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RESEARCH ARTICLE

A physician survey on research and implementation priorities for caffeine citrate use in newborn care in sub-Saharan Africa

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ABSTRACT

Background: Evidence on caffeine citrate (CC) for apnoea of prematurity (AOP) originate from high-income countries. This study aimed to develop consensus on research design for evidence in sub-Saharan Africa (SSA).

Methods: We surveyed physicians in newborn units across SSA to assess their opinions on CC research and their preferred study designs.

Participants rated four study designs: a) an observational before-and-after study; a randomized controlled trial (RCT) of b) caffeine versus placebo; c) caffeine versus aminophylline; d) a traditional or stepped wedge cluster trial. They assessed each design using a Likert scale for evidence, feasibility, and ethics considerations.

Results: Ninety-two newborn physicians across 21 SSA countries participated. Most respondents (72%) felt a trial on CC in SSA was important. An RCT of CC vs. aminophylline and a cluster RCT had the highest ratings for importance (82% and 73%), feasibility (75% and 69%), and ethical appropriateness (78% and 69%), while an RCT of CC vs. placebo received the lowest ratings in these categories.

Conclusions: Newborn SSA physicians agree that local research on CC is needed and rated an individual or cluster RCT comparing caffeine with aminophylline to evaluate CC's impact on key clinical outcomes.

Introduction

Caffeine citrate (CC) and aminophylline are methylxanthines used to prevent and treat apnoea of prematurity (AOP)[1-3]. Despite being equally effective in reducing AOP incidence[2] globally, CC is preferred because of its better side-effect profile, once-daily administration schedule, and non-requirement for routine blood monitoring[3]. Furthermore, CC has also been more extensively studied on its impact on invasive ventilator use, long-term neurodevelopment, and cost-effectiveness[3-5].

The evidence supporting the use of CC largely originates from high-income countries[3,4], where advanced respiratory support, continuous monitoring, and an adequate staff-to-patient ratio are standard. These conditions contrast sharply with the limited resources in neonatal units across sub-Saharan Africa (SSA). Infants enrolled in the landmark caffeine for apnoea trial were extremely premature, a group with low survival in SSA settings[6]. Of the 15 trials included in a recent systematic review of caffeine citrate for AOP treatment and neurodevelopment, only one originated from Africa (Egypt)[7].

Countries in SSA carry a high global annual rate of preterm births and deaths[8]. Despite WHO recommendations endorsing caffeine citrate for AOP in low-resource settings[4,9], it is unknown whether evidence from high-income countries is applicable in LMICs, where clinical resources are constrained, and the cost of CC is often prohibitive[10,11]. The situation is that the use of caffeine citrate is advocated in sub-Saharan Africa, despite a lack of evidence of its benefit in that setting. No adequately powered randomized controlled trials evaluating CC's impact on preterm outcomes have been conducted in SSA[6-8], and aminophylline remains the more accessible but risk-prone alternative[2,10,11]. Promoting CC as the preferred treatment without context-specific evidence may inadvertently reduce access to effective therapy if CC is unaffordable or inconsistently available. Clinicians' perspectives are critical for determining whether clinical trials of CC in sub-Saharan Africa are needed and which trial design would be preferred when feasibility and ethics are considered.

To the best of our knowledge, the views of clinicians working in Sub-Saharan Africa on the optimal study design to generate context-relevant evidence on CC use in newborn care have not yet been published. We conducted this study to 1) determine the perception of physicians practising in SSA on the priority clinical outcomes to evaluate within a clinical trial on Caffeine Citrate, and 2) explore physicians' preference for the type of study they perceive to be most suitable for evidence generation, feasible, and ethically appropriate.

Methods

STUDY DESIGN AND SAMPLING

We conducted an online survey among neonatologists and paediatricians caring for hospitalized newborns across SSA from the 1st of September 2022 to the 31st of January 2023. We used both convenience sampling and snowball recruitment methods[14]. We first recruited participants through two existing professional networks – the African Neonatal Association and the African Neonatal Nutrition Network. We asked members of these associations to share with their local networks and colleagues within and outside their country of practice. The survey link was sent via email and social media platforms, including WhatsApp®. All participants provided consent online before completing the survey. The survey was available in English and French to ensure we captured participants' views across Francophone countries in SSA.

DATA COLLECTION

The survey consisted of 34 questions, including one for consent. We collected basic participant demographics, newborn unit clinical respiratory care capability, and current caffeine use for AOP management. We also collected data on participants' perceptions of what clinical outcomes are important to evaluate in a CC clinical trial. Using the Patient, Intervention, Comparison, and Outcome (PICO) format, we presented and briefly described five different research designs investigating the impact of CC. The trial designs included 1) an observational study using a before-and-after trial design, 2) a blinded randomized placebo-controlled trial design, 3) a blinded randomized controlled trial of aminophylline vs CC, and 4) a traditional or stepped wedge cluster randomized trial.

Participants were asked to rate each study design using a five-point Likert scale based on the

importance of generating evidence, the feasibility or practicality of conducting it, and the ethical appropriateness of performing such a trial in their newborn unit. Free-text boxes allowed participants to suggest alternative study designs and share their impressions of each study design presented, including strengths and potential challenges not listed by the investigators. Completing the online survey took about 10–15 minutes.

ETHICAL CONSIDERATIONS

All participants provided informed consent, which was included in the survey. The survey was approved by the Research and Ethics Committee of the Liverpool School of Tropical Medicine (Research protocol 22-051) and the Research and Ethics Committee at Federal Teaching Hospital, Ido-Ekiti (ERC/2022/05/18/788B).

DATA MANAGEMENT AND ANALYSIS

De-identified data were imported into an Excel spreadsheet for analysis. Using descriptive statistics, we present the physicians' demographics, characteristics of the newborn unit, and Likert-scale ratings. We re-classified the Likert scale from 5 to 3 and summarized the results by the percentage of respondents' choices. These analyses were conducted using SPSS version 26. Content analysis was used to summarise the physicians' free-text perspectives on the study designs. These were systematically reviewed by two researchers (NE, OB) to determine the frequency of diverse perspectives on the study designs[15].

Results

We received responses from 92 Neonatologists and Paediatricians across 21 countries in SSA. It was not possible to determine the response rate, as the link was shared informally through networks. Most respondents (68,74%) had more than 5 years of clinical experience, and most (73, 79%) worked in neonatal units with invasive and/or non-invasive respiratory support. Twenty-one percent (19) of newborn care physicians worked in neonatal units with oxygen (nasal cannula with flow ≤2 litres per minute) as the only source of respiratory support, and 40% (37) admitted more than 200 very preterm babies annually. Less than half (42, 45%) reported regular use of caffeine, and 6 (6.5%) reported occasional use of caffeine. Of those who used caffeine, only 8 (16.7%) had access to oral caffeine, while the remaining used intravenous caffeine of various brands. **(Table 1)**

Table 1: Professional and clinical context of study participants

Variable	Frequency (%) N = 92
Years of clinical experience post qualification	
<5 years	24 (26)
>10 years	33(36)
>5-10 years	35(38)
Primary place of work: unit type	
Neonatal unit with CPAP or High Flow Nasal Cannula	37(40)
Neonatal unit with invasive ventilation & CPAP	36 (39)
Neonatal unit with low-flow oxygen as the sole method of respiratory support	19 (21)
Annual admissions of infants with a birthweight of < 1500g or gestation age< 32 weeks at birth	Number (%)
<50	9 (10)
50-99	19 (21)
100-149	19 (21)
150-199	8(9)
>200	37(40)
Use of caffeine citrate	
No use of oral or intravenous caffeine citrate	44 (48)
Occasional or no intravenous caffeine citrate; regular oral use	6 (7)
Regularly use intravenous & oral caffeine citrate.	42 (46)

PERCEPTION OF THE IMPORTANT STUDY OUTCOMES TO CONSIDER IN A CLINICAL TRIAL INVOLVING CAFFEINE CITRATE

Respondents selected the following clinical outcomes as priorities for evaluation in a clinical trial involving caffeine citrate: length of stay was the most frequently selected outcome (74, 80%). Over half of physicians also reported that bronchopulmonary dysplasia (69,75%), all-cause mortality (66,72%), retinopathy of prematurity (49,53%), and intraventricular haemorrhage grade 3/4 or periventricular leukomalacia (47,51%) as priority outcomes for a caffeine trial in Africa. (**Table 2**)

Table 2: Priority infant outcomes measures for future trials

Priority trial outcomes for physicians	Frequency (%) N=92
Length of hospital stay	74 (80)
Bronchopulmonary dysplasia	69 (75)
All-cause mortality	66 (72)
Retinopathy of prematurity	49 (53)
Intraventricular haemorrhage grade 3/4 or periventricular leukomalacia	47 (51)
Late-onset sepsis or necrotising enterocolitis	36 (39)

THE IMPORTANCE, FEASIBILITY, AND WILLINGNESS TO PARTICIPATE BY STUDY DESIGN

The physicians' perspectives on the strengths and limitations of four study designs, along with the associated research questions, are outlined below using the Population Intervention Comparator Outcome (PICO) structure. Direct quotes from respondents are summarized in the Appendix.

Most respondents (74, 82%) rated a randomized controlled trial of caffeine vs. aminophylline as the most important approach for generating high-quality evidence to support caffeine use, followed by a traditional or stepped-wedge randomized cluster trial (66, 73%). All trial designs were deemed feasible or very feasible to conduct by ≥50% of respondents. A randomized controlled trial of caffeine vs. placebo was considered the least ethical to conduct (44, 48%). (Table 3)

Table 3: Rating of study design

	Observational – before and after study	Individual randomized-controlled trial caffeine citrate vs. placebo	Individual randomized-controlled trial caffeine citrate vs. aminophylline	Cluster randomized controlled trial traditional or stepped wedge
Likert Measure	**N=90 (%)**	**N=92 (%)**	**N=90 (%)**	**N=90 (%)**
Important to generate evidence				
Very important or important	41 (46)	48 (52)	74 (82)	66 (73)
Neutral	29 (32)	11 (12)	7 (8)	13 (15)
Very Unimportant or unimportant	20 (22)	33 (36)	9 (10)	11 (12)
Feasible and practical to conduct				
Very feasible or feasible	59 (66)	45 (49)	67 (75)	62 (69)
Neutral	18 (20)	16 (17)	13 (14)	12 (13)
Not very feasible or not feasible	13 (14)	31 (34)	10 (11)	16 (18)
Ethically appropriate				
Very ethically appropriate or ethically appropriate	61 (68)	39 (42)	70 (78)	62 (69)
Neutral	10 (11)	9 (10)	7 (8)	13 (14)
Not very ethically appropriate or not ethically appropriate	19 (21)	44 (48)	13 (14)	15 (17)

Study design I: Observational study (before-and-after)

PICO research question: In preterm infants < 32 weeks or < 1500g (Population), does Caffeine Citrate (Intervention), compared to standard of care – aminophylline or placebo (Control), improve survival to NICU discharge (Outcome)?

Respondents generally thought that the study's strength was that it was the easiest to conduct, both logistically and financially. However, the risk of bias, the generation of low-quality evidence, and the possibility of not obtaining definitive, generalizable results were considered limitations of this study design. These concerns are identified in some of the responses.

> *"Study with high risk of bias and low data quality. Low quality of data with risk of several biases and results that may be inconclusive."*

> *"The scope of the observational study is less compared to a randomized controlled intervention study or a cluster study. It provides less evidence based on facts."*

> *"The strength and quality of evidence from an RCT is more than that of an observational study."*

> *"There will be a lot of bias. The results, therefore, will be difficult to generalise to non-study facilities."*

Study design II: Individual randomized controlled trial (caffeine citrate vs placebo)

PICO research question: In preterm infants < 32 weeks or < 1500g (Population), does Caffeine Citrate (Intervention), compared to placebo (Control), improve survival to NICU discharge (Outcome)?

Respondents considered the study design to be relevant only to centres where CC was not the standard of care. Participants noted important ethical challenges with this design because the standard of care for AOP was considered Caffeine Citrate, and the lack of availability was considered the primary reason for low uptake, rather than a lack of evidence. Given the current evidence, it was also thought that using a placebo would be difficult when known treatments are available. One respondent stated,

> *"I think it's unethical to put such babies on placebo-like normal saline knowing they are likely to go apnoeic."*

It was also thought that, given the current evidence, it would be difficult to use a placebo when known treatments are available. One such respondent stated,

> *"We shouldn't do an RCT as we already have the evidence. What we need is the availability of the drug."*

Another respondent stated, *"I will find it difficult to randomise any baby <32 weeks /2500g to placebo in our centre group, given what is known about caffeine and the fact that we use caffeine routinely."*

Study design III: Individual randomized controlled trial (caffeine citrate vs aminophylline)

PICO research question: In preterm infants < 32 weeks or < 1500g (Population), does Caffeine Citrate (Intervention), compared to aminophylline (Control), improve survival to NICU discharge (Outcome)?

The perceived strength of this study design was that this RCT could potentially make it possible to *"make a choice between caffeine and aminophylline."*

> *"This is okay, as most studies on this were among Caucasians. There may be a difference among our neonates."*

> *"I think this study would be necessary, especially in the African setting, where buying of caffeine is not prioritized due to cost. Generating evidence in the African setting would convince Ministries of Health to prioritize the procurement of caffeine."*

The affordability and availability of caffeine were common challenges raised by the respondents.

> *"In my opinion, what is needed now is how to make caffeine more available and affordable in LMICs."*

> *"If we are able to reduce the cost of caffeine and possibly a lower dose of aminophylline, this may add to the justification."*

Other challenges raised included the need for intravenous access to administer aminophylline and access to adjuvant therapies such as surfactant.

Study design IV: Cluster randomized controlled trial: traditional or step wedge (caffeine citrate vs aminophylline)

PICO research question: In preterm infants < 32 weeks or < 1500g (Population), does Caffeine Citrate (Intervention), compared to aminophylline (Control), improve survival to NICU discharge (Outcome)?

Respondent perceived the strength of this study type to be the elimination of bias and the fact that all participants would ultimately receive CC. However, the cost, technical challenges, and patient recruitment were identified as challenges for this study design. Other challenges raised by the stepped-wedge design included recruiting hospitals with differing resource availability, e.g., respiratory support. None of the respondents expressed any ethical concerns about this study type.

> *"A step wedge design would eliminate the possibility of using aminophylline. However, the (newborn) units involved would have to have more numbers, and this may exclude some countries with (newborn) units that have low numbers."*

> *"However, the step wedge design is also feasible as long as there is adequate logistics and would require a commitment to the study; we all work to achieve the required results, which is the reduction of preterm death from apnoea of prematurity. Only that it will require a longer duration compared to "Cluster Randomized Control Trials."*

Discussion

Evidence on the short- and long-term clinical impact of CC is predominantly from high-income countries[4,7,13] and may not be relevant to SSA, where patient populations and clinical care capabilities differ significantly[6,16,17]. This study thus sought to understand newborn care physicians' perspectives on the context-relevant study design and priority clinical outcomes to evaluate in generating evidence for CC use in newborn care across Africa. Of the 92 study participants from 21 countries, less than half used CC routinely. Their priority clinical outcomes to evaluate in a CC study were i) length of hospital stay, ii) bronchopulmonary dysplasia, and iii) all-cause mortality. Regarding study design, an individually randomized clinical trial comparing CC vs aminophylline was rated the most important for generating high-quality evidence to support caffeine use in SSA, followed by a traditional or stepped-wedge cluster-randomized trial design. However, an individually randomized controlled trial of caffeine vs placebo was considered the least ethical to conduct.

Study designs should be guided by the research's purpose and the nature of the research questions[18], as well as local stakeholders' research priorities. Our study, for the first time, presents the views of newborn care physicians across SSA on the most feasible, robust, and ethically appropriate study designs for evaluating the use of CC in the management of apnoea of prematurity. Randomized controlled trials are the gold standard for studying the causal relationships between interventions and outcomes[15,19]. However, RCTs are expensive and resource-intensive, and it may not be feasible to implement them in some resource-limited settings[19]. Taylor-Robinson et al in a recent paper examining the paucity of clinical trials in Africa echoed some of the responses on RCTs from our study such as the limitation in the number of trained investigators as well as challenges in supply chains for research materials and also pointed these out as barriers for conducting RCTS in Africa[20]. So even though many respondents agreed that an RCT of caffeine citrate vs aminophylline would be important to determine comparative clinical and cost-effectiveness in SSA settings, they were equally concerned about the practical challenges of large multicentre RCTs.

In today's era of shifting power balance in global health research that prioritises the voices of local stakeholders, our study demonstrates that newborn health physicians across Africa are willing and capable of determining their research priorities[21]. However, they acknowledged limitations in their capacity to access funding and in their technical ability to implement complex study designs, such as stepped-wedge RCTs. This

highlighted the need for ongoing partnerships with senior researchers in Africa and high-income countries for mentorship, support, and training to generate high-quality, context-relevant evidence on the use of caffeine in newborn care in Africa, alongside other impactful interventions. The evidence of the efficacy of caffeine in the management of AOP in high-income countries is clear[2,4,5,7,12]. However, recent systematic review still reiterate what this study reports, that robust policy-relevant studies are needed to determine the risks, benefits, and costs of CC use in the low-resource settings[22].

The major limitation of our study was that we did not include families and caregivers in this survey, a key aspect of research priority setting in maternal and child health research[20]. However, with this established network of stakeholders, there is an opportunity to reach out to them in subsequent studies and surveys.

Conclusion

Our survey showed that caffeine use in newborn care across SSA is limited, largely due to the prohibitively high cost and unavailability. Physicians across the continent are willing to contribute to the design and implementation of clinical trials for caffeine in newborn care to generate robust context-relevant data, but caffeine vs placebo trials were largely considered unethical. However, they are amenable to participating in pragmatic trials. Individual- or cluster-randomized trials comparing caffeine with aminophylline to evaluate caffeine citrate's impact on key clinical outcomes are needed in sub-Saharan Africa. Finally, this study highlights the recurring theme in implementation science that affordable access to caffeine citrate in healthcare systems in Africa is a priority and a prerequisite for future research[23-25].

Conflict of Interest Statement:

None.

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Appendix 1

	Study type I: Does Caffeine Citrate (Intervention) improve survival to NICU discharge (outcome) in preterm infants < 32 weeks or 1500g (population) when compared to placebo (control)	Study type II: RCT Question: Does caffeine Citrate (Intervention) improve survival to NICU discharge (outcome) in preterm infants <32 weeks or <1500g (population) when compared to aminophylline (control).	Study III: Step wedge design Question: Does caffeine Citrate (Intervention) improve survival to NICU discharge (outcome) in preterm infants <32 weeks or <1500g (population) when compared to aminophylline (control).	Study type IV: Observational study design
Perceived strengths of study type	"Only doable where caffeine is not standard of care."	"The study will help to make a choice between caffeine and aminophylline".	"A step wedge design would eliminate the possibility of using aminophylline. However, the units involved would have to have more numbers and this may exclude some countries with units that have low numbers".	"Observational studies are easier to conduct and will be applicable in centers who have used aminophylline in the past and have access to caffeine citrate considering availability and cost"
	"Doable, probably fewer big NICUs required, so also probably 1 year to collect data."	"This is okay as most studies on this were among Caucasians. There may be a difference among our neonates."	"I would welcome this study because all participants have the benefit of standard of care."	"Attractive because no funding required".
	"secondary outcomes could possibly look at why the uptake for caffeine has been so low in our set up"	"I think this study would be necessary, especially in the African setting where buying of caffeine is not prioritised due to cost. Generating evidence in the African setting would convince Ministries of Health to prioritise the procurement of caffeine."	"This might be easier as it removes the need for individual units to be running 2 blinded interventions"	"Quick to get started, might help in getting funding for a higher powered study"
Perceived challenges of study type	"Given the current evidence base, it will be difficult to test against a placebo"	"It would require finding out the units using aminophylline. we have not used this in our unit for several years."	"May be difficult to get 20 NICU with similar standards in our country".	"The strength and quality of evidence from a RCT is more than that of an observational study."
	"I think it's unethical to put such babies on placebo-like normal saline knowing they are likely to go apnoeic."	"Not in favour of it, aminophylline requires intravenous access, and we already know that it has more side effects"	"The Step-wedge design is also feasible if there are adequate logistics. It would require commitment to the study; we all work to achieve the required results which is the reduction of preterm death from apnoea of prematurity. It will however require a longer duration compared to Cluster RCTs"	"Study with high risk of bias and low data quality. low quality of data with risk of several biases and results that may be inconclusive".
	"I will find it difficult to randomise any baby <32 weeks /2500g to placebo in our centre group given what is known about caffeine and the fact that we use caffeine routinely"	"Given the adverse affect associated more with aminophylline, I would suggest a "non-inferiority" design. The main importance would be 1. Assess the impact of caffeine in a predominantly non invasive resp support setting, and 2. If truly caffeine is comparable to or superior to Aminophylline with less adverse effect, it would support advocacy for its availability."	"Good to do but the resources both human and Capital will be intensive. Recruiting babies will be another challenge"	"There will be a lot of biases. The results therefore will be difficult to generalise to non-study facilities".

Other comments on study type	"Availability of caffeine is very difficult in our country unless the study provides the necessary medications"	"If we are able to reduce the cost of caffeine and possibly a lower dose of aminophylline, this may add to the justification".	"The circumstances surrounding the trails may not be the same. So the outcomes in both study and control may be affected by difference circumstances, there the results may not be as reliable as the simple RCTs."	"The scope of the observational study is less compared to a randomized controlled intervention study or a cluster study. It provides less evidence based on facts."
	"Compare caffeine with current standard of care and not placebo"	"I think will be a good idea, and will also encourage the government to procure caffeine as recommended by WHO"	"For this study to be successful there should be adequate funding for the study. Also careful selection criteria will be required to control for confounding variables"	"An observational study would be of little interest compared to an interventional study."
	"Could the study compare the outcome of caffeine citrate and aminophylline? both have proven benefits because I foresee ethical issues if we are to have an arm on placebo"	"In my opinion, what is needed now is how to make Caffèine more available and affordable in LMICs"	"Not sure whether facilities using caffeine citrate already will feel confortable if randomized to aminophylline or will such facilities be seeded before randomization? may require 'naive' facilities?"	"Not neccesary. There have been previous observational studies in this direction. There are no new things to add to the body of knowledge from this type of study".