Research, Society and Development, v. 13, n. 5, e8713545785, 2024
(CC BY 4.0) | ISSN 2525-3409 | DOI: http://dx.doi.org/10.33448/rsd-v13i5.45785

Use of caffeine for managing apneia of premature

Uso de cafeína para manejo da apneia da prematuridade

Uso de cafeína para el manejo de la apneia del prematuro

Received: 05/03/2024 | Revised: 05/16/2024 | Accepted: 05/18/2024 | Published: 05/21/2024

José de Ribamar Barroso Jucá Neto
ORCID: https://orcid.org/0000-0003-2750-7621
Centro Universitário Christus, Brazil
E-mail: juca.neto.medicina@gmail.com
Lívia Fontelles Brasil
ORCID: https://orcid.org/0000-0002-8173-7332
Centro Universitário Christus, Brazil
E-mail: liviafontellesbrasil@gmail.com
Letícia Martins de Mendonça
ORCID: https://orcid.org/0009-0003-7377-2693
Centro Universitário Christus, Brazil
E-mail: leticiamartinsdemendonca@hotmail.com
Thiago Rocha Mapurunga
ORCID: https://orcid.org/0009-0007-2286-6437
Centro Universitário Christus, Brazil
E-mail: thiagormapurunga@gmail.com
Emanuelle Cordova de Souza
ORCID: https://orcid.org/0009-0004-6492-3979
Centro Universitário Christus, Brazil
E-mail: emanucsouza@gmail.com
Pedro Iughetti Morais
ORCID: https://orcid.org/0000-0003-0594-6180
Centro Universitário Christus, Brazil
E-mail: pedroiughettimed@gmail.com
Ângela Rocha Mapurunga
ORCID: https://orcid.org/0000-0002-1316-1597
Centro Universitário Christus, Brazil
E-mail: angelamapurunga@gmail.com

Abstract
Apnea of prematurity is a common diagnosis in neonatal intensive care units, especially in preterm patients under 35 weeks or patients born with low birth weight (<1500g). From this perspective, the use of caffeine citrate has short and long-term benefits in this pathology, in addition to reducing the incidence of complications. Methodology: A narrative review of the literature was carried out using the PUBMED database, using the following keywords: "Apnea Prematurity", "Caffeine" and "Treatment", with a 6-year filter, analyzing 164 articles, of which only 34 were included and 130 were excluded. Results and Discussion: Apnea of prematurity is a common pathology in preterm and extremely preterm infants, with an incidence of 10% of newborns after 34 weeks and 20-85% of newborns born between 30-34 weeks. The pathophysiology of the disease is explained by the immaturity of the central nervous system in maintaining respiratory drive, in addition to impaired sensitivity in response to chemoreceptors and difficulty in maintaining REM sleep, in addition to the chronic losses inherent to chronic hypoxia. Methylxanthines, the active ingredient in caffeine, have the activation mechanism of inhibiting adenosine A1 and A2 receptors coupled to G protein. The recommended initial dose for therapy is 10 mg/kg for apnea of prematurity, but it must be monitored with concentrations serum levels of the drug to a safe therapeutic range, in addition to monitoring side effects in view of the patient's clinical impairment. The main signs of side effects from the use of caffeine are tachycardia, hyperglycemia, reduced growth rate, jaundice, irritability, agitation and convulsions. Conclusion: Apnea of prematurity is a very prevalent pathology in preterm newborns and its therapeutic possibility must be taken into account in view of its possible short and long-term complications, since the use of methylxanthines has different evidence of clinical improvement.
Keywords: Apnea prematurity; Caffeine; Primary treatment; Infant, premature.

Resumo
Introdução: A apnéia da prematuridade é um diagnóstico comum em unidades de cuidados intensivos neonatais, especialmente, em pacientes pré-termos menores de 35 semanas ou pacientes que nasceram com baixo peso (<1500g). Nessa perspectiva, o uso do citrato de cafeína apresenta benefícios a curto e longo prazo nessa patologia, além de

reduzir a incidência de complicações. Metodologia: Foi realizada uma revisão narrativa da literatura com base de dados no PUBMED banco de dados, utilizando as seguintes palavras-chave: "Apnea Prematurity", "Caffeine" e "Treatment", com o filtro de 6 anos, sendo analisados 164 artigos, dos quais apenas 34 foram incluídos e 130 foram excluídos. Resultados e Discussão: A apneia da prematuridade é uma patologia comum em pré-termos e pré-termos extremos com incidência de 10% dos neonatos após 34 semanas e 20-85% nos neonatos nascidos entre 30-34 semanas. A fisiopatologia da doença é explicada pela imaturidade do sistema nervoso central em manter drive respiratório, além de prejuízo na sensibilidade de resposta à quimiorreceptores e dificuldade de manutenção do sono REM, além dos prejuízos crônicos inerentes à hipóxia crônica. As metilxantinas, princípio ativo da cafeína, tem como mecanismo de ativação inibir os receptores de adenosina A1 e A2 acoplados à proteína G. A dose inicial recomendada para terapêutica é 10 mg/kg para a apneia da prematuridade, porém deve ser acompanhado com as concentrações séricas da droga para faixa terapêutica segura, além de monitorar os efeitos colaterais diante do prejuízo clínico do paciente. Os principais sinais de efeitos colaterais do uso da cafeína: taquicardia, hiperglicemia, redução da taxa de crescimento, icterícia, irritabilidade, agitação e convulsões. Conclusão: Apneia da prematuridade é uma patologia bastante prevalente em neonatos pré-termos que deve ser levada em consideração sua possibilidade terapêutica diante de suas possíveis complicações a curto e longo prazo, uma vez que o uso de metilxantinas possuí diferentes evidências de melhora clínica.
Palavras-chave: Apneia da prematuridade; Cafeína; Treatmento primário; Récem-nascido prematuro.

Resumen

Introducción: La apnea del prematuro es un diagnóstico común en las unidades de cuidados intensivos neonatales, especialmente en pacientes prematuros menores de 35 semanas o pacientes nacidos con bajo peso al nacer (<1500g). Desde esta perspectiva, el uso de citrato de cafeína tiene beneficios a corto y largo plazo en esta patología, además de reducir la incidencia de complicaciones. Metodología: Se realizó una revisión narrativa de la literatura utilizando la base de datos PUBMED, utilizando las siguientes palabras clave: "Apnea Prematurity", "Caffeine" y "Treatment", con un filtro de 6 años, analizando 164 artículos, de los cuales solo 34 fueron incluidos y 130 excluidos. Resultados y Discusión: La apnea del prematuro es una patología común en los recién nacidos prematuros y extremadamente prematuros, con una incidencia del 10% de los recién nacidos después de las 34 semanas y del 20-85% de los recién nacidos entre las 30-34 semanas. La fisiopatología de la enfermedad se explica por la inmadurez del sistema nervioso central para mantener el impulso respiratorio, además de la alteración de la sensibilidad en respuesta a los quimiorreceptores y la dificultad para mantener el sueño REM, además de las pérdidas crónicas inherentes a la hipoxia crónica. Las metilxantinas, ingrediente activo de la cafeína, tienen el mecanismo de activación de inhibición de los receptores de adenosina A1 y A2 acoplados a la proteína G. La dosis inicial recomendada para el tratamiento es de 10 mg/kg para la apnea del prematuro, pero debe controlarse con concentraciones séricas. niveles del medicamento a un rango terapéutico seguro, además de monitorear los efectos secundarios en vista del deterioro clínico del paciente. Los principales signos de efectos secundarios del uso de cafeína son taquicardia, hiperglucemia, reducción de la tasa de crecimiento, ictericia, irritabilidad, agitación y convulsiones. Conclusión: La apnea del prematuro es una patología muy prevalente en los recién nacidos prematuros y se debe tener en cuenta su posibilidad terapéutica ante sus posibles complicaciones a corto y largo plazo, ya que el uso de metilxantinas tiene diferentes evidencias de mejoría clínica.
Palabras clave: Apnea del prematuro; Cafeína; Tratamiento primario; Recien nacido prematuro.

1. Introduction

Apnea of prematurity is defined as interruption of breathing for at least 20 seconds or more than 10 seconds if accompanied by bradycardia, cyanosis and/or desaturation in infants who were born at less than 37 weeks (Long et al., 2021; Yun et al., 2022; Schmidt et al., 2019) and can be classified as central, obstructive or mixed (Long et al., 2021; Guo et al, 2022). It is a very common diagnosis, especially in intensive care units (ICU), occurring in the majority of pre terms under 29 weeks and in half of those born between 32 and 35 weeks, in addition to affecting 85% of newborns born weighing less than 1500g. (Elmowafi et al., 2021; Miao et al., 2023, He et al., 2020). It has been seen that ventilatory responses to hypoxia and inhibitory reflexes are greater in premature infants, predisposing to the development of apnea. Furthermore, there is a genetic factor associated with this condition, a fact which leads to a greater predisposition for apnea to occur (Guo et al, 2022).

These episodes in recent Premature births generally occur between the third and seventh day of life in babies who have respiratory distress syndrome (Elmowafi et al., 2021). It is possible to say that episodes do not controlled, prolonged and

repeated apnea followed by hypoxia and bradycardia in the newborn can lead to numerous problems, such as the increased need for mechanical ventilation, difficulties in extubation and longer hospital stay (Guo et al, 2022; Kori et al., 2021).

Pharmacological therapy with methylxanthines, such as caffeine and theophylline, has been used for at least 40 years, being the therapy of choice for apnea of prematurity (Long et al., 2021). Of the two, caffeine is an adenosine receptor antagonist drug which leads to an increase in central respiratory drive, thus reducing the frequency of apneas. Due to this fact and its better effectiveness, fewer effects adverse effects, better absorption via the enteral route and longer half-life, caffeine is the methylxanthine of choice for treatment of apneas of prematurity (Miao et al., 2022; Elmowafi et al., 2021; He, et al., 2020). Caffeine citrate is generally used at a loading dose of 20 mg/kg followed by a maintenance dose of 5-10 mg/kg per day, which may be associated with a reduction in superior mesenteric artery flow for at least 2 hours. However, there is much debate about the optimized dose of this drug, as there is still no consensus defined on this aspect (Dai, et al., 2022; Rebentisch, Kovey, & Denslow, 2021).

The use of caffeine citrate has short and long-term benefits, including reducing the incidence of retinopathy of prematurity, bronchopulmonary dysplasia and benefits in motor function at 5 years (He et al., 2020). Despite this, it is possible to observe some side effects related to the use of this substance, being they tachycardia, increased oxygen consumption, food intolerance, nervousness and reduced heart rate growth (Philip et al., 2018; Zhang et al., 2020). It is worth noting that the answer varies between each individual, and apnea may persist in around 50% of treated babies, which can lead to some complications such as increased risk of intracranial bleeding and mortality during periods vulnerable in premature babies, in addition to increasing the need for more rigorous procedures, such as ventilation mechanics and intubation (Williamson et al., 2021; Shah, et al., 2023). Despite this, the The use of this substance is still quite controversial due to its future effects and the lack of studies that establish protocols for the use of this drug (Kelly et al., 2018; Mürner-Lavanchy et al., 2018).

Therefore, the objective of the current study is to analyze the scientific literature of the main database, the relationship of efficacy and safety in the use of caffeine and its active ingredients in the face of different managements therapeutics in neonatal intensive care units, since there is still no dose unification, in addition to the absence of monitoring protocols for the use of methylxanthines in view of their potential effects collateral, thus justifying the need for the current study to review and compare the information existing.

2. Methodology

A narrative review of the literature was carried out (Rother, E.T; 2007; Snyder, H.; 2019), based on the PUBMED database, using the following keywords: “Apnea Prematurity”, “Caffeine” and “Treatment”, with the 6 year old filter. 164 articles were analyzed, of which only 34 were included and 130 were excluded due to lack of have titles directly related to the keywords, abstracts unrelated to the topic, case reports, opinion articles, letters to the editors, dissertations or comments, or articles that had access restrictions online.

3. Results and Discussion

3.1 Epidemiology

It is extremely important to study the epidemiological characteristics of apnea of prematurity, as which alerts certain patients at high risk of developing this condition and, consequently, provides an earlier diagnosis, reducing the chances of hypoxemia and bradycardia that can lead to a severe disability and even death (Irimu et al., 2023).

Apnea of prematurity is a common condition in preterm newborns, especially in extreme preterms. Its incidence is closely related to gestational age of the newborn, as it occurs in around 10% of newborns born after 34 weeks and in around 20-85 %

of cases born between 30-34 weeks (Long et al., 2021). Furthermore, in live births under 30 weeks or with extremely low weight (< 1000g), the incidence varies from 90 - 100% of cases (Long et al., 2021; Miao et al., 2022).

It is worth mentioning that the frequent occurrence of apnea in newborns is one of the most common problems. challenging to manage in the neonatal ICU, greatly increasing hospitalization time. The biggest Some cases occur in the first three days of life, however, they normally begin 3 to 7 days after birth. birth in babies who have respiratory distress syndrome (Guo et al, 2022; Elmowafi et al., 2021; Du et al., 2020).

The severity of apnea of prematurity varies depending on several factors, including sex, as has been seen that boys are more susceptible to more severe conditions and, consequently, require more supplemental oxygen, ventilatory assistance and surfactant administration than premature women (McDonald et al., 2018).

Regarding the therapy used, caffeine citrate is one of the most used types of methylxanthine for treatment and the response related to its use in these newborns varies greatly, considering that approximately 50% of them show a reduction in apnea episodes after administration of this medication (Guo et al, 2022; Elmowafi et al., 2021).

3.2 Pathophysiology and Mechanism of action

Premature newborns may have difficulty breathing due to immaturity in the development of the neurological and respiratory system (Guo et al, 2022). The pathophysiology can be explained by consequences of this immaturity, which will cause central insufficiency of the drive respiratory system, hyperactive responses of peripheral chemoreceptors, difficulty in maintaining the airway and REM sleep prevalent (Williamson et al., 2021).

These phenomena will generate episodes of bradycardia, decreased saturation and a chronic state of hypoxia (Williamson, Poorun & Hartley, 2021). Hypoxia will cause increased instability respiratory, leading to an increase in the number of apneas. Furthermore, it has been shown that chronic hypoxia it also decreases anti-oxidative defenses and increases the production of reactive oxygen species (Laouafa et al., 2019). This becomes a vicious cycle, which can lead to possible complications due to damage in neurodevelopment (Du et al., 2020; Zhang, et al., 2020). The main risks are the need to extensive mechanical ventilation, retinopathy of prematurity, bronchopulmonary dysplasia and system disorders long-term neurological. (Guo et al, 2022; Lin et al., 2022; Yun et al., 2022).

Although the mechanism of methylxanthines, like caffeine, is not completely understood and explored (Lin et al., 2022), several studies demonstrate that caffeine acts on the nervous system peripheral and central nervous system in order to stimulate breathing (Daí et al., 2022). That stimulus will occur through the inhibition of adenosine receptors A1 and A2, which are receptors coupled to the G protein (Daí et al., 2022; Philip et al., 2018). After the inhibition of these receptors, the increased central sensitivity to carbon dioxide, generating greater activation of the respiratory response (Williamson et al., 2021).

This will generate an activation of the pro-inflammatory reaction cascade in newborns, improving contractility and action of the diaphragm, dilation of the bronchi, induction of surfactant protein B transcription cyclic adenosine and improves minute ventilation, reducing respiratory depression caused by hypoxia. (Miao et al., 2023; Zahra et al., 2019).

3.3 Therapeutic Management

Despite the frequent use of caffeine in neonatal practice, there are still controversies surrounding its therapeutic management and, mainly, about the ideal dose of administration and the need for monitoring therapeutic (TDM). Generally, caffeine is presented as caffeine citrate, in oral or injectables, with the dose of caffeine being half the dose of caffeine citrate (Long et al., 2021).

In 1977, the first study on the use of caffeine in the treatment of AOP was published, in which 18 preterm infants received an induction dose of 20 mg/kg of caffeine citrate, followed by doses maintenance dose of 5-10 mg/kg once to twice a day for two to three days, and a reduction in significant in apnea episodes (Heuzé et al., 2020; Rosen et al., 2021). In the following years, several studies with different samples were carried out, using the described scheme, becoming considered the standard dose of the medicine. (Du, 2020; Zhang, et al., 2020).

In 2006, a large multicenter, randomized, placebo-controlled study tested the same dose regimen and demonstrated its short-term and long-term efficacy and safety, such as higher survival rates without neurodevelopmental disabilities and lower incidences of retinopathy of prematurity severe cerebral palsy and cognitive delay (Long et al., 2021). Due to the study, the standard dose regimen caffeine remains widely used, including as prophylactic therapy in the first 24 hours of life, significantly decreasing the duration of oxygen therapy, invasive and non-invasive ventilation in preterm newborns (Elmowafi et al., 2021).

Despite the proof of efficacy and safety of the standard regimen, there is insufficient evidence regarding the use of higher doses, for example in the context of apnea refractory to high-dose caffeine therapy standard. In these cases, it is suggested to use therapeutic serum level monitoring (TDM) when performing dose optimization, due to the need to reach the desired target concentrations, since concentrations of caffeine in the blood of 5 to 20 or 8 to 20 mg/L are considered effective therapeutic concentrations, when in use of the standard dose (Zulqarnain et al., 2019; Long et al., 2021). Despite this, it is observed that the current therapy with standard dose of caffeine leads to variable clinical results, as seen in case reports of newborns that, although their caffeine levels were within the therapeutic concentration range, they did not they responded clinically satisfactorily (Zahra et al., 2019).

It is not yet clear which factors are associated with the response to caffeine therapy. However, it was since newborns born to pregnant women with gestational diabetes responded better to therapy with best doses of caffeine citrate, regardless of gestational age (Rosen et al., 2021). Furthermore, the study showed that groups with preterm infants of lower gestational age required higher doses (Zhang et al., 2019). In this scenario, the genetic variants AHR, ADORA2A and CLOCK were significantly associated with a better response to standard dose caffeine therapy (Xie & Lin., 2022).

In the context of drug refractoriness, the need to use higher doses is questioned to control apnea episodes in these newborns, who are subject to a greater risk of adverse reactions (Zhang et al., 2019). In order to establish consensus regarding the maintenance dose, studies compared the efficacy and safety of high and low maintenance doses, and evidence that the use of maintenance doses higher are more effective and safe (Gu. et al., 2020; Vliegenthart, R. et al., 2018), resulting in greater treatment efficacy and success rates for ventilator removal, as well as a lower incidence of dysplasia bronchopulmonary disease, lower extubation failure rates (Zhang et al., 2019; Heuzé et al., 2020), frequency and duration of apnea. The use of higher doses is associated with episodes of tachycardia, but without need to interrupt therapy or negative impacts on therapeutic effects or clinical outcome. There were no significant differences between the groups regarding other adverse events, including death hospital (Chen et al., 2018).

However, there is still controversy regarding the administration of high doses due to fear of reactions. adverse effects, also considering the heterogeneity of cases and individual characteristics, such as age and weight at birth, gender, genetic and environmental factors, and others among the studies analyzed. (Xie, Lin, 2022; He, et al., 2020). Therefore, a higher initial dose of caffeine citrate (up to 10 mg/kg) can be considered in the treatment of apnea of prematurity in premature newborns (≤ 29 weeks), however There is a recommendation to perform routine monitoring of serum levels, as the standard dose is effective and significantly maintains serum drug concentrations in a safe therapeutic range (He, 2020; Rosen et al., 2021).

3.4 Side Effects and Associated Risks

There is a vast literature that cites the possible risks of caffeine citrate in relation to the management of apnea in prematurity, these are: tachycardia, hyperglycemia, food intolerance, reduction in the rate of growth, jaundice, irritability, agitation, oxygen consumption, convulsions, necrotizing enterocolitis, peri-intraventricular hemorrhage, retinopathy of prematurity and neonatal mortality (Chen et al., 2018; Vliegenthart et al., 2018). However, these stand out in studies of populations of different ethnicities and age groups, in addition to the fact that, often, studies rule out previous diagnoses and disregard very high or very low dosages (Du et al., 2020; Miao et al., 2023).

First of all, it was observed that there is a difference in the risk potential of side effects to depend on the dose of caffeine citrate offered to the newborn (Rosen et al., 2021; Alhersh et al., 2020). Likewise, it has been considered that higher doses cause more tachycardia (Heuzé et al., 2020; Vliegenthart et al., 2018) and were more closely associated with abstinence (Long et al., 2021). But This is not sufficient to discontinue caffeine treatment in newborns. A lot of studies demonstrated that the use of higher doses of caffeine was more effective, with negligible adverse effects long term.

Furthermore, the literature compares the use of caffeine with other possible treatments such as aminophylline. In study therapy shows when compared, less tachycardia and food intolerance but similar risk when it comes to hyperglycemia, electrolyte disturbances and hypertension (Chen et al., 2018; Vliegenthart et al., 2018).

Recent studies have also shown that caffeine citrate increases metabolism and consumption of oxygen, which can lead to irritability in children. (Miao et al., 2022). Increased maturation of adenosinergic system in central cardiorespiratory areas could partially explain the effects pharmacological effects observed in premature babies (Guo et al, 2022). In some of these works, the effects side effects were not better explained by previous illnesses or interventions, so it was decided to discontinue the treatment (Elmowafi et al., 2021). Finally, it was seen that this treatment was not associated with significant adverse effects or that impact on the patient's quality of life (Du et al., 2020; Miao. et al., 2023; Kori et al., 2021).

The bibliography mentions that the risks involved with hypoxia, recurrent apnea and the threat of dysplasia bronchopulmonary disease is more deleterious than the risks involved with the therapy. The lack of it shows effects on cardiorespiratory function and neurocognitive outcome, such as changes in behavior and attention, which is very unfavorable in the long term (McDonald et al., 2018; Irimu, et al., 2023).

4. Conclusion

Therefore, given the pathophysiological impact and possible complications inherent to sleep apnea, prematurity, the use of caffeine and its active derivatives is extremely important for the clinical practice of neonatal intensive units. In this way, the correct management of therapeutic doses, as well as knowledge about its side effects are relevant to effectively treat apnea, reducing its risks and complications, and in the same way, without exposing the neonatal patient to immediate and future complications.

Still, more studies are needed to corroborate the clinical application of the medication, in addition to retrospective studies that evaluate neonatal patients who are currently in adulthood, in order to evaluate whether there are complications or neurological or behavioral changes associated with the neonatal use of caffeine and its active derivatives.

References

Alhersh, E., Abushanab, D., Al-Shaibi, S., & Al-Badriyeh, D. (2020). Caffeine for the Treatment of Apnea in the Neonatal Intensive Care Unit: A Systematic Overview of Meta-Analyses. *Paediatric Drugs*, 22(4), 399–408. https://doi.org/10.1007/s40272-020-00404-4

Chen, J., Jin, L., & Chen, X. (2018). Efficacy and Safety of Different Maintenance Doses of Caffeine Citrate for Treatment of Apnea in Premature Infants: A Systematic Review and Meta-Analysis. *BioMed Research International*, 2018, 1–11. https://doi.org/10.1155/2018/9061234

Dai, H.-R., Guo, H.-L., Hu, Y.-H., Xu, J., Ding, X.-S., Cheng, R., & Chen, F. (2022). Precision caffeine therapy for apnea of prematurity and circadian rhythms: New possibilities open up. *Frontiers in Pharmacology*, 13, 1053210. https://doi.org/10.3389/fphar.2022.1053210

Du, L., Tong, X., Chen, C., Gao, X., Gagnatelli, A., Li, J., Santoro, D., Nicolardi, S., & Fabbri, L. (2020). Caffeine Citrate for Apnea of Prematurity: A Prospective, Open-Label, Single-Arm Study in Chinese Neonates. *Frontiers in Pediatrics*, 8. https://doi.org/10.3389/fped.2020.00076

Elmowafi, M., Mohsen, N., Nour, I., & Nasef, N. (2021). Prophylactic versus therapeutic caffeine for apnea of prematurity: a randomized controlled trial. *The Journal of Maternal-Fetal & Neonatal Medicine*, 1–9. https://doi.org/10.1080/14767058.2021.1904873

Guo, A., Zhu, Z., Xue, J., Di, X., Fan, J., Huang, L., Zhao, P., Hu, X., & Xie, H. (2020). Population pharmacokinetic study of caffeine citrate in Chinese premature infants with apnea. *Journal of Clinical Pharmacy and Therapeutics*, 45(6), 1414–1421. https://doi.org/10.1111/jcpt.13240

Guo, H.-L., Long, J.-Y., Hu, Y.-H., Liu, Y., He, X., Li, L., Xia, Y., Ding, X.-S., Chen, F., Xu, J., & Cheng, R. (2022). Caffeine Therapy for Apnea of Prematurity: Role of the Circadian CLOCK Gene Polymorphism. *Frontiers in Pharmacology*, 12. https://doi.org/10.3389/fphar.2021.724145

He, T., Liao, Z. C., Ding, Y., Wang, M. J., Li, W., Gan, J. M., & Yue, S. J. (2020). *Zhongguo dang dai er ke za zhi = Chinese journal of contemporary pediatrics*, 22(7), 684–689. https://doi.org/10.7499/j.issn.1008-8830.2003276

He, X., Qiu, J.-C., Lu, K.-Y., Guo, H.-L., Li, L., Jia, W.-W., Ni, M.-M., Liu, Y., Xu, J., Chen, F., & Cheng, R. (2020). Therapy for Apnoea of Prematurity: A Retrospective Study on Effects of Standard Dose and Genetic Variability on Clinical Response to Caffeine Citrate in Chinese Preterm Infants. *Advances in Therapy*, 38(1), 607–626. https://doi.org/10.1007/s12325-020-01544-2

Irimu, G., Okwaro, F., Coleman, J., Waiyego, M., Murila, F., Chomba, D., Parsimei, M., Shitote, C., Ochieng, R., Shah, J., Ogero, M., Amy Sarah Ginsburg, J. Mark Ansermino, & Macharia, W. (2023). Developing and testing a clinical care bundle incorporating caffeine citrate to manage apnoea of prematurity in a resource-constrained setting: a mixed methods clinical feasibility study protocol. *Implementation Science Communications*, 4(1). https://doi.org/10.1186/s43058-023-00455-x

Kelly, C. E., Wenn Lynn Ooi, Joseph Yuan-Mou Yang, Chen, J., Adamson, C., Lee, K. J., Jeanie L.Y. Cheong, Anderson, P. J., Doyle, L. W., & Thompson, D. K. (2018). Caffeine for apnea of prematurity and brain development at 11 years of age. *Annals of Clinical and Translational Neurology*, 5(9), 1112–1127. https://doi.org/10.1002/acn3.628

Kori, Hans Van Rostenberghe, Nor Rosidah Ibrahim, Najib Majdi Yaacob, & Nasir, A. (2021). A Randomized Controlled Trial Comparing Two Doses of Caffeine for Apnoea in Prematurity. *International Journal of Environmental Research and Public Health*, 18(9), 4509–4509. https://doi.org/10.3390/ijerph18094509

Laouafa, S., Iturri, P., Arias-Reyes, C., Marcouiller, F., Gonzales, M., Joseph, V., Bairam, A., & Soliz, J. (2019). Erythropoietin and caffeine exert similar protective impact against neonatal intermittent hypoxia: Apnea of prematurity and sex dimorphism. *Experimental Neurology*, 320, 112985. https://doi.org/10.1016/j.expneurol.2019.112985

Lin, Y.-C., Tan, Y.-L., Yen, T.-A., Chen, C.-Y., Tsao, P.-N., & Chou, H.-C. (2022). Specific Premature Groups Have Better Benefits When Treating Apnea With Caffeine Than Aminophylline/Theophylline. *Frontiers in Pediatrics*, 10. https://doi.org/10.3389/fped.2022.817624

Long, J.-Y., Guo, H.-L., He, X., Hu, Y.-H., Xia, Y., Cheng, R., Ding, X.-S., Chen, F., & Xu, J. (2021). Caffeine for the Pharmacological Treatment of Apnea of Prematurity in the NICU: Dose Selection Conundrum, Therapeutic Drug Monitoring and Genetic Factors. *Frontiers in Pharmacology*, 12. https://doi.org/10.3389/fphar.2021.681842

McDonald, F. B., Dempsey, E. M., & O'Halloran, K. D. (2018). Caffeine therapy for apnoea of prematurity: Wake up to the fact that sex matters. *Experimental Physiology*, 103(10), 1294–1295. https://doi.org/10.1113/ep087222

Miao, Y., Liu, W., Zhao, S., Li, Y., Jiang, H., Wang, A., Teng, P., & Zhang, Y. (2023). Effect of prophylactic caffeine in the treatment of apnea in very low birth weight infants: a meta-analysis. *Journal of Maternal-Fetal & Neonatal Medicine*, 36(1). https://doi.org/10.1080/14767058.2023.2214659

Miao, Y., Zhou, Y., Zhao, S., Liu, W., Wang, A., Zhang, Y., Li, Y., & Jiang, H. (2022). Comparative efficacy and safety of caffeine citrate and aminophylline in treating apnea of prematurity: A systematic review and meta-analysis. *PLOS ONE*, 17(9), e0274882. https://doi.org/10.1371/journal.pone.0274882

Mürner-Lavanchy, I. M., Doyle, L. W., Schmidt, B., Roberts, R. S., Asztalos, E. V., Costantini, L., Davis, P. G., Dewey, D., D'Ilario, J., Grunau, R. E., Moddemann, D., Nelson, H., Ohlsson, A., Solimano, A., Tin, W., & Anderson, P. J. (2018). Neurobehavioral Outcomes 11 Years After Neonatal Caffeine Therapy for Apnea of Prematurity. *Pediatrics*, 141(5), e20174047. https://doi.org/10.1542/peds.2017-4047

N. Heuzé, Goyer, I., F. Porcheret, Denis, M., C. Faucon, Jokic, M., & D. Brossier. (2020). Caffeine treatment for bronchiolitis-related apnea in the pediatric intensive care unit. *Archives de Pédiatrie*, 27(1), 18–23. https://doi.org/10.1016/j.arcped.2019.10.009

Nagasato, A., Nakamura, M., & Kamimura, H. (2018). Comparative Study of the Efficacy and Safety of Caffeine and Aminophylline for the Treatment of Apnea in Preterm Infants. *Yakugaku Zasshi*, 138(2), 237–242. https://doi.org/10.1248/yakushi.17-00144

Philip, R. K., Ismail, A., Murphy, B., Mirza, A., Quinn, C., & Dunworth, M. (2018). Caffeine Treatment for Apnea of Prematurity and the Influence on Dose-Dependent Postnatal Weight Gain Observed Over 15 Years. *Journal of Caffeine and Adenosine Research*, 8(3), 99–106. https://doi.org/10.1089/caff.2018.0005

Rebentisch, A., Kovey, K., & Denslow, S. (2021). An Evaluation of Twice-Daily Dosing of Caffeine for Apnea of Prematurity. *The Journal of Pediatric Pharmacology and Therapeutics*, 26(3), 253–257. https://doi.org/10.5863/1551-6776-26.3.253

Rosen, C., Taran, C., Hanna, M., Gueta, I., Loebstein, R., Strauss, T., & Yarden-Bilavsky, H. (2021). Caffeine citrate for apnea of prematurity—One dose does not fit all a prospective study. *Journal of Perinatology*, 41(9), 2292–2297. https://doi.org/10.1038/s41372-021-01172-w

Rother, E. T. (2007). Systematic literature review X narrative review. *Acta Paulista de Enfermagem*, 20(2), v–vi. https://doi.org/10.1590/s0103-21002007000200001

Schmidt, B., Anderson, P. J., Asztalos, E. V., Doyle, L. W., Grunau, R. E., Moddemann, D., & Roberts, R. S. (2019). Self-reported Quality of Life at Middle School Age in Survivors of Very Preterm Birth. *JAMA Pediatrics*, 173(5), 487–487. https://doi.org/10.1001/jamapediatrics.2018.4853

Shah, A. S., Leu, R. M., Shah, S. P., Martinez, F., & Kasi, A. S. (2023). Images: Caffeine therapy for central sleep apnea, hypoxemia, and hypoventilation in a term neonate. *Journal of Clinical Sleep Medicine*, 19(5), 1005–1008. https://doi.org/10.5664/jcsm.10504

Snyder, H. (2019). Literature Review as a Research methodology: an Overview and Guidelines. *Journal of Business Research*, 104(1), 333–339. https://doi.org/10.1016/j.jbusres.2019.07.039

Vliegenthart, R., Miedema, M., Hutten, G. J., Kaam, A. H. van, & Onland, W. (2018). High versus standard dose caffeine for apnoea: a systematic review. *Archives of Disease in Childhood - Fetal and Neonatal Edition*, 103(6), F523–F529. https://doi.org/10.1136/archdischild-2017-313556

Williamson, M., Poorun, R., & Hartley, C. (2021). Apnoea of Prematurity and Neurodevelopmental Outcomes: Current Understanding and Future Prospects for Research. *Frontiers in Pediatrics*, 9. https://doi.org/10.3389/fped.2021.755677

Xie, J.-B., & Lin, X.-Z. (2022). [Recent research on gene polymorphisms related to caffeine therapy in preterm infants with apnea of prematurity]. PubMed, 24(7), 832–837. https://doi.org/10.7499/j.issn.1008-8830.2203134

Yun, W. Z., Kassab, Y. W., Yao, L. M., Khairuddin, N., Ming, L. C., & Hadi, M. A. (2022). Effectiveness and safety of early versus late caffeine therapy in managing apnoea of prematurity among preterm infants: a retrospective cohort study. *International Journal of Clinical Pharmacy*. https://doi.org/10.1007/s11096-022-01437-0

Zahra Fakoor, Ali Aghayar Makooie, Zahra Joudi, & Rasool Gharaaghaji Asl. (2019). The effect of venous caffeine on the prevention of apnea of prematurity in the very preterm infants in the neonatal intensive care unit of Shahid Motahhari Hospital, Urmia, during a year. *Journal of Advanced Pharmaceutical Technology & Research*, 10(1), 16–16. https://doi.org/10.4103/japtr.japtr_334_18

Zhang, C.-Y., Liu, D., Hua, S.-D., Guo, S., Li, X.-Y., Zhang, B., & An, L.-H. (2020). Caffeine versus aminophylline in combination with oxygen therapy for apnea of prematurity: A retrospective cohort study. *Experimental and Therapeutic Medicine*, 20(5), 1–1. https://doi.org/10.3892/etm.2020.9175

Zhang, X., Zhang, H. T., Lyu, Y., Wang, L. F., & Yang, Z. Y. (2019). *Zhongguo dang dai er ke za zhi = Chinese journal of contemporary pediatrics*, 21(6), 558–561. https://doi.org/10.7499/j.issn.1008-8830.2019.06.011

Zulqarnain, A., Hussain, M., Suleri, K. M., & Ali Ch., Z. (2019). Comparison of Caffeine versus Theophylline for apnea of prematurity. *Pakistan Journal of Medical Sciences*, 35(1). https://doi.org/10.12669/pjms.35.1.94