Is caffeine available and affordable in low and middle-income countries?

A survey in sub-Saharan Africa

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Abstract

Caffeine is the preferred pharmacologic treatment for apnea of prematurity. Little is known about the availability and affordability of caffeine in the low and middle-income countries of sub-Saharan Africa (SSA). We conducted an online survey in 2020 of newborn physicians in SSA to determine their access to caffeine. Of 90 invited participants, 55 responded (61%). They worked in 13 SSA countries and 48 hospitals. Caffeine was used in 6 countries. In 5 of these countries, the price of caffeine was reported and ranged from US $1.73 in Ghana to US $73.63 in Kenya per 3 mL vial. High drug prices and lack of drug availability for purchase were identified most frequently as primary barriers. Some respondents believed that other methylxanthines are adequate substitutes for caffeine. Only 31 of 53 (58%) respondents knew that caffeine is included in the essential drug list of the World Health Organization (WHO).

Keywords: Apnea of prematurity. Caffeine citrate. Sub-Saharan Africa.

Introduction

Caffeine is the preferred pharmacologic treatment of apnea of prematurity (AOP). [1] However, its widespread use is mostly limited to high-income countries. Surveys among neonatologists in the United States of America, Australia, New Zealand, and Thailand found that 96%, 98%, 98.9 %, and 78% use caffeine in their practice, respectively. [2, 3] Similar reports are unavailable in sub-Saharan African (SSA) countries [4], where the overall neonatal mortality rate in 2019 was 27 deaths per 1,000 live births − the highest globally. [5] Prematurity is the leading cause of neonatal mortality, and 28% of the global preterm births occur in SSA. [6] Combined, the low- and middle-income countries of SSA and South Asia account for 80% of all prematurity related deaths.[7]

The health systems in SSA countries are low-resourced. Many interventions that improve premature infants' survival, like antenatal corticosteroids, continuous positive airway pressure, surfactant, and mechanical ventilation, are not readily available. [8, 9] Therefore, the use of evidence-based, cost-effective, and low technology therapeutics, like caffeine, is desirable to augment the limited respiratory support in these settings. In recognition of caffeine's short and long-term efficacy and safety, the World Health Organization (WHO) has included caffeine citrate on its essential drug list for children as a specific medicine for neonatal care since 2009. [10, 11] This study aimed to determine the availability and affordability of caffeine in SSA countries and describe potential barriers to its widespread use.

Methods

Design and participants

The study was a cross-sectional online survey that assessed the use, price, known or perceived barriers to caffeine availability among neonatologists and newborn physicians in SSA countries. Survey participant's identification was via a snowball sampling technique. The authors used their professional networks to identify individuals and academic or research organizations working in an SSA country. The identified individuals and leaders of organizations then shared the survey link through email with their own academic or research networks in SSA. Participation was voluntary, and consent to participate was implied by the completion of the survey. The Indiana University institutional review board assessed this research as meeting the exemption conditions from full ethical review under section 45 code of federal regulation 46.101(b).

Definition of terms

- Sub-Saharan African Countries

All African countries that are south of the Saharan desert. Per the United Nations development program, 46 of the 54 African countries constitute SSA. [12]

- Low- and middle-income countries

The World Bank classifies countries based on gross national income (GNI) per capita. [13] For the current 2021 fiscal year, a low-income country has a GNI per capita of $1,035.00 or less in 2019. Lower middle-income countries are those with a GNI per capita between $1,036.00 and $4,045.00. Upper middle-income countries are those with a GNI per capita between $4,046.00 and $12,535.00. Of the 29 low-income countries in the World Bank listing, 23 are from SSA.[13]

- International Poverty Line

The international poverty line is a monetary threshold that classifies an individual to be living in poverty. The World Bank sets this monetary threshold at $1.90 per day, referencing the fiscal year 2011.[14] The proportion of individuals living below the poverty line is a national poverty index. Of the world's 28 poorest countries, 27 are in SSA.[15]

Measures

SurveyMonkey online software (www.surveymonkey.com, LLC; Palo Alto, CA, USA) was used to create and distribute the survey instrument. Participants received either an individualized email or a survey link to the questionnaire embedded in an invitation email with the study authors included in the distribution list. Participants received only one email request. The survey covered four domains:

1. General information about the respondents, type of hospital, newborn unit of practice, and broad patient characteristics.
2. Information on availability, affordability (price) of caffeine citrate, and where indicated, known or perceived barriers to caffeine availability in their clinical setting.
3. Perception of the clinical effectiveness of caffeine compared to other methylxanthines.
4. The knowledge that caffeine citrate is on the WHO's essential drug list.

Data analysis

Data are summarized using descriptive statistics.

Results

Respondents

We distributed 90 surveys and received 55 responses – a 61% response rate. Respondents represented 13 SSA countries (Table 1) and 48 different hospitals. Neonatologists comprised 54% (n=30) and general pediatricians caring for newborns, 38% (n=21) of respondents. The majority (73%, n=40) of respondents had been in practice for more than ten years, and 76% (n=42) practiced in a tertiary referral health setting. Seventy-two percent (n=39) of respondents practiced in newborn units with a patient capacity greater than 31, and 72% (n=39) reported caring for premature infants <750 grams at birth (Table 2). Two respondents answered few questions beyond those addressing their demographic characteristics.

(Insert Table 1)

(Insert Table 2)

Availability of caffeine citrate

Of the 53 physicians who responded to the question, "do you currently use caffeine citrate to treat AOP in your practice?" only 23 (43%) reported current use. These 23 physicians worked in 21 different hospitals in six countries – South Africa, Ghana, Nigeria, Kenya, Tanzania, and Uganda. Caffeine was used for both oral and intravenous administration in 48% (n=11), oral administration only in 29% (n=6) and intravenous administration only in 19% (n=4) of hospitals. Only respondents from tertiary hospitals used caffeine; 43% (n=10) obtained it through their hospital pharmacy, and the rest sourced it from private (outside of their hospital) pharmacies. Respondents who obtained caffeine from their in-hospital pharmacy reported reliable availability. Caffeine sourced from private pharmacies was inconsistently available and often substituted with aminophylline or theophylline. There were only two

countries (South Africa and Ghana), with two or more respondents representing different hospitals, where all of them reported using caffeine.

Thirty respondents did not currently use caffeine in their practice. However, 17% (n=5) had used caffeine in the past, and 40% (n=12) knew of another hospital in their country where caffeine is used. All of these countries that had already been identified by caffeine users. To treat AOP, of the 29 non-users of caffeine who answered the question, 97% (n=28) prescribe other methylxanthines and one respondent uses no medication.

Price of caffeine citrate

Among the 23 respondents who use caffeine in their hospitals, 15 reported the price (Table 3). Prices varied greatly between countries; the price for a 20mg/ml, 3ml vial of caffeine citrate was lowest at US $1.73 in Ghana, highest at US $73.63 in Kenya, and ranged from US $6.48 to $16.67 in Nigeria, Tanzania and Uganda. A respondent from Tanzania estimated the hospital spends US $200.00 per month for 8-10 babies, equivalent to US $20.00 to $25.00 per child per month.

(Insert Table 3)

Barriers to availability of caffeine citrate

South Africa was the only country where none of the respondents reported barriers to caffeine use. In a question on barriers to caffeine use that allowed multiple answers , the price of caffeine was the most frequently reported barrier (n=35), followed by its lack of availability for purchase (n=32). Of the 27 physicians who did not currently use caffeine in their practice and who responded to the question "what is the primary barrier to caffeine use in your country?" 70% (n=19) indicated that the price of caffeine was the main barrier. This was followed by the lack of availability for purchase 15%

(n=4). Although not technically a barrier, 15% (n=4) reported other methylxanthines were equivalent substitutes; hence there was no demand for caffeine.

In the open-ended responses to the question why caffeine was unavailable for purchase, few respondents knew the reason. A physician from Tanzania said, "Caffeine is not registered in my country." One respondent speculated whether "fear that it will be used by car/truck drivers to stay awake" may be a reason for government restriction.

A respondent from Botswana stated, "Complex governmental systems" are a barrier to caffeine availability. Drug registration goes "through many steps," said another respondent from Botswana. To describe the complexity involved in getting medications registered in-country, one respondent from Tanzania stated it took "eight years of paperwork to make surfactant available."

Perceived effectiveness of caffeine citrate in treating AOP over other methylxanthines

The majority of respondents believed caffeine is more effective than other methylxanthines (81%, n=43) in the treatment of AOP. This perception was more prevalent among respondents who currently use caffeine in their practice (91% vs. 73%).

Knowledge that caffeine is on the WHO essential drug list

Fifty-eight percent of respondents (31 of 53) were aware that caffeine is on the WHO essential drug list (Table 4).

(Insert Table 4)

Discussion

This cross-sectional survey aimed to determine the availability and affordability of caffeine citrate in the low- and middle-income countries of SSA. Respondents in less than half of the represented 13 countries used caffeine. Prices of caffeine citrate ranged from US $1.73 in Ghana to US $73.63 per 3 mL vial in Kenya. A high purchase price was the most frequently reported primary barrier, followed by drug unavailability.

Our findings suggest that the use of Caffeine in SSA countries is not widespread. Caffeine appeared to be consistently prescribed only in South Africa and Ghana. It is noteworthy that both countries have less than 20% of their population living under the international poverty line (< US$1.9 per day). [14] The proportion of the population living under the poverty line in the other countries in this survey averaged 42%. Given that drug affordability was the most frequently reported primary barrier to caffeine use, and parents have to pay for the drug, it seems obvious why caffeine utilization may be poor.

Lack of drug availability was the second most frequently reported primary barrier to the use of caffeine. Most respondents did not know why caffeine was unavailable in their countries. A few respondents attributed the unavailability of caffeine to complicated, often challenging government regulations. One commented that "the government might be restricting caffeine availability to prevent long-distance truck drivers from abusing it". Countries in SSA often have un-regulated pharmacies/dispensaries. It is typical to obtain non-narcotic medications, including antibiotics, without a prescription in SSA countries. If this respondent's hypothesis is correct, such governmental concerns might not be unfounded. Stricter regulation of caffeine distribution, similar to narcotics, may help make it more readily available for in-hospital use to treat AOP.

Previous authors have suggested that caffeine unavailability in SSA might be, in part, due to a lack of demand by practitioners. [4] This lack of demand may originate from a belief that other methylxanthines are suitable substitutes for caffeine. We found evidence for this belief among some practitioners in this survey. Such beliefs, and the finding that little more than half of the respondents were aware that caffeine is included in the WHO essential drug list, point to a sizeable knowledge gap that must be bridged. The WHO has listed caffeine citrate on its essential drug list for children as a specific medicine for neonatal care since 2009.[12,13] Importantly, the WHO essential drug list serves as a guide for the development of national essential drug lists.[16, 17]

In high-income countries, caffeine is often used adjunctively with positive pressure ventilation (non-invasive or invasive) to treat AOP, particularly in early life. Other evidence-based therapies for the management of respiratory distress are readily available in these settings. In low- and middle-income countries, even supplemental oxygen may be difficult to obtain in some health settings. [9, 18] One could argue that in a region where 27 deaths per 1,000 live births occur [5], the primary focus should be on interventions and therapies shown to improve mortality. In high-income countries, caffeine did not affect mortality, early or late. [19, 20] Most health settings in SSA, even tertiary referral centers, lack continuous positive airway pressure, ventilators, surfactant, or the ability to provide thermoregulation resulting in early neonatal deaths. [8] Thus, the beneficial effects of caffeine (fewer ventilator days, reduced incidence of bronchopulmonary dysplasia, and improved neurodevelopmental outcomes) may be lost on the medical providers and health settings in SSA and other low- and middle-income countries. Studies on the impact of caffeine on critical short, intermediate, and long-term neonatal outcomes in settings with limited resources are urgenty needed. This question is one of the WHO newborn research priorities.[9]

This study has several limitations. Respondents represented only a quarter of the countries in SSA, potentially leading to biased estimates of the true availability of caffeine in the region. However,

the countries represented in this survey are the most medically advanced of all SSA countries and therefore, the implementation of caffeine therapy for AOP is unlikely to be better in the remaining SSA countries. There were five countries where we only had one respondent. If the respondent in that country did not use caffeine, it might be implied that caffeine is not used in that country. As a proxy to determining availability in-country, we asked if respondents knew of any center in their country where caffeine was used but this question did not increase the list of countries where caffeine was prescribed. Lastly, differences in experience, practice environment, and knowledge about the clinical advantages of caffeine among pediatricians and neonatologists may affect responses and confound our results.

Conclusion

Caffeine availability and affordability vary between and within sub-Saharan African countries. The high price of caffeine in reference to the poverty rates in these low- and middle-income countries appears to be the most significant barrier to caffeine availability. Other factors limiting availability may be the presence of complex and challenging government regulations, and a lack of demand by practitioners founded on the belief that other methylxanthines are suitable substitutes for caffeine. Such beliefs, and poor knowledge that caffeine is on the WHO essential drug list, point to a sizeable knowledge gap that must be bridged.

Finally, the benefits of caffeine on the outcomes shown in high-income countries for very preterm infants may be seen as less important by clinicians in low- and middle-income countries, because they lack interventions that improve premature infants' survival. Research is needed to determine the short, intermediate, and long-term impact of caffeine in settings where resources are limited. Evidence generated from such research should help direct the implementation and dissemination of caffeine into low-resource clinical settings.

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Table 1: Distribution of countries representing survey respondents

Country	N (%)
Botswana	1
Ethiopia	2
The Gambia	1
Ghana	3
Kenya	7
Liberia	1
Malawi	1
Mozambique	1
Nigeria	15
South Africa	3
Tanzania	13
Uganda	5
Zambia	2

Table 2: Characteristics of respondents and their medical practice.

Characteristics	N (%)
Primary clinical specialty or sub-specialty	
• Neonatology	30 (54)
• General Pediatrics	21 (38)
• Pediatric surgery	1 (2)
• Emergency room physician	1 (2)
• Endocrinology	1 (2)
• Infectious disease	1 (2)
Number of years in clinical practice	
• ≤5 years	5 (9)
• 6 to 10 years	10 (18)
• >10 years	40 (73)
Type of practice	
• Tertiary	42 (76)
• Secondary/Distric/General Hospital	12 (22)
• Research Organization	1 (2)
Newborn unit patient capacity	
• <10	1 (2)
• 10-20	9 (17)
• 21-30	5 (9)
• ≥31	39 (72)
Patient population by birth weight category*	

• ≥2500 grams	54 (100%)
• 1500 to 2499 grams	51 (94)
• 1000 to 1499 grams	48 (89)
• 750 to 999 grams	46 (85)
• <750 grams	39 (72)

* 54 physicians provided data on their patient population by birth weight category and percentages in each row are for those physicians who care for this particular birth weight group.

Table 3: Price of a 3 mL vial of caffeine citrate by country

Country	Local price	U.S. Dollar equivalent in October 2020	The proportion of the population living under the international poverty line
Ghana	10 Cedi	$1.73	13%
Kenya	8,000 Kenyan Shilling	$73.63	37%
Nigeria	4,000-6,000 Naira	$11.11-16.67	53%
Tanzania	15,000 Shilling	$6.48	49%
Uganda	30,000-50,000 Shilling	$8.03-13.38	42%

Local currencies converted to U.S. Dollar using MSN money currency converter (found https://www.msn.com/en-us/money/currencyconverter)

Our survey did not distinguish between the prices for caffeine citrate for injection and caffeine citrate oral solution. However, in high-income countries, the prices are similar for both. Often, caffeine citrate for injection is also used for oral administration.

Table 4: Knowledge that caffeine is listed on the WHO essential drug list by current use of caffeine*

	Yes n (%)	No n (%)
Currently use caffeine	13 (57)	10 (43)
Do not currently use caffeine	18 (60)	12 (40)
Total	31 (58)	22 (42)

*N=53 because two respondents did not answer this question.