Effect of prophylactic caffeine in the treatment of apnea in very low birth weight infants: a meta-analysis

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Abstract

Objective: The purpose of this meta-analysis is to investigate the effect of prophylactic caffeine use in the treatment of apnea and other clinic outcomes in very low birth weight infants. **Methods:** From inception to 20 May 2022, PubMed, Embase, Web of Science, Scopus, EBSCO, CNKI, and Cochrane databases were systematically searched. The meta-analysis was carried out using STATA and RevMan software. **Results**: Eleven randomized controlled trials including a total of 4375 very low birth weight infants were evaluated. The pooled demonstrated that prophylactic caffeine use was linked with a significantly lower probability of AOP (OR 0.31, 95%CI: 0.19-0.49, $P<0.001$), duration of mechanical ventilation, and oxygen therapy when compared to control group. It also reduced the incidence of BPD (OR 0.62, 95%CI: 0.54-0.71, $P<0.001$), PDA (OR 0.49, 95%CI: 0.30-0.80, $P=0.005$) and ROP (OR 0.76, 95%CI: 0.65-0.90, $P=0.001$), without raising the risk of NEC, IVH and death before hospital discharge ($P>0.05$). **Conclusion**: This meta-analysis confirmed the beneficial effects of prophylactic caffeine for preventing apnea of prematurity as well as for improving clinical outcomes. However, further research is needed before recommending widespread use of caffeine as a prophylactic treatment in the management of all preterm infants.

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Results : Eleven randomized controlled trials including a total of 4375 very low birth weight infants were evaluated. The pooled demonstrated that prophylactic caffeine use was linked with a significantly lower probability of AOP (OR 0.31, 95%CI: 0.19-0.49,$P<$ 0.001), duration of mechanical ventilation, and oxygen therapy when compared to control group. It also reduced the incidence of BPD (OR 0.62, 95%CI: 0.54-0.71, $P<$ 0.001), PDA (OR 0.49, 95%CI: 0.30-0.80, P =0.005) and ROP (OR 0.76, 95%CI: 0.65-0.90, P =0.001), without raising the risk of NEC, IVH and death before hospital discharge (P >0.05).

Conclusion : This meta-analysis confirmed the beneficial effects of prophylactic caffeine for preventing apnea of prematurity as well as for improving clinical outcomes. However, further research is needed before recommending widespread use of caffeine as a prophylactic treatment in the management of all preterm infants.

Keywords: apnea of prematurity; caffeine; very low birth weight infants; meta-analysis

Abbreviations : AOP: apnea of prematurity; BPD: bronchopulmonary dysplasia; PDA: patent ductus arteriosus; ROP: retinopathy of prematurity; NEC: Necrotizing enterocolitis; IVH: intraventricular hemorrhage

Introduction

Apnea of prematurity (AOP) is defined as the abrupt cessation of breathing for at least 20 seconds in an infant with gestational age less than 37 weeks, followed by both bradycardia and oxygen desaturation[1]. AOP becomes more common with decreased birth weight, affecting 85% of neonates born weighing less than 1,500g[2]. For decades, Methylxanthines have been utilized to effectively treat apnea of prematurity. The preferred methylxanthine for this indication due to its broad therapeutic window and a prolonged serum half-life is caffeine citrate[3]. This finding has been validated in several independent experiments, leading to the widespread use of caffeine as the first-line AOP treatment[4].

Even though caffeine has been widely utilized in neonatal practice, there are no recognized and standardized caffeine administration protocols[5]. Concerns have been expressed about potential safety issues and adverse effects, some of which may be related to the use of caffeine prophylactically. Several studies have found that giving prophylactical caffeine to preterm infants at risk of apnea reduces the time they need for positive pressure ventilation[6]. Caffeine prophylaxis, in addition to its effect on reducing apnea of prematurity, has other benefits on infants multiple organ systems, that includes the brain, lungs, and cardiovascular systems, such as lowering the incidence of bronchopulmonary dysplasia and arterial catheter ligation. In contrast, there are findings suggest that taking caffeine prophylactically may increase the risk of overtreatment, including harms such as intracranial bleeding[7], plus research has found it may increase the mortality rate in premature during vulnerable periods[8].

Therefore, there is still controversy concerning whether the use of prophylactic caffeine improves clinical outcomes as compared to the strict use of caffeine as a therapeutic pharmacological agent. It is necessary to conduct definitive research to prove the comparative effects of prophylactic versus therapeutic caffeine. This meta-analysis aims to assess the effects of the prophylactic initiation of caffeine for apnea and related complications in very low birth weight infants to assist clinicians in continually optimizing their present practice.

Materials and methods

Systematic search and strategy

The meta-analysis was carried out by the Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA)[9]. After inception and before May 2022, PubMed, Embase, Web of Science, EBSCO, Cochrane, Scopus, and CNKI were among the databases searched for relevant articles. The search strategy addressed two of five elements of the PICOS model (Population, Intervention/Exposure). Using Boolean

operators, the search technique merged two areas as MeSH terms, keywords, and text words: ("Caffeine Citrate" OR "Caffeine" OR "Citrates") AND (Apnea) AND ("Preterm Infants" OR "Infant, Premature" OR "Very Low Birth Weight Infants " OR " Infant, Low Birth Weight " OR " Neonatal Prematurity")

Inclusion and exclusion criteria

The selected studies used for this meta-analysis had to match the following criteria:

(1) All infants born after <32 weeks of gestation and birth weight < 1500g; (2) Randomized controlled studies; (3) A group exposed to prophylactic caffeine citrate therapy (0-3 days of life), a control group of infants not receiving caffeine until they develop AOP, and a comparison between the two groups; (4) At least one of the parameters was included in the outcome measures: The primary outcomes of interest were apnea of prematurity (AOP), duration of mechanical ventilator(days) and duration of oxygen therapy(h); Secondary outcomes included: biparietal diameter (BPD), patent ductus arteriosus (PDA), retinopathy of prematurity (ROP), necrotizing enterocolitis (NEC), intra-ventricular hemorrhage (IVH) and death before hospital discharge. All diseases diagnosis relied on the recording of patient charts or surgical data.

Any study that met a specific exclusion criterion was removed from the meta-analysis:

Case reports, reviews, or animal trials; (2) The studies with unclear or inadequate exposure/outcome definitions; and (3) The studies with insufficient information for extraction data.

Data extraction and quality assessment

Two authors independently extracted the data from all of the full articles included in the research. The specific format is as follows: I) General characteristics of study: study, year, number of participants, gestation age. II) Intervention: dosage and duration. III) Outcomes. All discrepancies in data interpretation are handled by discussion with third-party reviewers. If there are inconsistent results indicator units in the research, the units should be uniformly converted before subtask data processing.

Two researchers independently assessed the methodological quality of RCTs using the Cochrane Collaboration's tool. Furthermore, after entering the evaluation data into the RevMan 5.4 software, the bias risk assessment chart could be obtained. Any disagreement was settled by a conversation with the third reviewer, and then the research was then reevaluated.

Data synthesis and analysis

In present article, analyses were conducted using STATA software version 12.0 (Stata Corp, College Station, TX). Weighted mean difference (WMD) and confidence interval (CI) of 95% were calculated for continuous outcomes, while pooled odds ratios (ORs) and confidence interval (CI) of 95% were estimated for dichotomous outcomes. We used I^2 statistics to examine the heterogeneity of the studies. The value of I^2 was reported as a percentage of total variation across studies, where $I^2 > 50\%$ indicates considerable heterogeneity. If no heterogeneity was found between studies, a fixed-effect model was used for meta-analysis. If there was significant heterogeneity among studies, a random-effects model was utilized for the analysis. Sensitivity analysis was performed by deleting each study sequentially to assess the robustness of the combined estimates. Funnel plots, Begg's and Egger's test were used to evaluate and test publication bias, respectively.

Results:

Search results

A total of 1691 studies found during the initial search, 221 duplicates were removed from. 42 articles remained after analyzing the abstracts and titles of 1470 studies. This meta-analysis includes 11 papers after 31 articles were removed through the full-text review. The search strategy is detailed in S Table1. The flow chart in Figure1 describes the selection procedures for the studies, and the PRISMA checklist is presented in the S Table2. Table 1 shows the characteristics of the included research.

The risk-of-bias assessment is depicted in minute detail in Figure 2. Only four studies showed a low risk of bias [10-13], whereas seven research found an unclear risk of bias[14-20]. Randomization was handled correctly in ten studies[10-19], while allocation-sequence concealment was performed adequately in six studies[10-13, 16, 18]. Information on participants and personnel blinding were provided in six studies[10-13, 15, 16], while eight others reported outcome assessor blinding[10-15, 17, 20]. The cause and number of withdrawals and dropouts were provided for each article.

Meta results

Apnea of prematurity

In terms of Apnea of prematurity, 581 participants were included for model was used to calculate overall effect. In the meta-analysis, we observed that the prophylactic caffeine group had lower incidence of apnea compared with control group (OR 0.31, 95%CI: 0.19-0.49,$P<$ 0.001). There was no significant heterogeneity between these studies (I^2=9.2%, P =0.354, Figure 3A). We thus conducted the meta-analysis using a fixed-effects model, and sensitivity analysis confirmed that the result was credible.

Duration of mechanical ventilation and oxygen therapy

Five studies reported duration of mechanical ventilation, and four studies reported duration of oxygen therapy. We observed that the duration of mechanical ventilation (OR -0.72, 95%CI: -0.92 - -0.51,$P<$0.001) and oxygen therapy duration (OR -6.05, 95%CI: -6.56 - -5.54, $P<$0.001) were considerably lower in the prophylactic caffeine group than in the control group. The random-effects model was employed because moderate heterogeneity in duration of mechanical ventilation was identified among the included studies (I^2=52.2%, P=0.079, Figure 3B). We used a fixed-effects model to evaluate the meta-analysis of the duration of oxygen therapy (I^2=23.5%, P=0.270, Figures 3C).

Bronchopulmonary dysplasia

The number of newborns with BPD in the prophylactic caffeine group and control group was observed in 8 trials (4113 infants). We indicated that the occurrence of BPD was lower in the caffeine group than that in the control group (OR 0.62, 95%CI: 0.54-0.71, $P<$ 0.001). There was no significant heterogeneity between these research (I^2 =0.0%, P = 0.639, Figure 4A).

Patent ductus arteriosus

Six studies involving 2962 prematurity included PDA as an outcome. Prematurity in the prophylactic caffeine group had a decreased chance of developing patent ductus arteriosus, according to a pooled analysis (OR 0.49, 95%CI: 0.30-0.80, P =0.005). Significant heterogeneity existed amongst these studies (I^2 =51.6%, P = 0.066, Figure 4B).

Retinopathy of prematurity .

ROP was included as an outcome between the two groups by 5 studies which involved 3499 infants. Compared to control group, neonates in the prophylactic caffeine group had a lower probability of retinopathy of prematurity (OR 0.76, 95%CI: 0.65-0.90, P=0.001). And the heterogeneity between studies was low (I^2=8.1%, P =0.360, Figure 4C).

Necrotizing enterocolitis, intra-ventricular hemorrhage and death before hospital discharge

The possibility of other neonatal complications was assessed. In terms of necrotizing enterocolitis (OR 0.77, 95%CI: 0.59-1.01,P =0.057, Figure 4D), intraventricular hemorrhage (OR 0.71, 95%CI: 0.45-1.12, P =0.145, Figure 4E) and death before hospital discharge (OR 1.13, 95%CI: 0.83-1.54, P =0.44, Figure 4F) , there was no significant statistical difference between the two groups.

Sensitivity analysis and publication bias

We performed a sensitivity analysis of each outcome by removing each study one by one, and we discovered that the meta-analysis results were relatively stable. We calculated publication bias using tools like funnel

plots for all outcomes, and there was no obvious asymmetry (S Figure). Moreover, Begg's and Egger's tests revealed no clear publication bias for all outcomes (P >0.05).

Discussion :

Caffeine citrate is a medication that is extensively used in neonatology and is regarded as the gold standard in the prevention and treatment of apnea of prematurity. The 2019 European consensus guidelines on the management of neonatal respiratory distress syndrome emphasized that prophylactic caffeine administration was associated with improving newborn prognosis[21]. But there were also reviews against the support of the use of prophylactic caffeine for preterm infants at risk of apnea[22]. Therefore, the purpose of this meta-analysis was to explored the effect of prophylactic caffeine on AOP and related complications in very low infants. Prophylactic caffeine use, as compared to the control group, was found to be substantially linked with a lower incidence of apnea, duration of mechanical ventilation and oxygen therapy, BPD, PDA, and ROP. The incidence of NEC, IVH and death before hospital discharge were similar in the two groups. In this review, strong evidence from multiple randomized trials supports prophylactic caffeine for the prevention of AOP and related complications. Firstly, we found that the caffeine-prevented group had fewer apnea events than the control group, which was consistent with several previous studies[23, 24]. Caffeine's primary effects on apnea prevention are respiratory center stimulation, increased minute ventilation, improved carbon dioxide sensitivity, and decreased periodic breathing[25]. It also was demonstrated to be a neuroprotective anti-inflammatory medication that may reduce premature infants' lung inflammation and prevent AOP by activating the pro-inflammatory cascade reaction in newborns[26]. Furthermore, Armanian[11] discovered that caffeine prophylaxis had a greater benefit on the occurrence and severity of apnea in more immature newborns. However, because our study only focuses on the impact on very low birth weight infants, further research is needed to classify the newborn weight.

Our results indicated that prophylactic initiation of caffeine significantly reduce the time for mechanical ventilation and oxygen therapy. Such findings were consistent with the current guideline and Park's previous reviews[27]. The rationale for prophylactic caffeine administration is to maintain spontaneous ventilation by boosting the infant's respiratory drive[28]. Caffeine may also improve respiratory function via bronchodilation, improved diaphragmatic contractility, a mild diuretic effect, and cyclic adenosine-induced transcription of surfactant protein B[29]. This may increase the efficacy rate of noninvasive ventilation while decreasing the need for and duration of invasive ventilation. At the same time, it is a manifestation of positive long-term effects on newborns, since mechanical ventilation and protracted oxygen therapy constitute risk factors for both BPD and poor neurodevelopmental outcomes[30]. Notably, we did not describe the effects of prophylactic caffeine use on the duration of nasal continuous positive airway pressure and CPAP due to a lack of original data, additional research is required to examine the relationships.

According to this meta-analysis, prophylactic caffeine use was associated with a significant reduction in the incidence of BPD. Our findings were consistent with those of Davis et al.[12], who discovered infants whose caffeine was initiated prophylactically showed a 52% decrease in the rate of BPD compared with only 23% in the therapeutic caffeine group. Patel et al. [31] also proposed that prophylactic caffeine use (earlier than 3 days of life) could reduce the risk of BPD or death, particularly in high-risk infants weighing less than 750 g. It was possible that the number of neutrophils in bronchoalveolar lavage fluid increases fastest shortly after birth and within 4 days of life[32], whereas preventive caffeine could reduce neutrophil infiltration in lung tissue, lower levels of CINC-1, MIP-2, McP-1, TNF-0, and IL-6, and thus block the onset of BPD development[33]. Another speculation is that caffeine reduces hyper oxygen lung damage by lowering the production of reactive oxygen species[34]. Furthermore, Chen[35] discovered that a high maintenance dose of prophylactic caffeine use appears to be more efficient in promoting lung maturity of premature infants. However, our study lacked original data and was not discussed, more research is needed to assess the safety of different maintenance doses of caffeine.

We have shown the prophylactic use of caffeine significantly reduced the incidence of PDA compared to the control group. The effect of caffeine on PDA may benefit from the fact that caffeine could stabilize hemodynamic changes in infants, such as improving cardiac output and blood pressure[36]. Another speculation

is that the diuretic effect and prostaglandin antagonistic properties of caffeine could promote the closure of arterial catheter and reduce the intervention rates of PDA[37]. Although observed in several trials[28], the mechanism of the decline of PDA incidence is difficult to explain, additional research on the prophylactic mechanism of caffeine on PDA is required. Furthermore, our study has demonstrated that caffeine has benefits decrease the incidence of ROP. Pharmacologic agents with anti-VGEF properties are ordinarily used for the prevention and treatment for ROP[38]. Caffeine has been shown in preliminary animal studies to prevent ROP by upregulating the sonic hedgehog signaling pathway through vascular endothelial growth factor and insulin-like growth factor, resulting in the conservation of retinal development and angiogenesis[39]. A previous systematic review[8] also found that infants given prophylactic caffeine had a significantly lower risk of PDA and ROP.

Caffeine prophylaxis was not related with a difference in the occurrence of NEC, IVH, and death before hospital discharge when compared to the control group. The conclusions of our systematic review were in accordance with previous studies on the same topic[27, 40]. NEC is an injury to the intestinal mucosa caused by blood flow redistribution under hypoxia stress. Although prophylactic caffeine use can reduce the occurrence of neonatal hypoxia stress, it will also increase gastric juice secretion, resulting in increased intestinal reflux and decreased peristalsis[41]. Caffeine also has both a direct neuroprotective effect as well as adverse effects on the developing brain[42]. As a result, the benefits and drawbacks for premature infants may be balanced. Nevertheless, Kua[8] has been conducted to suggest that prophylactic caffeine use would increase mortality rate. We speculate that the level of newborn care varies across countries. Another possible explanation is survival bias, which occurs when the overall survival rates of very low birth weight infants are low. It highlights the need for future research with more rigorous study design to explore the effects of prophylactic caffeine before strong conclusions can be made.

Limitations

It is worth noting that our meta-analysis has some limitations. Firstly, our study lacks original data on long-term clinical outcomes such as infant respiratory morbidity during the first year of life, demand for oxygen treatment after discharge, and lung function before adulthood, all of which should be further studied in properly designed RCTs. Furthermore, the standard and dosage scheme of prophylactic caffeine use in our included studies are not completely consistent, which may affect data interpretation.

Conclusion

According to our findings, prophylactic use of caffeine is beneficial compared to caffeine therapy in reducing the incidence of AOP, duration of mechanical ventilator and oxygen therapy, BPD, PDA and ROP. It is well appreciated that prophylactic caffeine without increasing the risk of NEC, IVH and death before discharge. Thus, we support on caffeine advocate prophylactic use in several publicly available national and international guidelines. Furthermore, future research is needed to investigate the optimal caffeine prophylaxis dosing and plan for long-term follow-up neonatal outcomes.

Supporting information

S Table1. Search strategy.

S Table2. PRISMA checklist.

S Figure. Funnel plot for the clinic outcomes.

Declarations

Competing interests

The authors report no conflicts of interest.

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Table 1. Characteristics of included studies.

Study	Year	number	Gestation age(weeks) caffeine	Gestation age(weeks) theophylline	intervention	Outcomes

Iranpour	2022	45/45	31.37 (1.55)	31.50 (1.50)	The initial loading dose of 10 mg/kg and a daily dose of 10 mg/kg of caffeine was used after birth, as the daily maintenance dose until the infants tolerated without respiratory support with NCPAP or free oxygen administration
Elmowafi	2021	90/91	28.6 ± 2.1	28.8 ± 1.8	Received intravenous caffeine citrate within the first 72 h of life before the existence of AOP or the need for MV. Caffeine citrate was given as a loading dose of 20 mg/kg/day and a maintenance dose of 10 mg/kg/day.

Chen K	2020	26/30	30.44±1.09	29.91±1.29	intravenous infusion of 20 mg/kg caffeine citrate each time within 8-12 hours after birth, Intravenous infusion at a dose of 5 mg/kg per day was given after 24 hours; the maintenance dose was increased to 10 mg/kg in the presence of persistent AOP
Fakoor	2019	50/50	29.04 ± 1.30	29.38 ± 1.0	20 mg/kg of venous caffeine was injected to Group A in the 2nd day of birth (24-48 h),Then, a maintenance dose was injected 24 h after the first injection with the daily dose of 5 mg/kg.

Ke H	2018	539/557	29.7±4.5	30.1±3.9	Give caffeine citrate immediately after admission, the first dose was 20mg/kg intravenously for 30min, and the maintenance dose was 10mg/(kg·d) 24h late
Amaro	2018	41/42	25.7 (24.3-27.0)	26.1 (24.2-28.4)	a loading dose of caffeine citrate 20 mg/kg from 24h after birth followed by a maintenance dose of 5 mg/kg/day.
Zhao Y	2017	66/66	29.15±1.67	29.67±1.65	intravenously for 30min from 24h after birth, the first dose was 20mg/kg, and maintained at 5mg/kg 24h later, every 24H1, until the gestational age reached 34 weeks

Zhao Z	2017	65/61	31.4±2.7	31.9±2.5	Caffeine citrate was administered immediately after birth (all doses were administered within 2h after birth). The first load dose was 20mg/kg, pumped intravenously at 30min, and the maintenance dose was 5mg/kg intravenously at 24h
Armanian	2016	26/26	28.7±1.95	28.57±2.06	caffeine 20 mg/kg (intravenously (IV)) was administered as the initial dose on the 1st day of life, and then 5 mg/kg (intravenously) daily was used as the maintenance dose for the first 10 days of life

Davis	2010	233/220	27.3(1.84)	27.8(1.76)	A loading dose of 20 mg of caffeine citrate per kilogram of body weight from 24h after birth was followed by a daily maintenance dose of 5 mg/kg
Schmidt	2006	1006/1000	27±2	27±2	loading dose of either 20 mg of caffeine citrate per kilogram of body weight from 24h after birth and followed by a daily maintenance dose of 5 mg per kilogram

Outcomes:AOPDuration of mechanical ventilationDuration of oxygen therapyBPDPDAROPNECIVHDeath before discharge

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