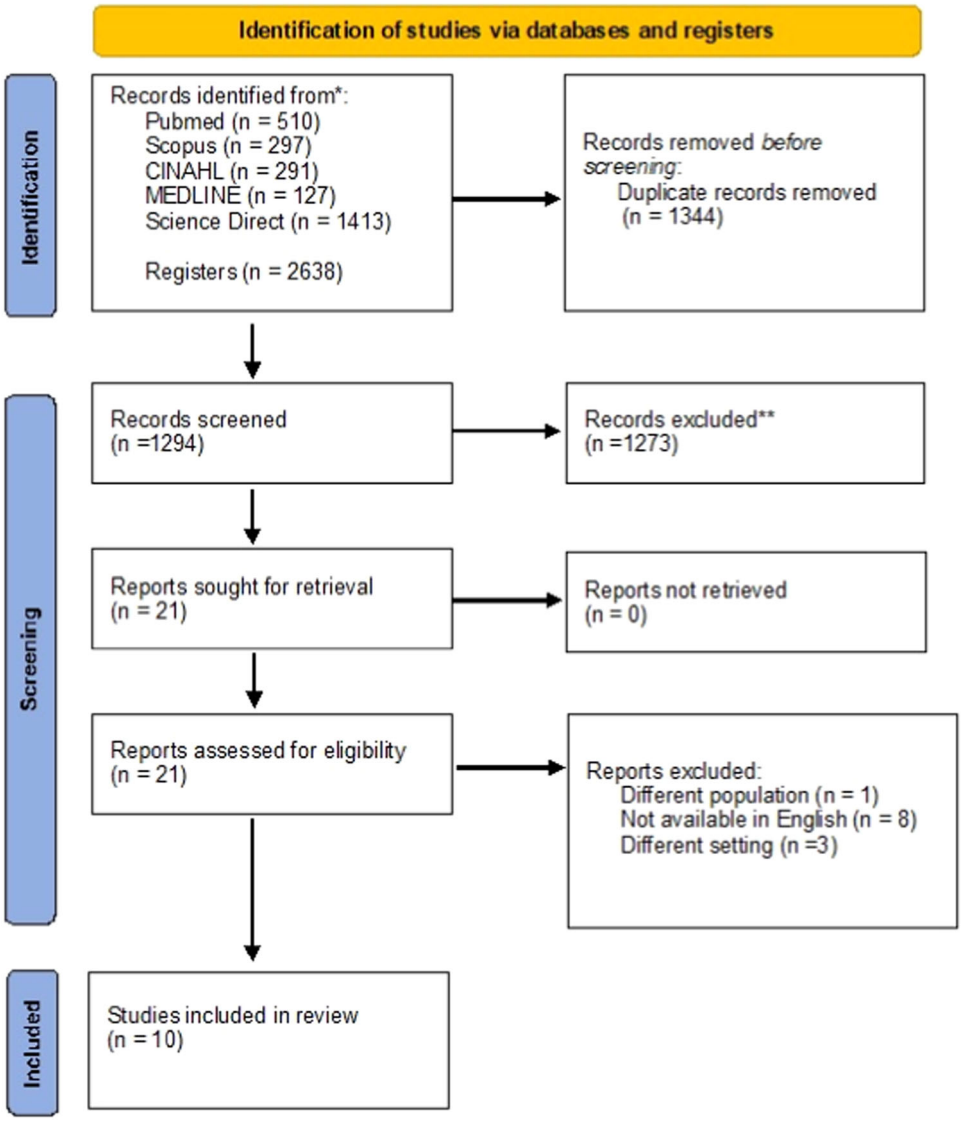

FIGURE 1 | PRISMA flowchart for a rapid review on the use of caffeine citrate in the management of neonatal apnea in low- and middle-income countries.

in LMICs. The search used the population, intervention, comparator, and outcome model, shown in Table 1. We searched studies that had neonates with apnea (defined as a cessation of breathing for 20 s or more), bradycardia (defined as a heart rate of less than 100 beats per minute), or oxygen desaturation (defined as a SpO_2 of less than 80%) that occurred more than 12 h after birth. For these studies, AOP had to be treated with caffeine citrate and a comparator, aminophylline.

2.2 | Search Strategy

Five bibliographic databases were searched for full-text articles published between January 1, 2000 and March 31, 2023. This period was selected due to significant changes in caffeine usage guidelines, the emergence of new research methodologies and findings related to AOP treatment. Post-2000, there has been a notable increase in research focused on neonatal

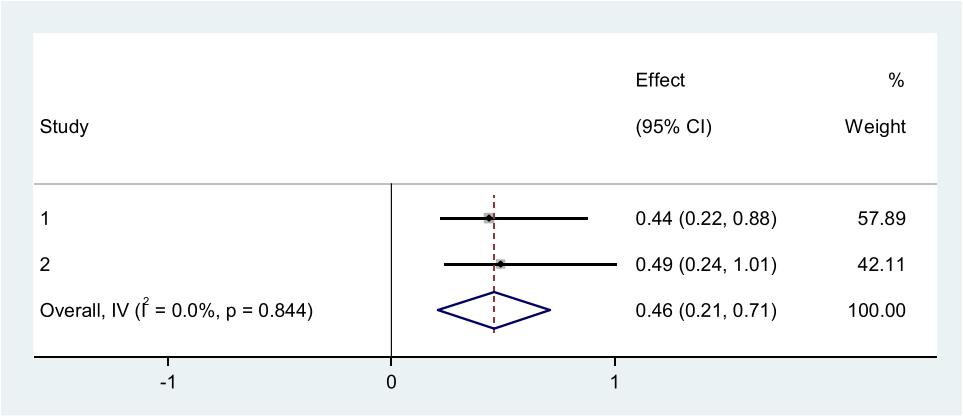

FIGURE 2 | Meta-analysis using the common-effect inverse-variance model to assess recurrent apnea associated with the use of caffeine citrate versus aminophylline in the management of neonatal apnea in observational studies included: Study 1—Zhang et al. [56]; Study 2—Xu et al. [36]. Effect estimate = relative risk (RR), the RR of 0.46 indicates the risk of recurrent apnea is reduced by 54% in the caffeine group compared to the aminophylline group. The confidence interval (CI) of 0.21–0.713 suggests that if the study were repeated multiple times, 95% of the time the true RR would fall within this range. The variance of the effect estimate (RR) for each study was calculated. The weights were calculated by dividing each study's inverse variance by the sum of the inverse variances of all included studies. The overall effect estimate (weighted average) was calculated by multiplying each study's effect estimate by its corresponding weight and summing the products.

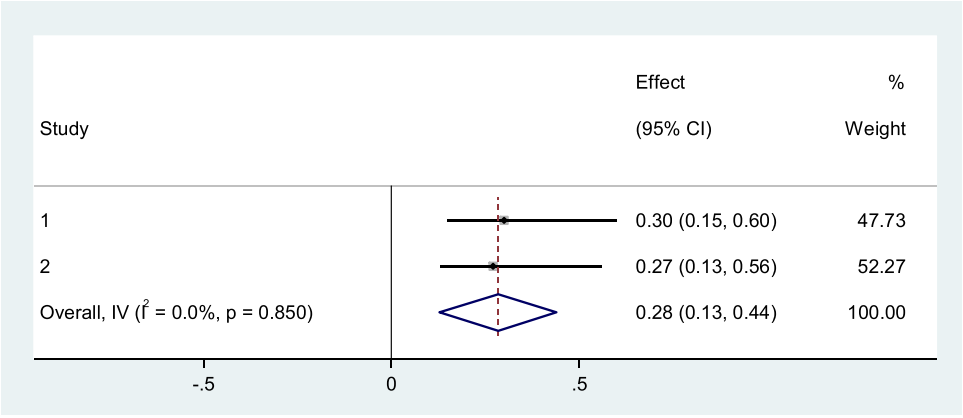

FIGURE 3 | Meta-analysis using the common-effect inverse-variance model to assess the relative risk of tachycardia adverse effects of caffeine citrate versus aminophylline in the management of neonatal apnea. Study 1—Shivakumar et al. [34]; Study 2—Shivakumar et al. [55]. Effect estimate = relative risk. The RR of 0.28 indicates that the risk of tachycardia is reduced by 72% in the caffeine group compared to the aminophylline group. The confidence interval (CI) of 0.13–0.44 suggests that if the study were repeated multiple times, 95% of the time the true RR would fall within this range. The variance of the effect estimate (RR) for each study was calculated. The weights were calculated by dividing each study's inverse variance by the sum of the inverse variances of all included studies. The overall effect estimate (weighted average) was calculated by multiplying each study's effect estimate by its corresponding weight and summing the products.

care and caffeine therapy, making this period pertinent for this review. The databases were ScienceDirect, Pub-Med, Cumulative Index to Nursing and Allied Health Literature, Medline, and Scopus. In the search, the following keyword combinations were used: “Caffeine Citrate” or “Caffeine” or “Citrates” and “Aminophylline” or “Theophylline” and “Apnea” or “Apnea” or “Neonatal apnea” and “Preterm infants” or “Infant, Premature” or “ Premature Infant” or “ Infants, Preterm” or “Neonatal Prematurity.” The inclusion of theophylline in the search strategy was due to its historical and clinical significance as an alternative methylxanthine used in treating AOP, providing a relevant comparator to caffeine. Data were extracted using the Mendeley program, and the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines were adhered to for the systematic review process, serving as a comprehensive framework for writing and reporting the review. All study abstracts and titles were screened. Editorials, reviews, and other non-original works were excluded to maintain the rigor and specificity of the review. This review exclusively focused on peer-reviewed articles and did not include gray literature. While this approach ensured the inclusion of rigorously reviewed studies, it may have limited the scope by excluding potentially relevant unpublished or non-peer-reviewed data. This was carried out to ensure that the studies included were relevant to the goals of the review. The PRISMA extension for scoping reviews (PRISMA-ScR) checklist was mapped using the PRISMA-P chart, which served as the basis for the selection process. The summary of the entire process and PRISMA flowchart is outlined in Figure 1.

2.3 | Eligibility Criteria

2.3.1 | Inclusion Criteria

We included studies reporting treatment of AOP (defined as a cessation of breathing for 20 s or more or a respiratory pause associated with oxygen desaturation and/or bradycardia) in LMICs. These included Observational and Randomized Control Trials. Also included were studies with a group receiving caffeine citrate (intervention) and a group receiving aminophylline (comparator). The articles published were in English and relevant to this study's overall research questions. We included articles published from January 1, 2000 to March 31, 2023. The UN classifies countries based on gross national income (GNI) per capita [28]. This study included countries with a GNI of less than $12,615, including low-income, upper-middle-income, and LMICs.

2.3.2 | Exclusion Criteria

We excluded articles with studies conducted in high-income countries, those with data collection and management practices unrelated to medicine, studies describing outcomes unrelated to the management of AOP, and studies that did not describe the population.

2.4 | Data Collation, Statistics, and Quality Control

The authors of this manuscript (C.M.N. and E.K.O.) were involved in the abstract review and data extraction process. Any disagreements in these processes were resolved by discussion between the two authors and the inclusion of the third author (S.K.A.). Each pertinent publication included in the review was electronically captured using a charting form. The form had details of the study's authors, country of study, year of publication, objectives/purposes, sample size, study population, methods used, research findings, and conclusion.

A thematic analysis was done to extract relevant information [29]. Publications included were appraised for information on caffeine citrate treatment outcomes in neonates with apnea conducted in LMICs. The content of the included studies was examined using Microsoft Excel 2016. Afterward, PRISMA-ScR was used to present the results. Results were presented as tables, graphs, or plots. A trend analysis was used to show how the study's circular trajectory changed over time. Furthermore, the common-effect inverse-variance model meta-analysis approach was used to assess the relative risk (RR) of either caffeine citrate or aminophylline to cause adverse effects. The common-effect inverse-variance model is a powerful tool that provides evidence from multiple studies and gives a more precise estimate of the true effect size [30]. The common-effect inverse-variance model was used because it allows researchers to account for variability across studies and draw more reliable conclusions about the relationship between variables of interest [31]. The chi-square test, Cochran and I2 statistics were used to assess study heterogeneity. Meta-analysis was conducted using the STATA software. A leave-one-out sensitivity analysis was

TABLE 2 | Number of neonates with recurrent apnea associated with the use of caffeine citrate versus aminophylline in the management of neonatal apnea.

Authors/year	Country	Caffeine (events)	Aminophylline (events)	Caffeine (risk)	Aminophylline (risk)	RR (95% CI)
Schellack et al. [32]	South Africa	1/15	3/16	0.067	0.188	0.356 (0.041–3.050)
Zhang et al. [56]	China	11/77	14/43	0.143	0.326	0.439 (0.219–0.880)
Yu et al. [37]	China	1/20	2/18	0.050	0.110	0.50 (0.047–5.34)
Khurana et al. [39]	India	28/73	17/70	0.380	0.240	1.570 (0.950–2.619
Zulqarnain et al. [40]	Pakistan	1/50	2/50	0.020	0.040	0.50 (0.047–5.340)
Xu et al. 2014 [36]	China	9/65	17/60	0.138	0.280	0.490 (0.236–1.011)

Note: RR < 1 – negative association, RR = 1 – no association, RR > 1 – positive association. Treatment = caffeine, Control = aminophylline, outcome measured in risk ratio, Event = the occurrence of recurrent apnea within the study population, Numerator = number of patients who had recurrent apnea within the study population, Denominator = study population, Risk = the probability of recurrent apnea occurring within the study population over a defined period.
Abbreviations: CI = confidence interval; RR = risk ratio.

TABLE 3 | Number of neonates with serum concentrations of aminophylline and caffeine citrate outside the recommended therapeutic range during the management of neonatal apnea.

Author/year	Country	Caffeine (events)	Aminophylline (events)	Caffeine (risk)	Aminophylline (risk)	RR (95% CI)
Schellack et al. [32]	South Africa	(1/16)	(1/13)	0.063	0.077	0.813 (0.056–11.774)
Shivakumar et al. [34]	India	(1/13)	(13/15)	0.077	0.087	0.089 (0.013–0.590)
Zulqarnain et al. [40]	Pakistan	(0/50)	(0/50)	0	0	N/A

Note: RR < 1 – negative association, RR = 1 – no association, RR > 1 – positive association. Treatment = caffeine, Control = aminophylline, outcome measured in risk ratio, Event = the occurrence of serum concentrations that fall outside of the recommended therapeutic range within the study population, Numerator = number of patients who had serum concentrations outside the recommended therapeutic range, Denominator = study population, Risk = the probability of nontherapeutic serum concentration range occurring within the study population over a defined period.
Abbreviations: CI, confidence interval; RR, risk ratio.

TABLE 4 | Occurrence of tachycardia adverse effects associated with the use of caffeine citrate in the management of neonatal apnea.

Author/year	Country	Caffeine (events)	Aminophylline (events)	Caffeine (risk)	Aminophylline (risk)	RR (95% CI)
Shivakumar et al. [34]	India	(6/77)	(20/79)	0.078	0.253	0.30 (0.15–0.60)
Xu et al. [37]	China	(1/69)	(9/60)	0.014	0.15	0.10 (0.01–0.79)
Schellack et al. [32]	South Africa					N/A

Note: RR < 1 – negative association, RR = 1 – no association, RR > 1 – positive association. Treatment = caffeine, Control = aminophylline, outcome measured in risk ratio, Event = the occurrence of tachycardia within the study population, Numerator = number of patients who had tachycardia within the study population, Denominator = study population, Risk = the probability of tachycardia occurring within the study population over a defined period.
Abbreviations: CI, confidence interval; RR, risk ratio.

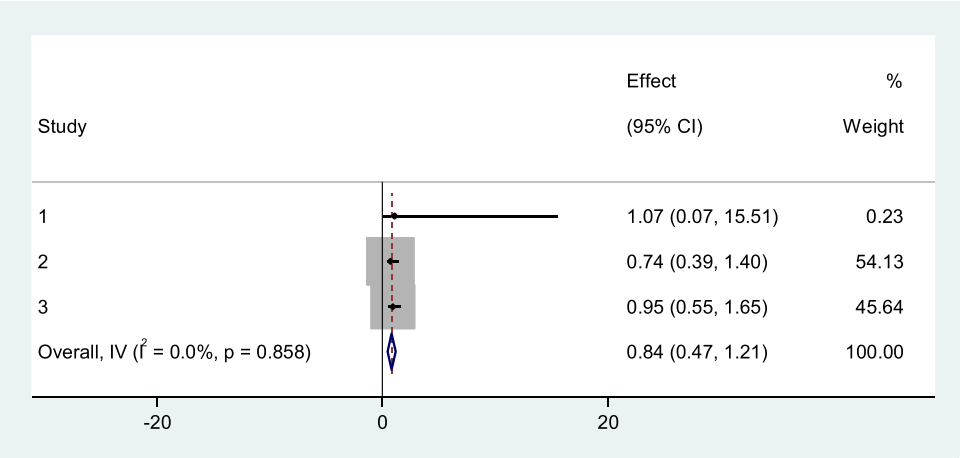

FIGURE 4 | Meta-analysis using the common-effect inverse-variance model to assess the relative risk of gastrointestinal adverse effects associated with the use of caffeine citrate versus aminophylline in the management of neonatal apnea in interventional studies. Study 1—Schellack et al. [32]; Study 2—Shivakumar et al. [34]; Study 3—Shivakumar et al. [55]. Effect estimate = relative risk. The RR of 0.845 indicates that the risk of gastrointestinal adverse effects is reduced by 16% in the caffeine group compared to the aminophylline group. The confidence interval (CI) of (0.47–1.21) suggests that if the study were repeated multiple times, 95% of the time the true RR would fall within this range. The variance of the effect estimate (RR) for each study was calculated. The weights were calculated by dividing each study's inverse variance by the sum of the inverse variances of all included studies. The overall effect estimate (weighted average) was calculated by multiplying each study's effect estimate by its corresponding weight and summing the products.

additionally conducted to assess the impact of a single study on the combined estimate of the other studies.

The Newcastle–Ottawa Scale was used to assess the risk of bias in cohort studies based on patient selection, comparability, and outcome assessment. Scores ranging from 7 to 9 represented high-quality articles, 5–7 represented moderate-quality studies, and 0–5 represented low-quality studies (Table S1). Sensitivity analysis was employed to determine the impact of a single study on the combined effect size of a single study on pooled estimates (Table S3). The Critical Appraisal Skills Program for Randomized Control Trials checklist was also used to evaluate the quality of Randomized Control Trials.

3 | Results

The databases searched yielded a total of 2638 potential articles. Each of the articles was evaluated based on the title and abstract. A total of 1294 potential articles were reviewed after 1344 duplicates were removed, including the bibliographic and gray literature searches. Then, 1197 studies were excluded by title and abstract screening. Finally, four observational studies and six randomized controlled trials were considered eligible for inclusion. The majority of the articles were from countries with an English-speaking population. India (n = 4) had the highest contributions.

3.1 | Efficacy of Caffeine Versus Aminophylline in the Management of AOP

3.1.1 | Recurrent Apnea

Recurrent apnea was included as an outcome of five studies involving 713 neonates. The meta-analysis from the observational studies revealed a reduced risk of recurrent apnea in the caffeine group compared to aminophylline (RR = 0.46, 95% CI = 0.21–0.71, $p < 0.05$). Meta-analysis using the common-effect inverse-variance model on recurrent apnea is summarized in Figure 2. Heterogeneity between the studies was low ($I^2 = 0\%$, $p = 0.84$). The meta-analysis from the interventional studies also revealed an increased risk of recurrent apnea in the caffeine group compared to aminophylline (RR = 1.25 95% CI = 0.59–1.92, $p < 0.05$). Meta-analysis using the common-effect inverse-variance model on recurrent apnea is summarized in Figure 3. Heterogeneity between the studies was low ($I^2 = 0\%$, $p = 0.48$). In a study conducted in South Africa, neonates on caffeine citrate experienced fewer apnea attacks than those on aminophylline [32]. In a related study that was a clinical trial carried out in South Africa, the researchers found that apnea did not occur when the participants stopped taking caffeine citrate following the recommended protocol [33]. On the contrary, a study carried out in India found that neonates who were administered aminophylline had significantly fewer episodes of apneic breathing after 4–7 days than those who were given caffeine [34, 35]. In another study carried out in China among preterm infants with apnea, the response rate of caffeine citrate was 86%, which was considerably greater ($p < 0.05$) than the response rate of aminophylline, which was 72% [36]. This corroborates two additional studies that were carried out in China that showed that infants who received caffeine citrate had a decreased frequency of apnea ($p < 0.01$) compared to infants who received aminophylline [37] (Table 2).

3.1.2 | Blood Concentrations

In premature newborns, the blood concentrations of aminophylline and caffeine were within the normal range (5–20 g/mL), according to a study in South Africa [32]. One patient in the aminophylline group had a blood concentration below the

TABLE 5 | Number of neonates with gastrointestinal adverse effects associated with the use of caffeine versus aminophylline in the management of neonatal apnea.

Author/year	Country	Caffeine (events)	Aminophylline (events)	Caffeine (risk)	Aminophylline (risk)	RR (95% CI)
Schellack et al. [32]	South Africa	(1/15)	(1/16)	0.067	0.063	1.067 (0.073–15.508)
Shivakumar et al. [34]	India	(13/77)	(18/79)	0.169	0.228	0.740 (0.390–1.40)
Xu et al. [36]	China	(7/65)	(15/60)	0.108	0.250	0.440 (0.189–0.983)
Zhang et al. [56]	China	0/77	1/43	0	0.022	N/A

Note: RR < 1 – negative association, RR = 1 – no association, RR > 1 – positive association. Treatment = caffeine, Control = aminophylline, outcome measured in risk ratio, Event = the occurrence of gastrointestinal adverse effects within the study population, Numerator = number of patients who developed gastrointestinal adverse effects, Denominator = study population, Risk = the probability of gastrointestinal adverse effects occurring within the study population over a defined period.
Abbreviations: CI, confidence interval; RR, risk ratio.

TABLE 6 | Occurrence of central nervous system adverse effects associated with the use of caffeine citrate in the management of apnea of prematurity.

Author/year	Country	Caffeine (events)	Aminophylline (events)	Caffeine (risk)	Aminophylline (risk)	RR (95% CI)
Schellack et al. [32]	South Africa					0
Shivakumar et al. [34]	India	(6/79)	(7/77)	0.0759	0.090	0.87 (0.31–2.49)
Khurana et al. [39]	India	(5/120)	(30/120)	0.04	0.25	0.16 (0.02–1.36)

Note: RR < 1 – negative association, RR = 1 – no association, RR > 1 – positive association. Treatment = caffeine, Control = aminophylline, outcome measured in risk ratio, Relative Risk = the likelihood of developing adverse effects in the central nervous system with the use of caffeine as compared to aminophylline, Event = the occurrence of central nervous adverse effects within the study population, Numerator = number of patients who developed central nervous system adverse effects, Denominator = study population, Risk = the probability of central nervous adverse effects occurring within the study population over a defined period.
Abbreviations: CI, confidence interval; RR, risk ratio.

therapeutic limit of 0.35 g/mL, and one in the caffeine group had a serum concentration above the therapeutic range of 22.59 g/mL. Both of these patients were excluded from the study. Shivakumar et al. [34] observed that 93% ($n = 39$) of patients who received caffeine citrate were within the therapeutic range, with a mean plasma concentration of 14.4 g/mL. In the group that received aminophylline ($n = 50$), plasma levels varied from 0.68 to 50.37 mg/L across the median (interquartile range). Most of these patients, 52% ($n = 26$), had aminophylline concentrations above the therapeutic range. In a study in Pakistan, the therapeutic range for caffeine was achieved by 92% of the neonates [40]. In summary, these studies concluded that levels of caffeine citrate in neonates were within acceptable therapeutic ranges compared to aminophylline (Table 3).

3.2 | Safety of Caffeine Versus Aminophylline in the Management of AOP

3.2.1 | Tachycardia

Tachycardia was included as an outcome of three studies involving 424 neonates. In the meta-analysis of the interventional studies included in this review, the caffeine group had a lower incidence of tachycardia than the aminophylline group (RR = 0.28, 95% CI = 0.13–0.44, $p < 0.05$). These studies, however, had no significant heterogeneity ($I^2 = 0.0\%$, $p = 0.850$).

The forest plot and results on tachycardia are summarized in Figure 3 and Table 4, respectively. In a study conducted in South Africa, the aminophylline arm had a higher median pulse rate (beats per minute) compared to the caffeine arm for 2 days: day 7: 160 versus 148 ($p = 0.019$); day 9: 168 versus 147 ($p = 0.020$) [32]. In one of the studies conducted in India, the caffeine group was less likely to develop tachycardia (RR = 0.30; 95% CI = 0.15–0.60; $p < 0.001$) [34]. A study conducted in China also found that aminophylline was linked to a higher risk of tachycardia [36].

3.2.2 | Gastrointestinal Adverse Effects

Gastrointestinal adverse effects were included as an outcome in the meta-analysis of four studies (455 neonates). Compared to aminophylline, preterm infants treated with caffeine citrate had a lower risk of gastrointestinal side effects (RR = 0.845, 95% CI = 0.47–1.21, $p > 0.050$) in interventional studies. Heterogeneity amongst studies was, however, low ($I^2 = 0.0\%$, $p = 0.858$, Figure 4). In a study conducted in South Africa, the neonates given aminophylline experienced difficulty breastfeeding and had to be given manually pumped breast milk [32]. According to another study conducted in the same region [33], caffeine citrate did not interfere with the feeding of premature infants. Xu et al. reported that neonates who received aminophylline experienced a considerably higher incidence of eating intolerance when compared to the caffeine-citrate group [36]. According to Shivakumar et al. [34], no significant statistical difference was found in patients who took caffeine citrate compared to patients who took aminophylline in terms of feeding intolerance (RR = 0.95; 95% CI = 0.55–1.65, $p > 0.05$). There is no significant difference in feeding intolerance between the aminophylline and the caffeine citrate groups (17% vs. 22.8%, RR = 0.74; 95% CI = 0.39–1.40, $p = 0.35$) (Table 5).

3.2.3 | Central Nervous System Adverse Effects

According to Schlelack et al. [32], neither the caffeine nor the aminophylline group had any jitteriness during the clinical trial. In another study, there was no statistical difference in terms of jitterness in patients who received caffeine and who took aminophylline (RR = 0.87; 95% CI = 0.31–2.4, $p > 0.05$) [34].

No statistical difference was observed between caffeine citrate and aminophylline in infants for cognitive impairment (RR = 0.16, 95% CI = 0.02–1.36, $p > 0.05$), developing motor deficits (RR = 0.50, 95% CI = 0.12–1.95, $p > 0.05$) and the development of linguistic issues (RR = 0.76; 95% CI = 0.36-1.58, $p > 0.05$) [39] (Table 6).

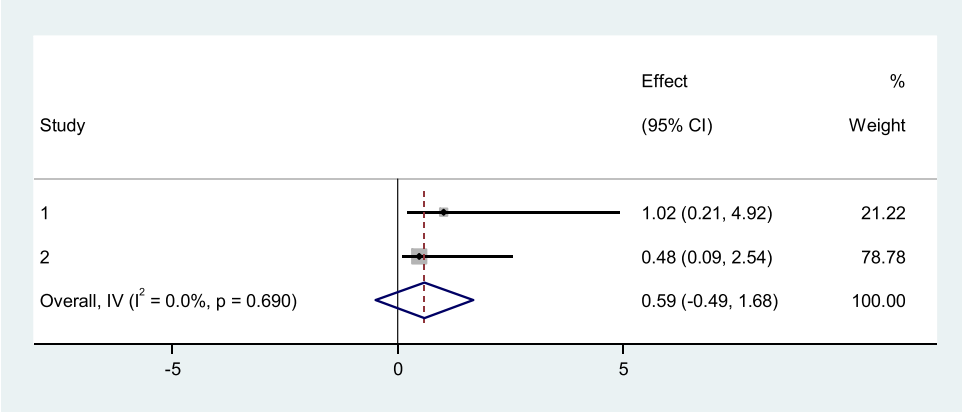

FIGURE 5 | Meta-analysis using the common-effect inverse-variance model to assess the relative risk of hyperglycemia adverse effects associated with the use of caffeine citrate versus aminophylline in the management of neonatal apnea in interventional studies. Study 1—Shivakumar et al. [34]; Study 2—Shivakumar et al. [55]. Effect estimate = relative risk. The RR of 0.59 indicates that the risk of hyperglycemia is reduced by 41% in the caffeine group compared to the aminophylline group. The confidence interval (CI) of 0.493–1.68 suggests that if the study were repeated multiple times, 95% of the time, the true RR would fall within this range. The variance of the effect estimate (RR) for each study was calculated. The weights were calculated by dividing each study's inverse variance by the sum of the inverse variances of all included studies. The overall effect estimate (weighted average) was calculated by multiplying each study's effect estimate by its corresponding weight and summing the products.

3.2.4 | Hyperglycemia

The meta-analysis from the interventional studies revealed no significant risk of hyperglycemia in the caffeine citrate group compared to aminophylline (RR = 0.59, 95% CI = −0.493 to 01.68, $p = 0.698$). Heterogeneity between the studies was low ($I^2 = 0.0\%$, $p = 0.69$, Figure 5). Three studies involving 424 neonates reported the relationship between caffeine citrate and aminophylline use on blood glucose levels in neonates (Table 7). Two of the studies concluded that the RR of developing hyperglycemia was 0.385 (95% CI = 0.144–1.023) and 0.480 (95% CI = 0.09–2.54) respectively [34, 36].

3.2.5 | Sensitivity Analysis

The meta-analysis results (Table S3) indicate that the findings are not disproportionately influenced by any one study, indicating consistent uncertainty about the effect of interventions on recurrent apnea.

3.3 | Cost-Effectiveness of Caffeine Citrate

In Ghana, Kenya, Nigeria, Tanzania, and Uganda, the price of caffeine citrate per 3 mL vial ranges from $1.73 to 73.63 (Figure 6). In Kenya, a 7-day course of caffeine citrate treatment can be about $600, which is significantly more than the average monthly income of most people. According to studies conducted in India [34], there was no significant difference in the length of hospital stays between the groups that received aminophylline or caffeine citrate. The average end-customer price for a 25 mg/mL vial of caffeine citrate was $2.7 in India [41].

4 | Discussion

This rapid systematic review aimed to provide evidence of caffeine citrate's efficacy, safety, and cost-effectiveness in managing AOP in LMICs. Although methylxanthines are widely used as a treatment for AOP in many countries, there appears to be a paucity of data on the use of caffeine citrate in LMICs. Undoubtedly, the global community seeks to address inequities in neonatal mortality between well-resourced and poorly-resourced countries. Thus, we highlight caffeine, among many essential medicines, as an example of this disparity in neonatal care.

When caffeine citrate was compared to aminophylline in the few studies conducted in LMICs, caffeine citrate significantly reduced the number of apnea episodes. These findings corroborate research in high-income countries [16, 42]. Indeed, it is always relevant to investigate the effects of drugs in different populations, considering genetic variation that may exist across continents [43]. Even though the total number of articles included in this scoping review was somewhat small, this review gives an initial assessment of the use of caffeine citrate in LMICs.

This review observed high serum aminophylline concentrations in some neonates, possibly due to the narrow therapeutic index

TABLE 7 | Number of neonates with hyperglycemia adverse effects associated with the use of caffeine or aminophylline in the management of apnea of prematurity.

Author/year	Country	Caffeine (events)	Aminophylline (events)	Caffeine (risk)	Aminophylline (risk)	RR (95% CI)
Xu et al. [36]	China	5/65	12/60	0.077	0.20	0.385 (0.144–1.023)
Shivakumar et al. [34]	India	2/77	2/79	0.026	0.025	1.026 (0.21–4.92)

Note: RR < 1 – negative association, RR = 1 – no association, RR > 1 – positive association. Treatment = caffeine, Control = aminophylline, outcome measured in risk ratio, Event = the occurrence of hyperglycemia within the study population, Numerator = number of patients who developed hyperglycemia, Denominator = study population, Risk = the probability of hyperglycemia occurring within the study population over a defined period.
Abbreviations: CI, confidence interval; RR, risk ratio.

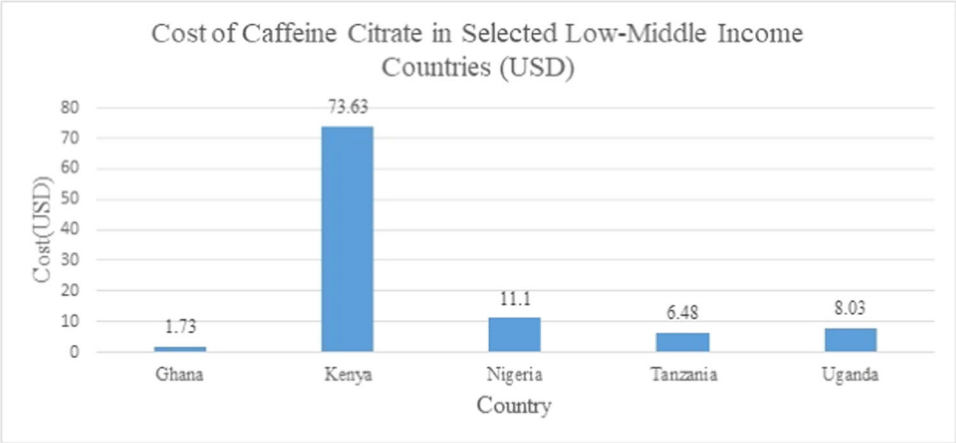

FIGURE 6 | Cost of caffeine citrate per 3 mL vial in some low- and middle-income countries.

of aminophylline [44]. Reports suggest that elevated serum levels of aminophylline are associated with an increased risk of adverse effects, including dehydration, fever, convulsions, and even death [45]. On the other hand, the therapeutic index of caffeine ranges between 3 and 30 mg/L and is considered relatively safe [46]. Moreover, caffeine has lesser plasma concentration fluctuations than aminophylline [47].

Methylxanthine use is often associated with some acute adverse effects, the commonest being tachycardia. According to the findings of this review, neonates who were given caffeine had a lower risk of developing tachycardia than those who were given aminophylline [34]. This finding corroborated with others conducted in high-income countries [48, 49], where caffeine stimulates the central nervous system more effectively than aminophylline. It is possible that the phenethyl alcohol present in aminophylline could directly activate the respiratory center, thereby increasing its sensitivity to carbon dioxide. This could increase the breathing rate and, consequently, the heart rate. Accordingly, neonates born prematurely who experience sinus tachycardia exhibit distinct toxicokinetics related to aminophylline [13]. Furthermore, this review revealed that neonates who received caffeine had a significantly reduced incidence of feeding intolerance [32, 36] compared to aminophylline, making the former less likely to promote adverse gastrointestinal tract effects.

In this review, caffeine use among neonates in LMICs showed fewer central nervous system adverse effects compared to aminophylline. Liu et al. [38] concluded that caffeine consumption over an extended period may offer direct protection from injury to the growing brain. Others also report that caffeine therapy for AOP enhanced visuospatial, visuoperceptual, and visuomotor capabilities [50]. General intelligence, attention, and behavior were also not adversely affected by caffeine, highlighting caffeine therapy's long-term safety for AOP in neonates [50]. Although this study did not reveal a lower incidence of hyperglycemia compared to aminophylline with caffeine use, aminophylline has been reported to raise blood glucose levels by promoting the release of stress hormones such as cortisol and adrenaline. These stress biomarkers can interfere with the action of insulin, promoting hyperglycemia [51].

In high-income countries, caffeine citrate is often used with positive pressure ventilation to treat acute obstructive pulmonary disease, particularly in the first few weeks of the life of infants [52]. Our findings align with the established benefits of caffeine documented in high-income countries, as highlighted by seminal studies. Schmidt et al. demonstrated that caffeine significantly reduces the risk of bronchopulmonary dysplasia, a common complication in preterm infants [53]. This benefit is crucial for LMICs with limited access to advanced neonatal care. Furthermore, the long-term follow-up studies by Schmidt et al. underscore the importance of early caffeine therapy in improving neurodevelopmental outcomes and reducing long-term disabilities [17, 53]. These findings are particularly relevant for LMICs, where the burden of disability from preterm births is a significant public health concern. From the findings of this review, it appears that caffeine citrate is not common in LMICs, particularly in the Sub-Saharan African region [54]. Some obstacles to using caffeine citrate for AOP in LMICs could be its expensive and limited availability [54]. Other factors limiting its availability could include complex and challenging government regulations and a lack of demand from medical practitioners who believe other methylxanthines are suitable substitutes for caffeine.

In summary, caffeine citrate is an excellent alternative to aminophylline for treating AOP. Most studies included in this review were randomized controlled trials, which gives an even better picture of caffeine versus aminophylline use for AOP. We believe that findings from this review could start discussions among industry, drug regulatory bodies, and the global health community on the need to enhance the availability and affordability of caffeine citrate for neonatal care in LMICs. It was noted that not all included RCTs provided detailed power calculations. However, most studies reported sample sizes that aligned with standard practices for clinical trials in neonatal research. Further investigation into the adequacy of sample sizes and power calculations in these RCTs would benefit future studies. Additionally, we believe that generating data on the efficacy and feasibility of caffeine citrate use in neonatal care in LMICs could lead to accelerated progress in improving the clinical outcomes of neonates in LMICs.

Author Contributions

Seth Kwabena Amponsah: conceptualization, supervision, writing – review and editing. **Chris Mensah Nartey:** conceptualization, formal analysis, writing – original draft. **Emmanuel Kwaku Ofori:** conceptualization, supervision, writing – original draft, writing – review and editing.

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Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

All data generated or analyzed during this study are included in this published article.

Transparency Statement

The lead author Emmanuel Kwaku Ofori affirms that this manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained.

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Supporting Information

Additional supporting information can be found online in the Supporting Information section.