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Caffeine for the care of preterm infants in sub-Saharan Africa: a missed opportunity?

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BACKGROUND

In 2019, 2.4million neonates (infants <28 days of age) died globally. Of these, over 80% were preterm infants (<37 weeks gestation), with the majority born in low-income and middle-income countries.[1] Complications of preterm birth, largely from respiratory distress syndrome due to surfactant deficiency, pneumonia or apnoea of prematurity (AOP), are now the leading cause of under 5 mortality globally.[1] These conditions are frequently fatal in the absence of effective ventilatory support which is commonplace in neonatal units across sub-Saharan Africa. Although the global neonatal mortality rate (NMR) has halved over the past three decades, significant regional disparities remain. These correlate with World Bank and International Monetary Fund estimates of the proportion of the population living on less than US$1.90a day, with the majority of poorer countries being in sub-Saharan Africa.[1 2] As the region with the highest NMR of 27 per 1000 live births, it is estimated that a baby born in in sub-Saharan Africa is 10 times more likely to die than one born in a high income country.[1] Countries in sub-Saharan Africa are unlikely to meet the global target of no more than 12 newborn deaths per 1000 live births by 2030.[3] In 2017, 75 countries (almost half from sub-Saharan Africa) signed up to the 'Every Newborn Action Plan' that has strategic global and national actions and milestones to address gaps in maternal and newborn care.[4] This ambitious commitment requires evidence-based interventions[5] and innovative strategies to improve neonatal survival and longer-term outcomes.

CAFFEINE CITRATE: AN EVIDENCE-BASED THERAPY USED WIDELY IN HIGH-INCOME AND MIDDLE-INCOME COUNTRIES

AOP, a common complication of preterm birth, would likely be better prevented and treated in low-income countries if caffeine citrate was more widely available.[1 6] High-quality randomised controlled trial data, predominantly from high-income countries, strongly support the use of caffeine citrate to prevent adverse outcomes of prematurity and treat AOP[7] (table 1).

Four decades of use in high-income countries confirms the low-risk profile of caffeine citrate and its ease of administration[7 8] (online supplemental table 1). It is one of the most widely prescribed drugs in neonatal units in high-income settings.[9] Although WHO included caffeine citrate in the Model list of Essential Medicines for Children—'Medicines administered to the neonate' in 2019 (caffeine citrate for injection and oral formulation—20 mg/mL, equivalent to 10 mg caffeine base/mL),[10] to our knowledge, it is not in widespread use in sub-Saharan Africa.

Summary box

- The majority of the estimated 15 million preterm infants (<37 weeks gestation) delivered worldwide are born in low-income and middle-income countries.
- In sub-Saharan Africa, nearly half of very preterm infants (<32 weeks gestation) die in the first 28 days and sparse data indicates neurodevelopmental impairment in many of those who survive.
- Apnoea of prematurity (AOP), a common complication of very preterm infants, contributes significantly to mortality and morbidity.
- In resource-limited settings, aminophylline is used for prevention and treatment of AOP but concerns remain about its safety and efficacy given limited therapeutic drug monitoring.
- Caffeine citrate, the drug of choice for the prevention and treatment of AOP in high-income countries, is either unavailable or prohibitively expensive in sub-Saharan Africa.
- Use of caffeine citrate for AOP in sub-Saharan Africa could significantly reduce mortality and morbidity in very preterm infants.

Table 1 Summary of findings from research studies of caffeine citrate in preterm infants

Infant population	Benefits	Source of evidence
Birth weight 500–1250 g	1. Reduced risk of neurodisability at 18–21 months 2. Improved cognitive development at 18–21 months	High-income countries
Infants ≤34 weeks gestation	1. Reduction in apnoea (equivocal) 2. Reduction in bronchopulmonary dysplasia (chronic lung disease) 3. Reduction in severe retinopathy of prematurity	High-income and low-income and middle-income countries

WHY IS CAFFEINE NOT USED IN SUB-SAHARAN AFRICA, AND WHAT ALTERNATIVES ARE AVAILABLE?

Caffeine citrate is largely unavailable in sub-Saharan Africa due to its high cost. A 7-day course for a preterm infant could cost as much as US$600 in Kenya, which would far exceed the monthly income of most families and prevents widespread access.[11] The only available alternative is intravenous aminophylline, which to avert side effects, demands therapeutic drug monitoring (TDM)[12] (online supplemental table 2). An efficacy trial with 31 preterm infants in South Africa comparing oral caffeine citrate to intravenous aminophylline found caffeine as efficacious as aminophylline in treating AOP. Most importantly, caffeine use facilitated breastfeeding and was more practical requiring no TDM.[13] This is consistent with studies in high-income settings showing advantages of caffeine over aminophylline.[7] Finally, vital sign monitoring of small sick newborn infants to identify potentially life-threatening AOP is often not feasible due to shortages of neonatal nurses and monitoring equipment. Therefore, introducing a drug that is easy to administer with a low risk profile may be specifically relevant to this setting.[14]

In a recent survey of neonatologists in sub-Saharan Africa, 55 respondents from 13 countries noted that country-specific regulations hindered caffeine accessibility. This was compounded by monopoly of suppliers with unregulated and high prices.[11] Ironically, many of these countries are coffee-producing countries. Generic drug usage allows for local manufacture of drugs, therefore, bypassing the logistical challenges and expenses of importing. However, this must be appropriately regulated to ensure quality control measures and avoiding counterfeit medicines.[15] Such considerations raise the question of whether the costs of local production may exceed the current costs. Several neonatal units in high-income countries use locally prepared oral caffeine citrate formulations for neonatal care using stringent protocols and quality control measures because it is far cheaper than currently approved preparations (personal communication). To ensure sustainability, the WHO clinical recommendations for caffeine citrate use in neonatal care would require regulatory changes to allow national/regional pharmacies in sub-Saharan Africa to prepare formulations for within-country use. Pilot studies to evaluate the feasibility and acceptability of implementing locally produced caffeine citrate for neonatal care in the sub-Saharan African context are currently underway and may provide key insights into the feasibility of this approach.

The way forward

To expedite the routine use of caffeine citrate in neonatal care in sub-Saharan Africa, we recommend these pragmatic steps:

- Conduct a multicentre randomised controlled trial to assess the efficacy and safety of caffeine citrate versus standard of care (either aminophylline or placebo depending on setting) for the prevention and/or treatment of AOP in sub-Saharan Africa.
- Begin discussions with in-country partners, industry and drug regulatory bodies to explore means of enhancing the safety, availability and affordability of caffeine citrate for neonatal care in sub-Saharan Africa.

The global community seeks to address inequities in neonatal mortality between well-resourced and poorly resourced countries. We highlight this key inequity in the availability of one among many essential medicines for neonatal care. We believe firmly that generating evidence on the efficacy and feasibility of caffeine citrate use in neonatal care in sub-Saharan Africa could lead to accelerated progress in improving the survival and long-term outcomes of preterm infants in this and other resource-limited settings.

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What is the efficacy and safety of methylxanthines (caffeine, theophylline — in intravenous form named aminophylline) for the prevention and treatment of apnea of prematurity?

Table 1: Caffeine vs placebo

N	Author Year	Setting	Interventions	Sample size	Participants	Main Outcome	Risk Ratio (95%CI)
1	Murat 1981	HIC France	Caffeine for treatment of AOP	n=18	29 to 35 weeks gestation	0/9 vs 6/9 failed apnea reduction 2-7 days of therapy.	0.08 (0, 1.19)
2	Levitt 1988	HIC UK	Caffeine for prevention of AOP	n=54	Infants	12/27 vs 14/27 failed apnea reduction 2-10 days of therapy.	0.87 (0.52, 1.45)
3	Erenberg 2000	HIC USA	Caffeine for treatment of AOP	n=82	28-32 weeks gestation	14/45 vs 20/37 failed apnea reduction 7-10 days of therapy. 2/45 vs 1/37 death before discharge	0.58 (0.34, 0.97) 1.64 (0.16, 17.43)
4	Schmidt (Caffeine for Apnea of Prematurity Trial Group, CAP) 2006	HIC Multi-country	Caffeine for prevention of AOP	n=2006	Birth weight 500 to 1250 g	293/867 vs 329/858 cognitive delay at 18 to 21 months 52/1006 vs 55/1000 death before discharge	0.81(0.66, 0.99) 0.96 (0.64, 1.44)
5	Schmidt (CAP) 2007	HIC Multi-country	Caffeine for prevention of AOP	n=2006	Birth weight 500 to 1250 g	40/909 vs 66/901 cerebral palsy at 18 to 21 months 377/937 vs 431/932 died or survived with a neurodisability at 18 to 21 months	0.58 (0.39, 0.87) 0.77 (0.64, 0.93)

HIC- high income country

Table 2: Aminophylline (theophylline) vs control

N	Author Year	Setting	Interventions	Sample size	Participants	Main Outcome	Risk Ratio (95%CI)
1	Gupta 1981	HIC Australia	Theophylline	n=29	Infants	5/15 vs 14/14 failed apnea reduction 2-7 days of therapy. 1/15 vs 3/14 death before discharge	0.36 (0.18, 0.7) 0.31 (0.04, 2.65)
2	Sims 1985	HIC USA	Theophylline	n=43	Infants	9/21 vs 17/22 failed apnea reduction 2-7 days of therapy. Death before discharge	0.55 (0.32, 0.95) 0.21 (0.01, 4.11)
3	Pellowski 1990	HIC Canada	Theophylline 2/10	n=10	Infants	2/10 vs 8/10 failed Apnea Reduction 2-7 days of therapy.	0.25 (0.07, 0.9)

HIC- high income country

Table 3: Caffeine vs Aminophylline (theophylline)

N	Author Year	Setting	Interventions	Sample size	Participants	Main Outcome	Risk Ratio (95%CI)
1	Brouard 1985	HIC France	Caffeine vs theophylline for treatment of AOP	n=16	Infants	Mean Apnea rate/ 100 min at 1-3 days	Mean diff: 0.01 (-0.19, 0.21)
2	Bairam 1987	HIC France		n=20	Infants	3/10 vs 2/10 failed apnea reduction 2-7 days of therapy.	1.35 (0.41, 4.52)

						Mean Apnea rate/ 100 min at 1-3 days	Mean diff: 0.29 (-0.06, 0.64)
3	Fuglsang 1989	HIC Denmark	Caffeine vs Theophylline	n=18	Infants	Mean Apnea rate/ 100 min at 1-3 days	Mean diff: 0.04 (-0.14,0.22)
4	Scanlon 1992	HIC UK	Caffeine (higher vs standard dose) vs Theophylline for treatment of AOP	n=44	<31 weeks gestation	5/16 vs 1/14 vs 0/14 failed apnea reduction by 48 hours of therapy.	1.35 (0.41, 4.52)
5	Kumar 1992	HIC USA	Caffeine vs Aminophylline	n=24	Infants	Mean Apnea rate/ 100 min at 1-3 days	Mean diff: 0.09 (-0.28, 0.46)
6	Larsen 1995	HIC Denmark	Caffeine vs Aminophylline 2.5	n = 180	≤33 weeks gestation	No of apnea in 10 days.	No difference
7	Skouroliakou 2009	HIC Greece	Caffeine 4 (day 1-3) 0 (day 4-7) vs Aminophylline 5 (day 1-3) 0 (day 4-7)	n=70	<33 weeks gestation	Mean apnea events per day	No difference
8	Shivakumar 2016	LMIC (India)	Caffeine vs aminophylline	n=240	≤34 weeks gestation	Median Apnea rates at day 8-14	No difference
9	Khurana 2017	LMIC (India)	Caffeine (n=43) Cognitive 105.37 ± 13.75 Language 100.39 ± 15.05 Motor 102.72 ± 12.79 vs Aminophylline	n=240	Infants	Composite scores of BSID III components at 18–24 months of corrected age	No difference

			(n=36) Cognitive 99.97 ± 19.09 Language 101.63 ± 19.1 Motor 104.02 ± 20.0				
10	Afzal 2018	LMIC (Pakistan)	Caffeine 1.9±0.18 (1-3) 1.4±1.8 (4-7) 0.98±0.15 (15-21) vs Aminophylline 0.4±0.24 (1-3) 0.3±1.6 (4-7) 0.69±0.15 (15-21)	n=100	<34 weeks gestation	Mean apnea per day	Aminophylline significantly better in the following interval days 1-3, 4-7 and 15-21.
11	Zulqarnain 2019	LMIC (Pakistan)	Caffeine 2 (day 1-3) 2 (day 4-7) vs Theophylline 1 (day 1-3) 2 (day 4-7)	n=100	<33 weeks gestation	Mean apnea per day	Caffeine significantly better in the following interval days 1-3 and 4-7 p<0.05

HIC- high income country LMIC- low- and middle-income country