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Recent evidence in Brazil regarding the use of xanthines in premature infants and their impact on bronchopulmonary dysplasia

Recent evidence in Brazil regarding the use of xanthines in Premature Infants and their impact on Bronchopulmonary Dysplasia

Recent evidence in Brazil on the use of xanthines in premature and premature newborns its impact on bronchopulmonary dysplasia

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Summary

Objective: To analyze the efficacy of methylxanthines, with emphasis on caffeine citrate, in prevention of Bronchopulmonary Dysplasia (BPD) and improvement of clinical outcomes of Premature newborns in Neonatal Intensive Care Units in Brazil.

Methods: A narrative literature review with a qualitative approach was conducted. consulting the PubMed, SciELO, and BVS databases. The time frame covers High-impact articles and national guidelines published between 2021 and 2026, focusing on in clinical reports from Brazilian reference centers and in protocols of the Society Brazilian Journal of Pediatrics. **Results:** The data show that early administration Caffeine (in the first 48 hours of life) acts in antagonism of adenosine. endogenous, facilitating weaning from mechanical ventilation and significantly reducing the time. Oxygen therapy. Reports from institutions in São Paulo, Rio de Janeiro, Brasilia and Curitiba show a reduction of up to 25% in the incidence of BPD. moderate to severe, as well as better neurodevelopmental outcomes at 24 months of age. corrected. It was also observed that caffeine has a superior safety profile to other xanthines, with a lower rate of adverse cardiovascular effects. **Conclusion:** The Current evidence supports the use of methylxanthines as a pneumoprotective strategy. essential in Brazilian neonatology. Given the positive impact on public health and To reduce hospital costs, it is urgent to include caffeine citrate in the list of essential medicines of the Unified Health System (SUS) in order to guarantee equity. in neonatal care throughout the country.

Keywords: Premature Newborn; Bronchopulmonary Dysplasia; Xanthines; Caffeine Citrate; Brazil.

Abstract

Objective: Analyze the effectiveness of methylxanthines, with emphasis on caffeine citrate, in the prevention of Bronchopulmonary Dysplasia (BPD) and in improving clinical outcomes of premature newborns in Neonatal Intensive Care Units in Brazil.

Methods: A narrative literature review with a qualitative approach was conducted, consulting the PubMed, SciELO, and VHL databases. The time frame includes high-impact articles and national guidelines published between 2021 and 2026, focusing on clinical reports from Brazilian reference centers and protocols from the Brazilian Society of Pediatrics. **Results:** The data show that early administration of caffeine (within the first 48 hours of life) acts by antagonizing endogenous adenosine, facilitating ventilatory weaning and significantly reducing the duration of oxygen

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Therapy. Reports from institutions in São Paulo, Rio de Janeiro, Brasília, and Curitiba. demonstrate a reduction of up to 25% in the incidence of moderate-to-severe BPD, as as well as improved neurodevelopmental outcomes at 24 months corrected age. It was also observed that caffeine has a superior safety profile compared to other xanthines, with a lower rate of cardiovascular adverse effects. **Conclusion:** Current evidence consolidates the use of methylxanthines as an essential lung-protective strategy in Brazilian neonatology. Given the positive impact on public health and the reduction of hospital costs, the urgency of including caffeine citrate in the list of essential medications of the Unified Health System (SUS) is highlighted, aiming to ensure equity in neonatal care across the country.

Keywords: Premature Newborn; Bronchopulmonary Dysplasia; Xanthines; Caffeine Citrate; Brazil.

Introduction

Bronchopulmonary dysplasia (BPD) remains the leading respiratory challenge in very low birth weight newborns in Neonatal Intensive Care Units (NICUs) Brazilian. Characterized by an interruption in alveolar and vascular development, Its incidence in Brazil reflects not only pulmonary immaturity, but also impact of prolonged invasive ventilatory support [1, 2]. Recent Network Data Brazilian Neonatal Research Association points out that, despite the optimization of the use of Despite the use of surfactant and protective ventilation techniques, BPD remains associated with high rates. high morbidity and hospital costs in the national context [2].

In this context, the strategic use of methylxanthines, especially caffeine citrate, It has established itself as one of the most robust pharmacological interventions for prevention of this pathology. Between 2021 and 2026, consensus from the Brazilian Society of Pediatrics and national clinical studies have reinforced the idea that caffeine acts as a facilitator. critical for weaning from mechanical ventilation, reducing the time of exposure to oxygen and to Positive pressure, which are the main triggers of inflammatory lung injury [1,3,4]. A The superiority of caffeine citrate over other xanthines, such as aminophylline, lies in... in its safety profile and pharmacokinetic stability required for the management of extremely premature babies [4].

This work is justified by the need to analyze the latest clinical reports and outcomes observed in Brazilian hospitals, seeking to synthesize how the Standardization of the early use of these substances has impacted neonatal prognosis.

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When reviewing evidence from scientific journals covering the last five years,
The aim is to offer an updated overview of the effectiveness of xanthines in reducing
of DBP and in improving the quality of life of prematurity survivors in
Brazil 5, 8.

Theoretical Framework

The theoretical foundation regarding Bronchopulmonary Dysplasia (BPD) encompasses,
necessarily, due to an understanding of pulmonary immaturity and its deleterious effects.
endogenous adenosine in premature newborns. BPD is characterized by a
interruption of alveolization and vascular development, a process that is aggravated
due to the presence of inflammatory mediators and invasive ventilatory support. [1]. In that
In this scenario, adenosine, produced endogenously by the neonatal organism, acts as a
potent inhibitor of central respiratory drive and negative modulator of mechanics
Pulmonary function occurs when interacting with A1 and A2A receptors, which predisposes the neonate to
Frequent episodes of apnea and extubation failures, perpetuating the need for
oxygen therapy and positive pressure [3, 6].
Methylxanthines, especially caffeine citrate, play a therapeutic role.
through competitive antagonism of these adenosine receptors, resulting in
Direct stimulation of the bulbar respiratory center and increased sensitivity to carbon dioxide.
dioxide (CO_2) levels.[4,7]. In addition to the central effect, these substances promote improved carbon
diaphragmatic contractility and mild bronchodilation, which optimizes compliance.
pulmonary and reduces respiratory muscle fatigue. [5] Published scientific evidence
Between 2021 and 2026, caffeine citrate was consolidated as the gold standard in...
In Brazilian neonatology, it surpasses aminophylline due to its pharmacokinetic profile.
More stable, with a prolonged half-life of approximately 100 hours and a lower incidence.
of cardiovascular and gastrointestinal side effects [4, 8].
The clinical application of this knowledge in Neonatal Intensive Care Units of
Brazil has focused on the strategy of early administration, initiated
preferably within the first 48 hours of life of a very low birth weight newborn
weight [2] Contemporary clinical reports demonstrate that this intervention is crucial.
to facilitate successful weaning from mechanical ventilation, minimizing volutrauma and
barotrauma on friable lung parenchyma 5,7. Therefore, the use
The protocol for xanthines is not limited to the treatment of apnea alone, but also constitutes...
as an essential neuro and pneumoprotective strategy, capable of reducing

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significantly reduce the incidence of BPD and improve long-term functional outcomes.
in the national scenario 1, 8.

Materials and methods

This is a narrative literature review, conducted through a search.
Bibliographic search in the PubMed, SciELO and BVS databases, covering the period from 2021.
until 2026. The selection prioritized high-impact articles and guidelines from the Brazilian Society.
Department of Pediatrics, with an exclusive focus on studies that analyzed clinical outcomes in Brazil.
Regarding the use of methylxanthines in the prevention of bronchopulmonary dysplasia (BPD). [1, 4].
The inclusion criteria focused on research conducted with newborns.
preterm infants in national hospital centers, using the descriptors: "Newborn
"Premature," "Caffeine Citrate," and "Brazil." The data analysis synthesized the results.
Practical observations in Brazilian neonatal ICUs, evaluating the impact of early use.
xanthines in extubation success and in reducing chronic respiratory morbidity 2, 5,
[8].

Results

The analysis of clinical reports collected from reference institutions, such as the Hospital of
Clinics at USP (HCFMUSP) and the Hospital de Clínicas at UNICAMP reveal that the use of
Caffeine citrate in newborns weighing less than 1,250 grams reduced the
The need for invasive mechanical ventilation has increased in approximately 30% of cases in recent years.
five years 2.5. Data from the Brazilian Neonatal Research Network (RBPN).
which includes 20 university centers in Brazil, indicate that "early caffeine"
(administered before 48 hours of life) is the predominant therapeutic standard in
In the South and Southeast regions, there was a 72% success rate in extubation on the first attempt.
a significant increase compared to the 2021 data, 9 .
At the Brasília Maternal and Child Hospital (HMIB) and at the Brasília University Hospital
(HUB), observational cohort studies have demonstrated that, in addition to the improvement
Respiratory problems: neonates who received xanthines early showed lower respiratory rates.
incidence of patent ductus arteriosus (PDA) with hemodynamic repercussions,
suggesting a beneficial systemic effect of the drug 7, 10. In Curitiba, data from the Hospital of
Clinics at UFPR corroborate these findings, documenting that the total time of
The average length of stay in the NICU was reduced by 12 days in patients who reached the
Early respiratory stability with caffeine, directly impacting the reduction of

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hospital costs [8, 11].

Reports originating from units in the Northeast, such as the Royal Portuguese Hospital (Recife) and leading maternity hospitals in Bahia highlight that the replacement of aminophylline with Ready-to-use caffeine citrate dramatically reduced episodes of tachycardia. supraventricular and necrotizing enterocolitis 4, 12. In these units, the incidence of BPD severe — defined by the need for oxygen with an inspired fraction (FiO2) above 30% at 36 weeks of age post-completion — fell from 18% to 11% after the Standardization of the caffeine protocol according to the 2024 SBP guidelines 1, 12 .

Discussion

The interpretation of the results observed in Brazilian hospitals confirms that the The effectiveness of xanthines in preventing BPD is intrinsically linked to the duration of treatment. The onset of therapy and antagonism of endogenous adenosine. As demonstrated in Literature between 2021 and 2026 studies the accumulation of adenosine during episodes of hypoxia. In neonatal therapy, it acts as a suppressor of the ventilatory drive and promoter of interstitial edema; Early blockade of these receptors prevents recurrent alveolar collapse. 6, 13.

Documented success in centers like IFF/Fiocruz reinforces that caffeine should be considered not only a treatment for sleep apnea, but also an agent A fundamental pneumoprotective agent in the management of extreme prematurity. [5, 14].

The clinical superiority of caffeine over aminophylline, evidenced in reports of Several Brazilian centers justify its use due to its stable pharmacokinetics. While the Aminophylline requires constant serum monitoring due to its narrow therapeutic index. Caffeine citrate allows for a single daily dose with less plasma fluctuation. which is crucial in services with high demand and limited human resources 4, 7 . In addition Furthermore, the reduction in the need for postnatal rescue corticosteroid therapy is an outcome of The extreme clinical relevance discussed in current Brazilian studies, given the use of Steroid use is associated with increased risks of cerebral palsy and motor deficits. [1, 15].

Finally, the discussion on the long-term neuroevolutionary impact, based on the data. Follow-up studies from Curitiba and Brasília suggest that preventing xanthine-mediated BPD reduces the burden of intermittent hypoxia in the developing brain 3, 8. A Stabilizing the respiratory rate prevents sudden fluctuations in cerebral blood flow. This explains the better psychomotor scores observed at 24 months. However, National researchers highlight the disparity in access to caffeine citrate.

The gap between different regions of Brazil is still an obstacle to the universalization of these [access to healthcare].

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positive results, making it necessary to permanently include this medication in the list of essential medicines in all spheres of the SUS [2, 16].

Conclusion

The scientific evidence and national clinical reports accumulated between 2021 and 2026 They confirm that the use of xanthines, specifically caffeine citrate, is a An indispensable intervention in neonatal practice for the prevention of dysplasia. bronchopulmonary [1, 4]. The strategic administration of this substance has proven to be a a determining factor for the success of early ventilator weaning and for protection. of developing lung tissue, significantly reducing dependence Oxygen deficiency and chronic respiratory morbidity in preterm newborns [5, 8]. The positive outcomes observed in long-term follow-up reiterate that This therapeutic approach preserves not only lung function, but also the The neurodevelopmental potential of children, minimizing the consequences of prematurity. extreme [7, 15]. Therefore, the documented effectiveness in recent years validates the protocolized use. of these substances as a highly safe measure with immediate clinical impact. in the Brazilian scenario [2, 12].

Given the strength of these results, it is urgent to democratize access to this therapy throughout the country. It is essential that the relevant authorities... Governments should promote the definitive inclusion of caffeine citrate in the list of drugs covered by the Unified Health System (SUS). [1, 16] This measure is essential to eliminate the regional disparities in neonatal care, ensuring that technology Cutting-edge pharmacological treatment should be available in all public healthcare facilities in Brazil. ensuring equity and better chances of survival and quality of life for all premature babies.

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Required Declarations (to be filled in)

Ethical approval (CEP/CONEP or equivalent)
( ) Yes (X) Not applicable
Opinion/Registration Number: Informed _____
Consent Form: ( ) Yes (X) Not applicable
Study registration (when applicable): ( ) ReBEC ( ) ICTRP/WHO ( ) ClinicalTrials.gov ( )
Others: _____

Registration number: _____
Reporting guideline (EQUATOR): ( ) CONSORT ( ) STROBE ( ) PRISMA ( ) CARE ( )
COREQ/SRQR ( ) SQUIRE ( ) Other: _____

Data Sharing Statement (ICMJE)
Anonymized data: ( ) will be shared (X) will not be shared
What data: _____
Additional documents (protocol/plan/methods): _____
Availability period: _____
Access conditions: _____