Effectiveness of Low-Dose Theophylline for the Management of Biomass-Associated COPD

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Low-dose Theophylline for the Management of Biomass Associated COPD

Introduction

The majority of morbidity and mortality related to COPD occurs in low- and middle-income countries (LMICs). Despite the growing burden of biomass smoke-related COPD, few studies have been conducted to assess the effectiveness of respiratory medications in this setting. Low-dose theophylline, an oral once-daily medication, has been recommended for the treatment of COPD in LMICs without the use of inhaled steroids or bronchodilators. The Low-dose Theophylline for the Management of Biomass-Associated COPD (LODO-BCOPD) study aims to explore the drug's clinical efficacy and cost-effectiveness in the treatment of biomass-related COPD in low-income populations.

Research Hypothesis

The study hypotheses are:

- Low dose theophylline results in improved quality of life among those with BCOPD compared to placebo.
- Low dose theophylline is cost-effectiveness for the management of biomass-associated COPD in a low-income setting.

Study design and participants.

This was a parallel arm placebo-controlled randomized trial. 100 participants were randomized a 1:1 allocation ratio to receive either the Intervention or the placebo. The trial design is fully described in the protocol paper (Siddharthan et al. Trials 2021)

Selection of clinic and participants.

This trial was conducted in Nakaseke district, at Nakaseke hospital.
Participants were eligibility criteria included:

- Age 30 years and above.
- Full time residents of the study area (Nakaseke district),
- Current use of traditional stoves only for cooking,

- Post-bronchodilator FEV_1/FVC < the lower limit of normal of the Global Lung Initiative Mixed Ethnic reference population.
- Grade B-D COPD
- Daily biomass exposure.

Participants were excluded from the study for the following reasons:

- Planning to move within one year of study commencement.
- Having uncontrolled hypertension
- Pregnancy.
- Use of chronic respiratory medication.
- History of post-treatment pulmonary tuberculosis.
- Greater than 10 pack year tobacco smoking history.
- Known intolerance or contraindication to theophylline.

Interventions.

Participants both on the intervention and control arm received the standard of care as per the WHO guidelines for the management of COPD in LMICs i.e. (COPD specific education and salbutamol inhalers). In addition to the standard of care, those randomised to the intervention arm received 200 mg ER low-dose theophylline daily. Drugs were dispensed monthly for each of the participants for a period of 12 months by the research assistants.

Trial procedures.

Patients were screened from the community at Nakaseke hospital and those who were eligible were then enrolled into the study. Participants were then randomised to receive either the placebo or investigational product by the research pharmacist. Spirometry and baseline data was collected by trained research assistants from each of the study participants and a participant visit schedule was then created for each of the participants. Spirometry and Demographic data were then collected at the different timepoints (3 months, 6 months, and 12 months) by the trial research nurses.

Outcomes.

The primary outcome measure of the trial was change in the mean St. George's Respiratory Questionnaire (SGRQ) scores at 12 months. The key exposures and secondary outcomes are summarized in the table below. Secondary outcome include change in SGRQ at 3 months with 95% CI provided.

Table 1. Primary and secondary outcomes.

Outcome	(baseline)	3 months	6 months	9 months	12 months
Primary outcomes					
SGRQ	**X**		**X**		**X**
Secondary outcomes					
SF-36	**X**		**X**		**X**
PEF	**X**		**X**		**X**
FEV_1	**X**		**X**		**X**
FVC	**X**		**X**		**X**
Biomarkers	**X**		**X**		**X**

Abbreviations: SF-36, Short Form 36 survey; SGRQ, St. George Respiratory Questionnaire; PEF, peak expiratory flow; FEV1, forced expiratory volume in 1 second; FVC, forced vital capacity

Sample Sizes.

A sample of 99 participants with COPD total were required to have an 80% two-sided confidence interval that excludes a 4-point difference in SGRQ under the scenario of a 7.8-point difference in means. Adjusting for a 10% loss to follow up rate we planned to recruit 110 participants.

Duration of intervention

The intervention was implemented for 12 months, with endpoint data collected after 3 and 12 months.

Randomisation.

The allocation sequence for the random assignment of the intervention was generated using STATA version 16.0 and this was then uploaded to the Redcap data management software where the random assignment of participants to one of the two arms was done. We used block randomisation with block sizes of 4. The allocation sequence was uploaded directly onto

the redcap platform by the trial statisticians this enabled us to conceal the sequence up to the point of randomisation.

Randomisation Implementation.

The trial statistician developed the allocation sequence, and the research study nurses enrolled participants in the study. Following enrolment into the study, the trial pharmacist used the Redcap data management tool to assign each participant to a particular arm.

Blinding.

Study participants, research nurses, the principal investigators, and the research study coordinator were all blinded to which randomisation arm of the participant. Placebo pills manufactured in identical packaging as the active drug dispensed to those on the intervention arm were used to maintain the blinding of participants and information about the study arm was only known to the research pharmacist to maintain the blinding of the other study staff.

Statistical analysis.

The baseline characteristics of participants were compared between the two arms using medians (IQR) for continuous variables and proportions for categorical variables. Outcomes were analyzed by both the intention-to-treat and per-protocol analysis method using linear mixed-effects regression methods for the primary and secondary continuous outcomes and random effects logistic regression methods for binary outcomes. Baseline imbalances were adjusted for in both the primary and secondary analysis, and results both unadjusted and adjusted analyses will be presented. All analyses were adjusted for arm, baseline outcome scores summarize.

Missing Data.

Missing data on outcomes and key covariates will be assessed prior to analyses. Where missingness is greater than 5% we will implement therefore multiple imputation (MI) methods appropriate for random effects models. Data will be assumed to be missing at random (MAR), and respondents with missing data will be described by clinic and key sociodemographic characteristics.

Planned subgroup and secondary analyses.

Subgroup analyses for the differences in the effectiveness of the intervention in affecting primary and selected secondary outcomes will be assessed age (continuous), sex (male/female), BMI (categorical), socioeconomic status (categorical), education (categorical), tobacco use (yes/no) and medication adherence (>80%).

Analysis of secondary outcomes will include change in COPD Assessment Test (CAT), exacerbations and respiratory-related hospitalizations, inflammatory biomarkers (e.g. fibrinogen, hs-CRP) and lung function. We will additionally conduct exploratory analysis to compare the exposure-response relationship between 2.5μg and FEV_1 between study arms to assess whether theophylline attenuates the association. For the exposure-response associations, analyses will be conducted within the intervention and the control groups separately, as well as in a combined analysis. Non-linear associations between exposure and health outcomes will be examined using generalized additive models and other spline-based approaches.

Lastly, we will utilize measurements of the EQ-5D at baseline and months 3 and 6 to convert scores into health utility estimates using validated conversion formula. The incremental number of QALYs gained, comparing intervention participants to controls, can then be calculated by measuring the longitudinal values of health utility over the intervention period in each arm.

Two-sided P values of 0.05 or less will be considered to indicate statistical significance. Analysis will be performed with STATA version 18 software. Analysis will be independently replicated and reported.

Tables.

Figure 1: Overall Study Status

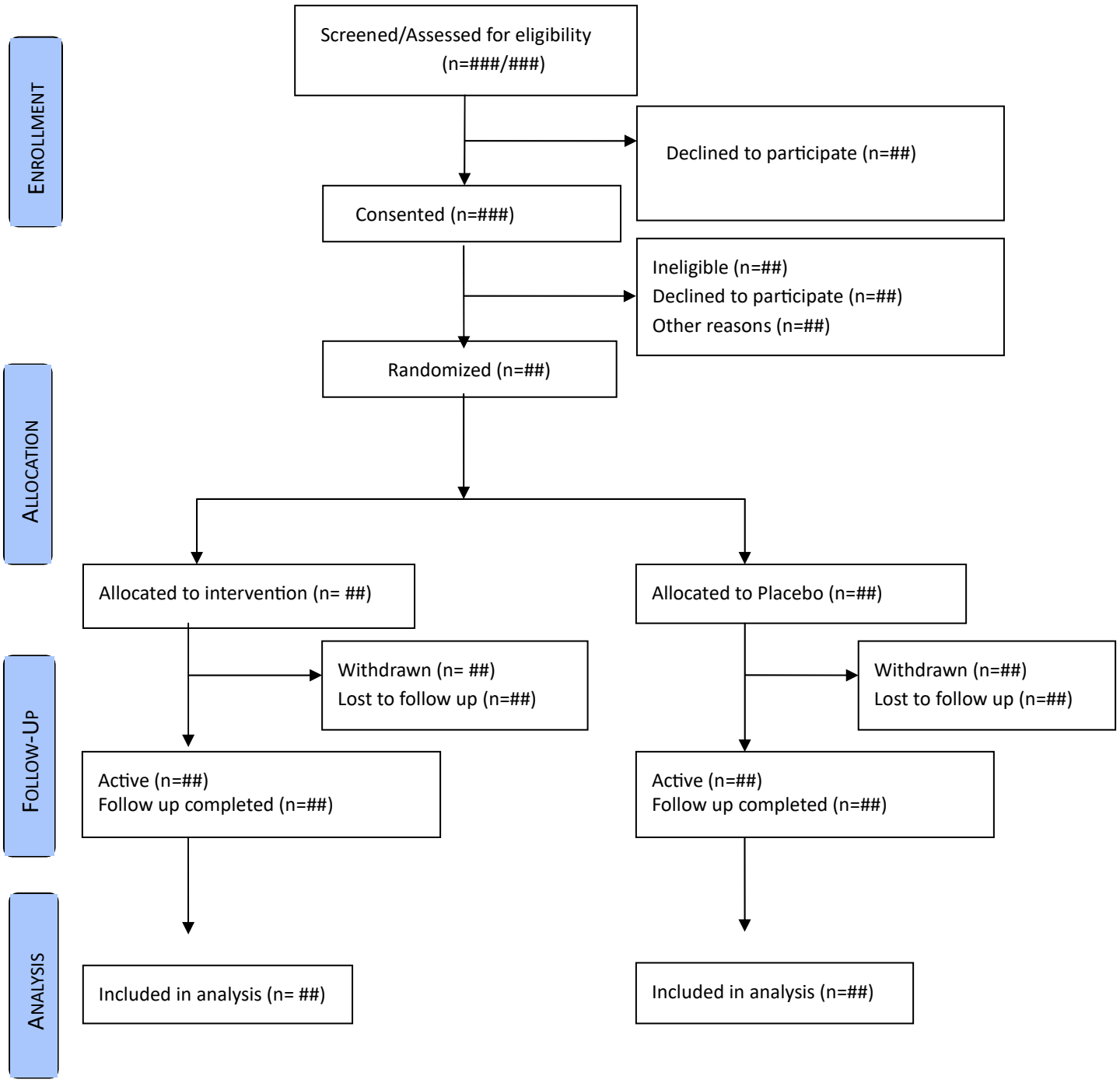

Table 1. Baseline characteristics of study population

	Intervention N=###)	**Placebo(, N=###)**
Facility-level (N=40)		
Age (years)	##.# (##.#)	##.# (##.#)
BMI (kg/m^2)	##.# (##.#)	##.# (##.#)
Sex		
Female	##.# (##.#)	##.# (##.#)
Male	##.# (##.#)	##.# (##.#)
Marital status		
Never married	##.# (##.#)	##.# (##.#)
Married or living as married	##.# (##.#)	##.# (##.#)
Widowed	##.# (##.#)	##.# (##.#)
Separated or divorced	##.# (##.#)	##.# (##.#)
Educational attainment		
No formal education	##.# (##.#)	##.# (##.#)
Primary education	##.# (##.#)	##.# (##.#)
Secondary or tertiary education	##.# (##.#)	##.# (##.#)
Employment status		
??	##.# (##.#)	##.# (##.#)
??	##.# (##.#)	##.# (##.#)
Wealth index tertile*		
Lowest	##.# (##.#)	##.# (##.#)
Middle	##.# (##.#)	##.# (##.#)
Highest	##.# (##.#)	##.# (##.#)
Medical History		
Hypertension	##.# (##.#)	##.# (##.#)
Heart disease	##.# (##.#)	##.# (##.#)
Diabetes	##.# (##.#)	##.# (##.#)
Pulmonary Tuberculosis	##.# (##.#)	##.# (##.#)
Asthma	##.# (##.#)	##.# (##.#)
COPD	##.# (##.#)	##.# (##.#)
Smoking History		
Current	##.# (##.#)	##.# (##.#)
Former	##.# (##.#)	##.# (##.#)
Never	##.# (##.#)	##.# (##.#)

Table 2. Impact of intervention on primary and secondary outcomes

Outcome	**INTERVENTION mean (SD)**	**(N)**	**EUC mean (SD)**	**HIV+D (N)**	**AMD**	**95% CI**	**p-value**	**k**
Primary outcome: Mean SGRQ score at 3 months	## (##)	##	## (##)	##	###	(###, ###)	####	####
Secondary outcomes								
Mean SGRQ score at 12 months	## (##)	##	## (##)	##	###	(###, ###)	####	####

Table 3. Analysis of primary and selected secondary outcomes by subgroup

Outcome	HIV+D mean (SD) or n/N	EUC mean (SD) or n/N	AMD/OR	95% CI	p-value	Total	p-value for interaction
Sex							
Primary outcome: Mean SGRQ score, after 3 months after enrolment							
Female	## (##)	## (##)	###	(###, ###)	####	####	####
Male	## (##)	## (##)	###	(###, ###)	####	####	####
Secondary outcomes							
Mean SGRQ score, after 12 months after enrolment.	## (##)	## (##)	###	(###, ###)	####	####	####
Female	## (##)	## (##)	###	(###, ###)	####	####	####
Male	## (##)	## (##)	###	(###, ###)	####	####	####