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Effect of pre-operative bicarbonate infusion on Maternal and Perinatal outcomes of obstructed labour; A study protocol for a Randomised Controlled Trial

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Title:

Effect of pre-operative bicarbonate infusion on Maternal and Perinatal outcomes of obstructed labour; A study protocol for a Randomised Controlled Trial

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ABSTRACT

Introduction

To improve maternal and fetal outcomes among patients with obstructed labour (OL) in low resource settings, the associated electrolyte and metabolic derangements must be adequately corrected. Oral fluid intake during labour and pre-operative intravenous fluid replacement following OL corrects the associated dehydration and electrolyte changes, but it doesn't completely reverse the metabolic acidosis which is a known cause of intrapartum birth asphyxia and a risk factor for primary postpartum haemorrhage due to uterine atony.

Sodium bicarbonate is a safe, effective, cheap and readily available acid buffer that is widely used by sportsmen to improve performance. It appears to also improve fetal and maternal outcomes in abnormally progressing labour. However, the effect of sodium bicarbonate on maternal and fetal outcomes among patients with OL is unknown. This study aims to establish the effect of a pre-operative bicarbonate infusion on maternal and perinatal outcomes among patients with OL in Mbale Regional Referral Hospital.

Methods

This will be a double blind, Randomised Controlled Clinical phase III trial. We will randomize 308 patients with OL to receive either 50mls of placebo with standard pre-operative infusion of Normal Saline (1.5 L) or 4.2g of sodium bicarbonate solution (50mls of 50mmol/L) with the pre-operative infusion of Normal Saline (1.5 L). The primary outcome will be mean lactate levels in maternal capillary blood at one hour after onset of study drug administration, and in the arterial cord blood at birth. Secondary outcomes will include maternal and fetal morbidity and mortality up to 14 days postpartum. Ethical approval has been sought from the School of Medicine Research and Ethics committee at Makerere University College of

Health Sciences, Uganda National Council for Science and Technology and the Mbale Hospital Research and Ethics Committee. The trial has been registered (PACTR201805003364421).

Strengths and limitations of this study;

Strengths,

i. **This is among the 1st studies to investigate effect of preoperative bicarbonate infusion on maternal and fetal outcomes among patients with OL.**
ii. **The primary maternal and fetal outcomes are both 'hard outcomes' (mean blood lactate levels), measured at the bedside using a hand-held device (Lactate Pro 2).**

Limitations,

i. **We will only report about the efficacy and not the effectiveness of the sodium bicarbonate**
ii. **Given the short duration of follow up, we will not have any information regarding the long-term effects of sodium bicarbonate on maternal and perinatal outcomes.**
iii. **Prior to admission at the referral hospital, patients will have received other interventions such as intravenous fluids and herbal medications which we may not be able to capture accurately.**

Introduction

Globally, the annual number of maternal deaths (MD) decreased from 532,000 in 1990 to 303,000 in 2015.[1,2] But almost all (99.6%) occur in Sub-Saharan Africa (66.3%) and South-Central Asia,[1] where it is estimated that the lifetime risk of MD is as high as 1 in 16 and 1 in 46 respectively, compared to 1 in 2,800 in developed regions.[1,2] Although primary postpartum haemorrhage (PPH) and sepsis are the leading causes of MD, obstructed labour (OL) indirectly contributes to more than 70% of these deaths. [3] Directly, OL causes 8% of all the MD[4,5] and up to 90% of the perinatal deaths due to birth asphyxia.[6] In the 2015/16 financial year, of the 246 maternal deaths reported to the Uganda Ministry of Health (MOH), 9% were due to OL, 39% were due to haemorrhage and 20% were due to sepsis.[7] In addition, 69.3% of 411 perinatal deaths were due to birth asphyxia although the contribution of OL was not specified.

The prevalence of OL varies from 2– 8 % worldwide. It is highest in low and middle income countries (LMICs) and is almost none-existent in developed countries. [4,5] In LMICs many patients experience delays in accessing quality emergency obstetric and neonatal care services, so they end up with neglected OL which causes significant maternal morbidity (dehydration, uterine rupture, sepsis, vesico/rectovaginal fistulae and postpartum haemorrhage) and neonatal morbidity (asphyxia and sepsis).[3,8] Obstructed labour occurs when the fetal presenting part does not descend into the maternal pelvis despite adequate uterine contractions. [4] Usually, the obstruction can only be safely relieved by an operative delivery.[6] In fact OL is the commonest indication for primary caesarean section and a major risk factor for infective morbidity (puerperal and neonatal sepsis) especially in LMICs.[3,9]

Obstructed Labour is associated with higher levels of lactate in blood and amniotic fluid compared to normal labour, and this correlates directly with perinatal outcomes.[10] Lactate is a by-product of anaerobic respiration by both the fetus and the myometrium in response to intermittent hypoxia during labour.[11] In OL, the episodes of hypoxia are prolonged leading to accumulation of lactic acid (metabolic acidosis) from anaerobic break down of glucose. Although impaired uterine contractility caused by myometrial acidosis increases the risk of primary PPH, it is beneficial to the fetus because it increases feto-placental oxygenation which is protective against intrapartum birth asphyxia.[10,12] The transfer of excess hydrogen ions across the placenta to the fetus is associated with low fetal PH, fetal distress and poor APGAR. [13]

Oral bicarbonate is a widely used acid buffer in sports science, to improve physical performance in vigorous exercises because it can reverse lactic acidosis.[14] Bicarbonate does not cross the placental barrier,[15] but it plays a key role in regulating the maternal and fetal acid-base chemistry.[13] There are conflicting reports regarding its benefits in labour. Earlier studies involving the use of Bicarbonate in normal labour showed improvements in pH, base excess and plasma bicarbonate, but none reported

APGAR scores. A recent RCT involving the use of oral bicarbonate solution in abnormal (dystocic) labour reported a significant improvement in both maternal and perinatal outcomes. [14] Significantly, none of these studies reported adverse maternal and perinatal effects or included participants with OL. Currently, pre-operative intravenous infusion with at least 1.5L of fluid is recommended as a key element of the standard care. This is adequate to correct the dehydration and electrolyte imbalance but it probably doesn't completely reverse the associated metabolic acidosis.[16,17]

Various formulations and doses of sodium bicarbonate have been safely used for both clinical indications and research purposes with no reported adverse clinical reactions. A single pre-operative infusion of 4.2g of sodium bicarbonate solution (50mls of 50mmol/L) will be given as a single dose at enrolment, since OL is an obstetric emergency which requires urgent intervention. [18] The same dose was used orally in the recent trial in which bicarbonate solution was administered to women with dystocia in labour. [14] The main outcome of this study will be to assess whether bicarbonate changes the maternal and fetal lactate levels among patients with OL. Lactate is easier to measure than full blood gas analysis using maintenance free, battery operated pocket size devices like the lactate Pro2 (Arkray). Lactate is comparable to pH and base deficit with respect to sensitivity, specificity and predictive values of various perinatal complications.[13] Establishing the effect of bicarbonate on maternal and fetal lactate levels among patients with OL is important because it could be included in the pre-operative care package as an acid buffer.

We hypothesize that supplementation with preoperative sodium bicarbonate infusion as an acid buffer can reduce maternal and fetal acidosis among patients with OL. Bicarbonate is safe, effective, cheap and already widely used.[18] Establishing its effect on maternal and foetal outcomes following OL is necessary because it could be added to the standard preoperative care package as a form of tertiary prevention. This study aims to establish the effect of a single dose preoperative infusion of sodium bicarbonate on maternal and fetal lactate levels and clinical outcomes among patients with OL.

Methods/Design

Study design

This will be a superiority, double blind, Randomised Controlled Clinical phase III trial. Half of the 308 patients with OL will receive the intervention (sodium bicarbonate infusion) with pre-operative normal saline infusion, and the other half will receive the standard of care (pre-operative saline infusion) alone.

Study setting

The study will be conducted at Mbale Regional Referral Hospital located at the heart of Mbale Municipal Council, 214km to the east of the capital city Kampala. It is the main referral hospital, serving 14 districts in the Elgon zone, bordering western Kenya. This is a government run, not-for-profit, charge-free, 470-bed hospital with 52 maternity beds. The Department of Obstetrics and Gynaecology has one consultant, two specialists, three medical officers and 21 Midwives. In terms of outputs, the labour and delivery suit is only second to the Mulago National Referral Hospital labour suit. Annually, about 12,000 childbirths occur in this hospital with a caesarean section rate of 35% and nearly 500 mothers have OL. It has been ranked as the best performing regional referral hospital by the Ministry of Health in Uganda for the last 4 years.

Participants

This study will be carried out among patients with OL admitted to the labour suite in Mbale Regional Referral Hospital during the period of the study. OL will be diagnosed by either a Medical Officer or specialist on duty using the ACOG definition: in the 1st stage of labour she should have cervical dilatation >6cm with ruptured membranes, adequate contractions lasting > 4hrs with no change in cervical dilatation, OR, delay in the 2nd active stage of labour (nullipara > 2hrs, multipara > 1 hr.) with adequate uterine contractions. IN ADDITION, ANY TWO OF: the obvious signs of severe obstruction such

as caput formation, severe moulding, Bandl's ring, sub-conjunctival hemorrhages, or an oedematous vulva.

We will include patients with OL carrying singleton, term pregnancies (≥37 weeks of gestation) in cephalic presentation. We will exclude patients with other obstetric emergencies such as (antepartum haemorrhage, Pre-eclampsia and eclampsia (defined as elevated blood pressure of at least 140/90 mmHg, urine protein of at least 2+ ,any of the danger signs and fits), premature rupture of membranes and intrauterine fetal death; comorbidities such as diabetes mellitus, Sickle cell disease, renal disease, liver disease & heart disease; and those with a hypernatraemia > 148mmol/L and/or alkalosis > 22mmol/L .

Randomization

A sequence of random numbers will be generated by an independent biostatician using the online randomisation service of www.sealedenvelop.com in permuted block sizes of four, six and eight. Based on this sequence, OL patients will be randomly allocated to either intervention or control arms in a 1:1 ratio. Concealment will be done by an independent pharmacist not involved in the recruitment of study participants, who will prepare and label sequentially numbered, identical study drug packages each containing five similar 10ml glass vials with all the original labels removed. After consent for inclusion has been confirmed, a study nurse will take the next study drug package and administer its contents to participant.

Intervention

The intervention will be a pre-operative infusion of 50mls of sodium bicarbonate 8.4% solution equivalent to 4.2g or 50mmol/L of bicarbonate (Martindale Pharma, Essex) in 10ml glass vials. The sodium bicarbonate will be administered intravenously as a bolus immediately after recruitment by

trained research assistants who are all experienced midwives working in the labour suite, followed by 1.5L of Normal Saline over the next hour.

Comparator;

Participants in the control arm will receive a pre-operative infusion of Normal Saline which is the standard of care. Fifty mls of sodium chloride 0.9% in identical 10ml glass vials (AccuHealth Care, Gujarat) will be administered intravenously as a bolus immediately after recruitment by trained research assistants, who are all experienced midwives working in the labour suite, followed by 1.5L Normal Saline over the next hour.

In addition, recruits will receive the standard pre-operative care which includes pre-operative antibiotic prophylaxis, at least 1.5L of intravenous fluids pre-operatively, bladder emptying, administration of oxygen, and lying in left lateral position.[16]

Measurements;

The primary outcomes in this study will be the mean lactate levels in maternal capillary blood at one hour after the onset of study drug administration and in arterial cord blood within 1 minute of birth. Lactate will be measured at the bedside using a hand-held Lactate Pro 2 device (Arkray Factory Inc, Shiga).

Secondary maternal outcomes will include myometrial lactate levels at caesarean section, maternal morbidities such as primary PPH, birth canal injuries, duration of admission, puerperal sepsis (Persistent fever >38°C,Chills and general malaise, Pain in the lower abdomen, Persistent bloody/pus discharge (lochia) from genital tract, which may have an unpleasant smell, Tenderness on palpating the uterus y Uterine sub-involution, wound dehiscence/ burst abdomen),[16] fistulae, readmissions and death up to the 14 days postpartum. Secondary perinatal outcomes will include mean lactate in venous cord blood,

Apgar score, admission to the NICU, asphyxia, neonatal sepsis (irritability, poorly breastfeeding, bulging anterior fontanelle)[16] and perinatal death up to 7 days postpartum.

Sociodemographic, clinical and laboratory characteristics;

Using an interviewer administered questionnaire and available records (antenatal cards, facility registers and case report files), sociodemographic and clinical characteristics will be collected by trained research assistants. At baseline, 5 mls of blood will be collected in the appropriate vaccutainers for a complete blood count, renal function tests, liver function tests and electrolytes. Ten mls of fresh urine will be collected in a sterile container for analysis. All these specimens will be delivered to MBN clinical laboratories within 1 hour of collection for analysis. Figure 1 shows the CONSORT flow diagram for this study. Patients will be followed up to 14 days postnatally either by phone call if they are discharged or by direct visits if they are still admitted.

Sample size and power calculation;

We used Open Epi to detect a 15% difference in mean lactate levels between the intervention and control arms, assuming an equal number of participants in each group, a two-sided significance level of 0.05 for a 95% confidence interval, a power of 80%, and a student's t-test for comparison of means.

The mean and standard deviation (SD) of the maternal venous lactate at the end of second stage of labour is 2.6 ± 1.0 mmol/L[19] without any use of bicarbonate. To detect a difference of 15% (0.39mmol/L) and assuming the same S.D. of ±1 in both arms, 278 participants will be required. Correcting for an attrition rate of 10%,[14] gives a total sample size of 308.

The mean arterial cord blood lactate at 37 weeks of gestation is 4.3 ± 1.9 mmol/L[20] without any use of bicarbonate. In order detect a difference of 15% (0.645mmol/L) and assuming the same S.D of ±1.9 in

both groups, 274 participants will be recruited. Correcting for an attrition rate of 10%,[14] gives a total sample size of 304. A sample size of 308 was therefore planned to provide power for both hypotheses.

Data collection and management;

Well trained RA will collect data using a pretested interviewer administered electronic questionnaire on password protected smart phones using the Open Data Kit software. To increase accuracy the data will be triangulated with a review of relevant health facility records such as the antenatal cards, the maternity and theatre registers, and the participants' case report forms. The questionnaire will be coded with checks for internal consistency. Data on sociodemographic, clinical and laboratory parameters will be collected at baseline, at one hour after onset of study drug administration for the primary maternal outcome, at the time of child birth for the primary neonatal outcome, and at 7 and 14 days postpartum for the secondary perinatal and maternal outcomes as summarised in table 2.[24] The PI will review the entries from the Google aggregate server every 24 hours to ensure data quality and completeness.

Table 1; Summary of the study procedures and timelines

Procedure	**At admission (Baseline)**	**1 hour after onset of study drug administration**	**At birth**	**At 7 days postpartum**	**At 14 days postpartum**
Assessment of eligibility	x				
Randomisation	x				
Data collection for baseline parameters	x				
Study drug administration	x				
Questionnaire administration	x	x	x	x	x
Data collection for primary outcome		x	x		
Data collection for secondary outcome			x	x	x

Statistical analysis;

This will be conducted using STATA version 14 software or higher using the principle of 'intention to treat'. Descriptive statistics will be used to summarise baseline characteristics of the study participants and assess if randomisation was successful. The primary maternal outcome will be the difference in capillary blood lactate levels at one hour after onset of study drug administration. The paired sample t-test will be used to compare the difference in means at baseline and one hour after onset of study drug administration within each arm. The independent student t- test will be used to compare the mean lactate levels in the two arms at one hour after onset of study drug administration.

For the primary fetal outcome of mean arterial cord blood lactate at birth, the independent student t-test will be used to compare the mean lactate levels in the two arms within 1 minute of childbirth.

The secondary outcomes will be reported as proportions in each of the two arms. Categorical variables will be compared using the Chi-square and Fishers exact tests. Potential confounders and effect modifiers unbalanced at baseline and associated with the outcome ($p< 0.05$) will be adjusted for using multivariable linear or/and logistic regression. Proportions and the number needed to treat/harm (NNT/NNH) will be reported for the secondary maternal and fetal outcomes.

Quality control;

A dry run will be conducted for a period of one month before the intervention is introduced to train all the research assistants in the study protocol procedures, filling of study questionnaires using the ODK software, accurate measurement of lactate at the bedside using the Lactate Pro 2 device and the ideal technique for collection of samples especially blood to avoid haemolysis. The MBN clinical laboratories are internationally accredited and they are involved in regular internal and external quality control checks.

Ethical approval has been sought from the s

School of Medicine Research and Ethics Committee (#REC REF 2017-103), the Uganda National Council for Science and Technology (HS217ES), and the Mbale Regional Referral Research and Ethics Committee.

Participant safety;

All serious adverse events will be actively identified and reported to the IRB within 24 hours of occurrence using the School of Medicine Research Ethics Committee reporting form throughout the study period up to the end of puerperium (6 weeks after birth). The independent data monitoring committee will review unblinded data when 1/3 of the participants have been enrolled and followed up to completion, and at any other time that they request. In addition, only qualified health workers will be recruited and trained in the protocol to work as research assistants on this trial.

Dissemination and communication of results;

Results will be disseminated to the study participants through the local radio stations and local council community meeting at the village level. Findings will be shared with colleagues and administrators in Mbale Regional Referral Hospital/Busitema University Faculty of Health Sciences and the Uganda ministry of health through workshops and seminars. To reach the wider scientific community, the findings will be published in open access peer reviewed journals and presented at both local and international conferences.

Patient and Public involvement;

The patients and public were not involved in the design and conceptualisation of this study.

Discussion;

If a preoperative infusion of sodium bicarbonate is safe and it improves maternal and perinatal outcomes among patients with OL, the data from this trial might facilitate the inclusion of sodium bicarbonate infusion in the standard pre-operative care for patients with OL in low resource settings. Its

adoption will help to mitigate adverse maternal and perinatal outcomes associated with OL as a tertiary preventive measure. Obstructed labour is still an important clinical and public health problem in low resource settings because of the associated maternal and perinatal morbidity and mortality caused by accompanying electrolyte and metabolic changes. Therefore, identifying an effective, cheap, safe and readily available acid buffer like sodium bicarbonate might offer immense health benefits.

Acknowledgements;

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Author contributions;

Musaba Milton Wamboko (MMW) conceptualised, designed, developed the protocol and drafted the manuscript. Justus K Barageine(JKB), Julius N Wandabwa(JNW), Grace Ndeezi (GN) and Andrew Weeks (AW) all participated in the conceptualization, design, development of the protocol and writing of the manuscript by providing critical review and refinement of the research idea as supervisors of my PhD studies. All the authors reviewed and approved the final draft of the manuscript for submission.

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Competing interests statement; None declared

Patients consent; Required

Ethics approval;

Provenance and peer review; Not commissioned; externally peer reviewed.

Open Access;

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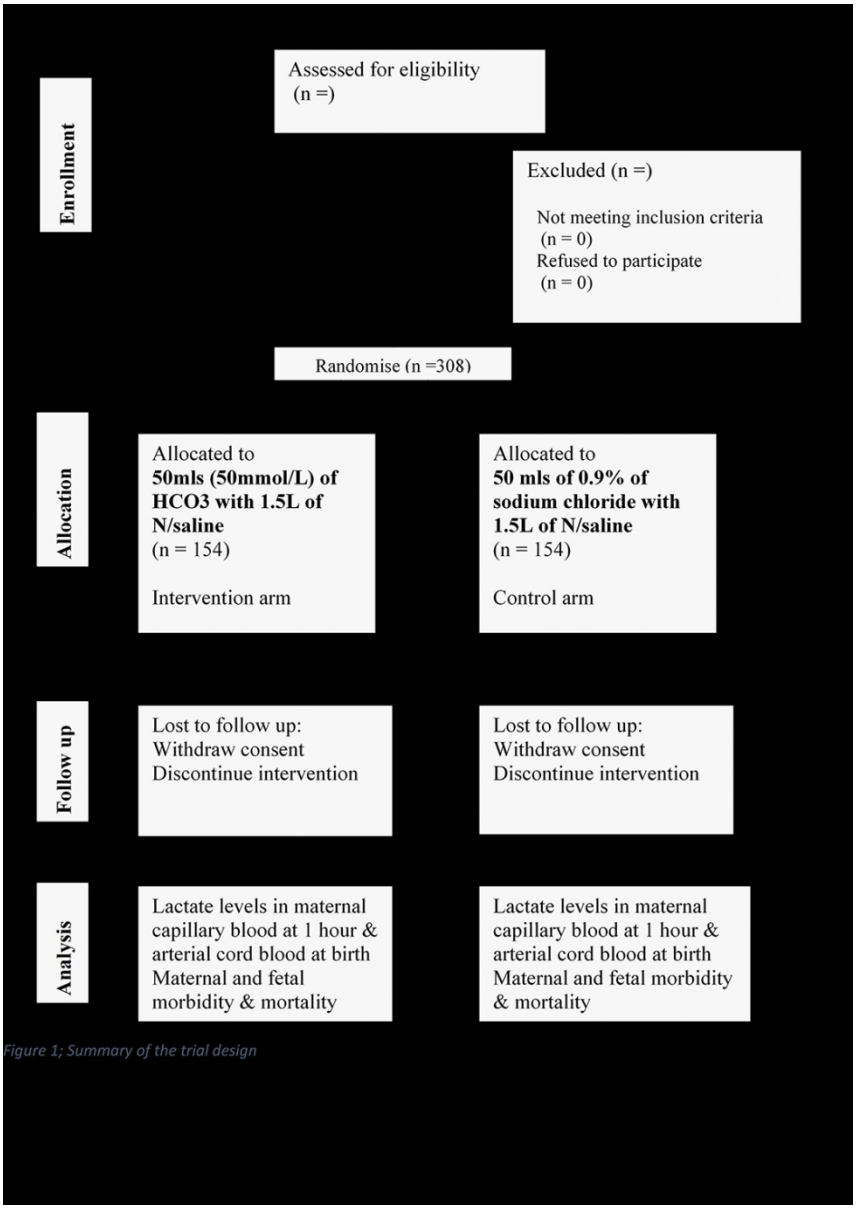

Figure 1; Summary of the trial design

90x126mm (300 x 300 DPI)

SPIRIT
STANDARD PROTOCOL ITEMS: RECOMMENDATIONS FOR INTERVENTIONAL TRIALS

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	Item No	Description
Administrative information		
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym **YES on the title page**
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry **YES at the end of the abstract**
	2b	All items from the World Health Organization Trial Registration Data Set
Protocol version	3	Date and version identifier **Yes**
Funding	4	Sources and types of financial, material, and other support **Yes on page 14**
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors **Yes on the title page**
	5b	Name and contact information for the trial sponsor **Yes page 14**
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities **Yes page 14**
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee) **NA**
Introduction		
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention **Yes page 3 to 5**
	6b	Explanation for choice of comparators **Yes 6&7**
Objectives	7	Specific objectives or hypotheses **Yes page 5**

Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory) **Yes page 6**
Methods: Participants, interventions, and outcomes		
Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained **Yes page 6**
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists) **Yes Page 6&7**
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered **Yes page 7 & 8**
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease) **NA**
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests) **NA**
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial **NA**
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended **Yes page 8**
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (**see Figure 2**)
Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations **Yes page 11&10**
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size **NA**
Methods: Assignment of interventions (for controlled trials)		
Allocation:		

Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions **Yes see page 7 under randomisation**
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned **Yes see page 7 under randomisation**
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions **Yes see page 7 under randomisation**
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how **Yes see page 7 under randomisation**
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial **Yes see page 7 under randomisation**
Methods: Data collection, management, and analysis		
Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol **Yes see page 11**
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols **NA**
Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol **Yes see page 11**
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol **Yes see page 12**
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses) **NA**

	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation) **NA**
Methods: Monitoring		
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed **Yes see page 13**
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial **Yes see page 13**
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct **Yes see page 13**
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor **Yes see page 13**
Ethics and dissemination		
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval **Yes see page 11**
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators) **NA**
Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how **(see attached consent)**
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable **NA**
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial **Yes see page 11**
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site **see page 14**
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators **NA**

Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation **(see attached consent form)**
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions **Yes see page 13**
	31b	Authorship eligibility guidelines and any intended use of professional writers **NA**
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code **NA**
Appendices		
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates **(Attached to submission)**
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable **(Yes see attached consent)**

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.

BMJ Open

Effect of pre-operative bicarbonate infusion on Maternal and Perinatal outcomes of obstructed labour; A study protocol for a Randomised Controlled Trial

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Effect of pre-operative bicarbonate infusion on Maternal and Perinatal outcomes of obstructed labour; A study protocol for a Randomised Controlled Trial

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ABSTRACT

Introduction

To improve maternal and fetal outcomes among patients with obstructed labour (OL) in low resource settings, the associated electrolyte and metabolic derangements must be adequately corrected. Oral fluid intake during labour and pre-operative intravenous fluid replacement following OL corrects the associated dehydration and electrolyte changes, but it doesn't completely reverse the metabolic acidosis which is a known cause of intrapartum birth asphyxia and a risk factor for primary postpartum haemorrhage due to uterine atony.

Sodium bicarbonate is a safe, effective, cheap and readily available acid buffer that is widely used by sportspeople to improve performance. It appears to also improve fetal and maternal outcomes in abnormally progressing labour. However, the effect of sodium bicarbonate on maternal and fetal outcomes among patients with OL is unknown. This study aims to establish the effect of a pre-operative bicarbonate infusion on maternal and perinatal outcomes among patients with OL in Mbale Regional Referral Hospital.

Methods and analysis

This will be a double blind, randomised controlled clinical phase III trial. We will randomize 308 patients with OL to receive either 50mls of placebo with standard pre-operative infusion of Normal Saline (1.5 L) or 4.2g of sodium bicarbonate solution (50mls of 50mmol/L) with the pre-operative infusion of Normal Saline (1.5 L). The primary outcome will be mean lactate levels in maternal capillary blood at one hour after onset of study drug administration, and in the arterial cord blood at birth. We will use the intention to treat analysis approach. Secondary outcomes will include maternal and fetal morbidity and mortality up to 14 days postpartum.

Ethics and Dissemination

This protocol is approved by the Makerere University School of Medicine Research and Ethics Committee and Uganda National Council for Science and Technology. Each participant will give informed consent at enrollment. The trial registration number is PACTR201805003364421.

Strengths and limitations of this study;

Strengths,

i. This is among the 1st studies to investigate effect of preoperative bicarbonate infusion on maternal and fetal outcomes among patients with OL, using a randomized control design.
ii. Measurement of maternal lactate levels and fetal cord blood lactate at the bedside using a hand-held device (Lactate Pro 2), instead of a blood gas analyser that is expensive to acquire and operate in a resource-limited setting.

Limitations,

i. This study will only ascertain the efficacy and not the effectiveness of the preoperative sodium bicarbonate infusion
ii. Given the short duration of follow up, we will not have any information regarding the long-term effects of sodium bicarbonate on maternal and perinatal outcomes.
iii. Improving maternal and fetal lactate levels may not improve the fetal outcome in Obstructed Labour, as the tocolytic effect of the lactate may be a fetal protective mechanism.

Introduction

Globally, the annual number of maternal deaths (MD) decreased from 532,000 in 1990 to 303,000 in 2015.[1,2] But almost all (99.6%) occur in Sub-Saharan Africa (66.3%) and South-Central Asia,[1] where it is estimated that the lifetime risk of MD is as high as 1 in 16 and 1 in 46 respectively, compared to 1 in 2,800 in developed regions.[1,2] Although primary postpartum haemorrhage (PPH) and sepsis are the leading causes of MD, obstructed labour (OL) indirectly contributes to more than 70% of these deaths. [3] Directly, OL causes 8% of all the MD[4,5] and up to 90% of the perinatal deaths due to birth asphyxia.[6] In the 2015/16 financial year, of the 246 maternal deaths reported to the Uganda Ministry of Health

(MOH), 9% were due to OL, 39% were due to haemorrhage and 20% were due to sepsis.[7] In addition, 69.3% of 411 perinatal deaths were due to birth asphyxia although the contribution of OL was not specified.

The prevalence of OL varies from 2– 8 % worldwide. It is highest in low and middle income countries (LMICs) and is almost none-existent in developed countries. [4,5] In LMICs many patients experience delays in accessing quality emergency obstetric and neonatal care services, so they end up with neglected OL which causes significant maternal morbidity (dehydration, uterine rupture, sepsis, vesico/rectovaginal fistulae and postpartum haemorrhage) and neonatal morbidity (asphyxia and sepsis).[3,8] Obstructed labour occurs when the fetal presenting part does not descend into the maternal pelvis despite adequate uterine contractions. [4] Usually, the obstruction can only be safely relieved by an operative delivery.[6] In fact OL is the commonest indication for primary caesarean section and a major risk factor for infective morbidity (puerperal and neonatal sepsis) especially in LMICs.[3,9]

Obstructed Labour is associated with higher levels of lactate in blood and amniotic fluid compared to normal labour, and this correlates directly with perinatal outcomes.[10] Lactate is a by-product of anaerobic respiration by both the fetus and the myometrium in response to intermittent hypoxia during labour.[11] In OL, the episodes of hypoxia are prolonged leading to accumulation of lactic acid (metabolic acidosis) from anaerobic break down of glucose. Although impaired uterine contractility caused by myometrial acidosis increases the risk of primary PPH, it is beneficial to the fetus because it increases feto-placental oxygenation which is protective against intrapartum birth asphyxia.[10,12] The transfer of excess hydrogen ions across the placenta to the fetus is associated with low fetal PH, fetal distress and poor APGAR. [13]

Oral bicarbonate is a widely used acid buffer in sports science, to improve physical performance in vigorous exercises because it can reverse lactic acidosis.[14] Bicarbonate does not cross the placental

barrier,[15] but it plays a key role in regulating the maternal and fetal acid-base chemistry.[13] There are conflicting reports regarding its benefits in labour. Earlier studies involving the use of Bicarbonate in normal labour showed improvements in pH, base excess and plasma bicarbonate, but none reported APGAR scores. A recent RCT involving the use of oral bicarbonate solution in abnormal (dystocic) labour reported a significant improvement in both maternal and perinatal outcomes. [14] Significantly, none of these studies reported adverse maternal and perinatal effects or included participants with OL. Currently, pre-operative intravenous infusion with at least 1.5L of fluid is recommended as a key element of the standard care. This is adequate to correct the dehydration and electrolyte imbalance but it probably doesn't completely reverse the associated metabolic acidosis.[16,17]

Various formulations and doses of sodium bicarbonate have been safely used for both clinical indications and research purposes with no reported adverse clinical reactions. A single pre-operative infusion of 4.2g of sodium bicarbonate solution (50mls of 50mmol/L) will be given as a single dose at enrolment, since OL is an obstetric emergency which requires urgent intervention. [18] The same dose was used orally in the recent trial in which bicarbonate solution was administered to women with dystocia in labour. [14] The main outcome of this study will be to assess whether bicarbonate changes the maternal and fetal lactate levels among patients with OL. Lactate is easier to measure than full blood gas analysis using maintenance free, battery operated pocket size devices like the lactate Pro2 (Arkray). This device produces accurate results in a short time with a high intraclass correlation coefficient (ICC) which is comparable to that of gold standard in a given population i.e. 0.90 versus 0.92.[18]Lactate is comparable to pH and base deficit with respect to sensitivity, specificity and predictive values of various perinatal complications.[13] Establishing the effect of bicarbonate on maternal and fetal lactate levels among patients with OL is important because it could be included in the pre-operative care package as an acid buffer.

We hypothesize that supplementation with preoperative sodium bicarbonate infusion as an acid buffer among patients with OL can reduce maternal acidosis at one hour after administration, while their

newborns in the bicarbonate group will have less acidosis in cord blood at birth. Bicarbonate is safe, effective, cheap and already widely used.[19] Establishing its effect on maternal and fetal outcomes following OL is necessary because it could be added to the standard preoperative care package as a form of tertiary prevention. This study aims to establish the effect of a single dose preoperative infusion of sodium bicarbonate on maternal and fetal lactate levels and clinical outcomes among patients with OL.

Methods/Design

Study design

This will be a superiority, double blind, randomised controlled clinical phase III trial. Half of the 308 patients with OL will receive the intervention (sodium bicarbonate infusion) with pre-operative normal saline infusion, and the other half will receive the standard of care (pre-operative saline infusion) alone.

Study setting

The study will be conducted at Mbale Regional Referral Hospital located at the heart of Mbale Municipal Council, 214km to the east of the capital city Kampala. It is the main referral hospital, serving 14 districts in the Elgon zone, bordering western Kenya. This is a government run, not-for-profit, charge-free, 470-bed hospital with 52 maternity beds. The Department of Obstetrics and Gynaecology has one consultant, two specialists, three medical officers and 21 Midwives. In terms of outputs, the labour and delivery suit is only second to the Mulago National Referral Hospital labour suit. Annually, about 12,000 childbirths occur in this hospital with a caesarean section rate of 35% and nearly 500 mothers have OL. It has been ranked as the best performing regional referral hospital by the Ministry of Health in Uganda for the last 4 years.

Participants

This study will be carried out among patients with OL admitted to the labour suite in Mbale Regional Referral Hospital for emergency cesarean section during the period of the study. OL will be diagnosed by either a Medical Officer or specialist on duty using the ACOG definition: in the 1st stage of labour she should have cervical dilatation >6cm with ruptured membranes, adequate contractions lasting > 4hrs with no change in cervical dilatation, OR, delay in the 2nd active stage of labour (nullipara > 2hrs, multipara > 1 hr.) with adequate uterine contractions. IN ADDITION, ANY TWO OF: the obvious signs of severe obstruction such as caput formation, severe moulding, Bandl's ring, sub-conjunctival hemorrhages, or an oedematous vulva.

We will include patients with OL carrying singleton, term pregnancies (≥37 weeks of gestation) in cephalic presentation. We will exclude patients with other obstetric emergencies such as (antepartum haemorrhage, Pre-eclampsia and eclampsia (defined as elevated blood pressure of at least 140/90 mmHg, urine protein of at least 2+ ,any of the danger signs and fits), premature rupture of membranes and intrauterine fetal death. Patients with comorbidities such as diabetes mellitus, Sickle cell disease, renal disease, liver disease & heart disease; and those with a hypernatraemia > 148mmol/L and/or alkalosis > 22mmol/L.

Randomization

A sequence of random numbers will be generated by an independent biostatician using the online randomisation service of www.sealedenvelope.com in permuted block sizes of four, six and eight. Based on this sequence, OL patients will be randomly allocated to either intervention or control arms in a 1:1 ratio. Concealment will be done by an independent pharmacist not involved in the recruitment of study participants, who will prepare and label sequentially numbered, identical study drug packages each containing five similar 10ml glass vials with all the original labels removed. After consent for inclusion has

been confirmed, a study nurse will take the next study drug package and administer its contents to participant.

Intervention;

The intervention will be a pre-operative infusion of 50mls of sodium bicarbonate 8.4% solution equivalent to 4.2g or 50mmol/L of bicarbonate (Martindale Pharma, Essex) in 10ml glass vials. The sodium bicarbonate will be administered intravenously as a bolus immediately after recruitment by trained research assistants who are all experienced midwives working in the labour suite, followed by 1.5L of Normal Saline over the next hour.

Comparator;

Participants in the control arm will receive a pre-operative infusion of Normal Saline which is the standard of care. Fifty mls of sodium chloride 0.9% in identical 10ml glass vials (AccuHealth Care, Gujarat) will be administered intravenously as a bolus immediately after recruitment by trained research assistants, who are all experienced midwives working in the labour suite, followed by 1.5L Normal Saline over the next hour.

In addition, recruits will receive the standard pre-operative care which includes pre-operative antibiotic prophylaxis, at least 1.5L of intravenous fluids pre-operatively, bladder emptying, administration of oxygen, and lying in left lateral position.[16]

Measurements;

The primary outcomes in this study will be the mean lactate levels in maternal capillary blood at one hour after the onset of study drug administration and in arterial cord blood within 1 minute of birth. Lactate will be measured at the bedside using a hand-held Lactate Pro 2 device (Arkray Factory Inc, Shiga).

Secondary maternal outcomes will include myometrial lactate levels at caesarean section, maternal morbidities such as primary PPH, birth canal injuries, duration of admission, puerperal sepsis (Persistent fever >38°C,Chills and general malaise, Pain in the lower abdomen, Persistent bloody/pus discharge (lochia) from genital tract, which may have an unpleasant smell, Tenderness on palpating the uterus y Uterine sub-involution, wound dehiscence/ burst abdomen),[16] fistulae, readmissions and death up to the 14 days postpartum. Secondary perinatal outcomes will include mean lactate in venous cord blood, Apgar score, admission to the NICU, asphyxia, neonatal sepsis (irritability, poorly breastfeeding, bulging anterior fontanelle)[16] and perinatal death up to 7 days postpartum.

Sociodemographic, clinical and laboratory characteristics;

Using an interviewer administered questionnaire and available records (antenatal cards, facility registers and case report files), sociodemographic and clinical characteristics will be collected by trained research assistants. At baseline, 5 mls of blood will be collected in the appropriate vaccutainers for a complete blood count, renal function tests, liver function tests and electrolytes. Ten mls of fresh urine will be collected in a sterile container for analysis. All these specimens will be delivered to MBN clinical laboratories within 1 hour of collection for analysis. Figure 1 shows the CONSORT flow diagram for this study. Patients will be followed up to 14 days postnatally either by phone call if they are discharged or by direct visits if they are still admitted.

Sample size and power calculation;

We used Open Epi[20] to detect a 15% difference in mean lactate levels between the intervention and control arms, assuming an equal number of participants in each group, a two-sided significance level of 0.05 for a 95% confidence interval, a power of 80%, and a student's t-test for comparison of means.

The mean and standard deviation (SD) of the maternal venous lactate at the end of second stage of labour is 2.6 ± 1.0 mmol/L[21] without any use of bicarbonate. To detect a difference of 15% (0.39mmol/L) at

one hour and assuming the same S.D. of ±1 in both arms, 278 participants will be required. Correcting for an attrition rate of 10%,[14] gives a total sample size of 308.

The mean arterial umbilical cord blood lactate at 37 weeks of gestation is 4.3 ± 1.9 mmol/L[22] without any use of bicarbonate. In order detect a difference of 15% (0.645mmol/L) at birth and assuming the same S.D of ±1.9 in both groups, 274 participants will be recruited. Correcting for an attrition rate of 10%,[14] gives a total sample size of 304. A sample size of 308 was therefore planned to provide power for both hypotheses.

Data collection and management;

Well trained RAs will collect data using a pretested interviewer administered electronic questionnaire on password protected smart phones using the Open Data Kit software. To increase accuracy the data will be triangulated with a review of relevant health facility records such as the antenatal cards, the maternity and theatre registers, and the participants' case report forms. The questionnaire will be coded with checks for internal consistency. Data on sociodemographic, clinical and laboratory parameters will be collected at baseline, at one hour after onset of study drug administration for the primary maternal outcome, at the time of childbirth for the primary neonatal outcome, and at 7 and 14 days postpartum for the secondary perinatal and maternal outcomes as summarised in table 1. The PI will review the entries from the Google aggregate server every 24 hours to ensure data quality and completeness.

Table 1; Summary of the study procedures and timelines

Procedure	**At admission (Baseline)**	**1 hour after onset of study drug administration**	**At birth**	**At 7 days postpartum**	**At 14 days postpartum**
Assessment of eligibility	x				
Randomisation	x				
Data collection for baseline parameters	x				

Study drug administration	x				
Questionnaire administration	x	x	x	x	x
Data collection for primary outcome		x	x		
Data collection for secondary outcome			x	x	x

Statistical analysis;

This will be conducted using STATA version 14 software or higher using the principle of 'intention to treat'. Descriptive statistics will be used to summarise baseline characteristics of the study participants and assess if randomisation was successful. The primary maternal outcome will be the difference in capillary blood lactate levels at one hour after onset of study drug administration. The paired sample t-test will be used to compare the difference in means at baseline and one hour after onset of study drug administration within each arm. The independent student t- test will be used to compare the mean lactate levels in the two arms at one hour after onset of study drug administration

For the primary fetal outcome of mean arterial cord blood lactate at birth, the independent student t- test will be used to compare the mean lactate levels in the two arms within 1 minute of childbirth.

We will use the Holm-Bonferroni method to compute an adjusted P valve for multiple comparisons of the dependent maternal and foetal primary outcomes.[23,24]

The secondary outcomes will be reported as proportions in each of the two arms. Categorical variables will be compared using the Chi-square and Fishers exact tests. Potential confounders and effect modifiers unbalanced at baseline and associated with the outcome ($p< 0.05$) will be adjusted for using multivariable linear or/and logistic regression. Proportions and the number needed to treat/harm (NNT/NNH) will be reported for the secondary maternal and fetal outcomes.

We will do a sub-group analysis of patients admitted as referrals with a diagnosis of OL (to represent patients most likely to have neglected OL) to compare them with those that are diagnosed with OL within the referral hospital. A second sub-group analysis will be for those patients that give birth more than two hours after administration of the study drug, when we expect the effect of the intervention to have worn off.

Quality control;

We run will conduct a dry run for a period of one month before introducing the intervention. To facilitate the training all the research assistants in the study protocol procedures, filling of study questionnaires using the ODK software,[25] accurate measurement of lactate at the bedside using the Lactate Pro 2 device and the ideal technique for collection of samples especially blood to avoid haemolysis. The MBN clinical laboratories are internationally accredited and they are involved in regular internal and external quality control checks.

Ethics and dissemination;

The protocol is approved by the Makerere University School of Medicine Research and Ethics Committee (#REC REF 2017-103), the Uganda National Council for Science and Technology (HS217ES) and the Mbale Regional Referral Research and Ethics Committee(MRRH-REC IN-COM 00/2018). Participant safety;

All serious adverse events will be actively identified and reported to the IRB within 24 hours of occurrence using the School of Medicine Research Ethics Committee reporting form throughout the study period up to the end of puerperium (6 weeks after birth). The independent data monitoring committee will review unblinded data when 1/3 of the participants have been enrolled and followed up to completion, and at any other time that they request. In addition, only qualified health workers will be recruited and trained in the protocol to work as research assistants on this trial.

Dissemination plan;

Results will be disseminated to the study participants through the local radio stations and local council community meeting at the village level. Findings will be shared with colleagues and administrators in Mbale Regional Referral Hospital/Busitema University Faculty of Health Sciences and the Uganda ministry of health through workshops and seminars. To reach the wider scientific community, the findings will be published in open access peer reviewed journals and presented at both local and international conferences. The data sets will be provided free of charge by the primary author on request.

Patient and Public involvement;

The patients and public were not involved in the design and conceptualisation of this study.

Discussion;

If the preoperative infusion of sodium bicarbonate is safe and effective in reducing maternal and fetal lactatemia (acidosis) among patients with OL, then the data from this trial will inform the design of future trials that will facilitate the inclusion of sodium bicarbonate infusion in the standard pre-operative care for patients with OL in low resource settings. Its adoption will help to mitigate adverse maternal and perinatal outcomes associated with OL as a tertiary preventive measure for intrauterine maternal and fetal resuscitation. Obstructed labour is still an important clinical and public health problem in low resource settings because of the associated maternal and perinatal morbidity and mortality caused by accompanying electrolyte and metabolic changes. Therefore, identifying an effective, cheap, safe and readily available acid buffer like sodium bicarbonate might offer immense health benefits.

In obstructed labour, lactatemia might be a protective mechanism to prevent uterine rupture especially in the multiparous patients and fetal hypoxia by causing relaxation of the myometrium in order to improve fetal placental circulation.[10–12] Therefore, reversal of lactic acidosis might result in stronger uterine

contractions and increase the degree of fetal hypoxia or risk of uterine rupture especially if the surgical intervention is delayed. Thus, although this study will help us to understand whether 50mmol of bicarbonate is effective at reversing lactic acidosis, further studies will be required to ascertain its effects on maternal and fetal morbidity.

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Author contributions;

Musaba Milton Wamboko (MMW) conceptualised, designed, developed the protocol and drafted the manuscript. Justus K Barageine(JKB), Julius N Wandabwa(JNW), Grace Ndeezi (GN) and Andrew Weeks (AW) all participated in the conceptualization, design, development of the protocol and writing of the manuscript by providing critical review and refinement of the research idea as supervisors of my PhD studies. All the authors reviewed and approved the final draft of the manuscript for submission.

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Competing interests statement; None declared

Patients consent; Required

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Figure1 Flow diagram of study participants in the trial

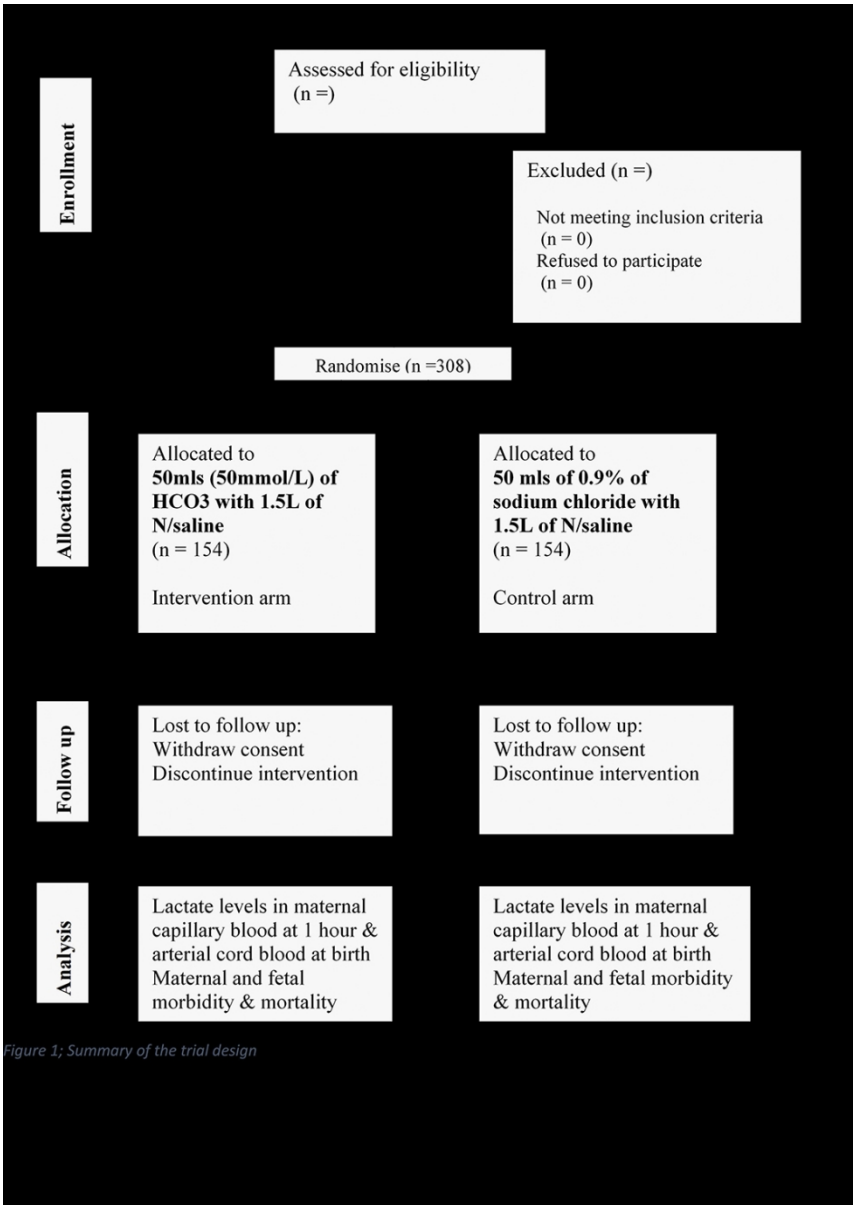

Figure 1; Summary of the trial design

90x126mm (300 x 300 DPI)

SPIRIT

STANDARD PROTOCOL ITEMS: RECOMMENDATIONS FOR INTERVENTIONAL TRIALS

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	Item No	Description
Administrative information		
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym **YES on the title page**
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry **YES at the end of the abstract**
	2b	All items from the World Health Organization Trial Registration Data Set
Protocol version	3	Date and version identifier **Yes**
Funding	4	Sources and types of financial, material, and other support **Yes on page 14**
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors **Yes on the title page**
	5b	Name and contact information for the trial sponsor **Yes page 14**
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities **Yes page 14**
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee) **NA**
Introduction		
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention **Yes page 3 to 5**
	6b	Explanation for choice of comparators **Yes 6&7**
Objectives	7	Specific objectives or hypotheses **Yes page 5**

Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory) **Yes page 6**
Methods: Participants, interventions, and outcomes		
Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained **Yes page 6**
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists) **Yes Page 6&7**
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered **Yes page 7 & 8**
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease) **NA**
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests) **NA**
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial **NA**
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended **Yes page 8**
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (**see Figure 2**)
Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations **Yes page 11&10**
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size **NA**
Methods: Assignment of interventions (for controlled trials)		
Allocation:		

Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions **Yes see page 7 under randomisation**
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned **Yes see page 7 under randomisation**
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions **Yes see page 7 under randomisation**
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how **Yes see page 7 under randomisation**
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial **Yes see page 7 under randomisation**
Methods: Data collection, management, and analysis		
Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol **Yes see page 11**
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols **NA**
Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol **Yes see page 11**
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol **Yes see page 12**
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses) **NA**

	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation) **NA**
Methods: Monitoring		
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed **Yes see page 13**
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial **Yes see page 13**
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct **Yes see page 13**
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor **Yes see page 13**
Ethics and dissemination		
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval **Yes see page 11**
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators) **NA**
Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how **(see attached consent)**
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable **NA**
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial **Yes see page 11**
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site **see page 14**
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators **NA**

Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation **(see attached consent form)**
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions **Yes see page 13**
	31b	Authorship eligibility guidelines and any intended use of professional writers **NA**
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code **NA**
Appendices		
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates **(Attached to submission)**
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable **(Yes see attached consent)**

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.

BMJ Open

Effect of preoperative bicarbonate infusion on Maternal and Perinatal outcomes of obstructed labour in Mbale Regional Referral Hospital; A study protocol for a Randomised Controlled Trial

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Effect of preoperative bicarbonate infusion on Maternal and Perinatal outcomes of obstructed labour in Mbale Regional Referral Hospital; A study protocol for a Randomised Controlled Trial

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ABSTRACT

Introduction

To improve maternal and fetal outcomes among patients with obstructed labour (OL) in low resource settings, the associated electrolyte and metabolic derangements must be adequately corrected. Oral fluid intake during labour and preoperative intravenous fluid replacement following OL corrects the associated dehydration and electrolyte changes, but it does not completely reverse the metabolic acidosis that is a cause of intrapartum birth asphyxia and a risk factor for primary postpartum haemorrhage due to uterine atony.

Sodium bicarbonate is a safe, effective, cheap and readily available acid buffer that is widely used by sportspeople to improve performance. It also appears to improve fetal and maternal outcomes in abnormally progressing labour. However, its effects on maternal and fetal outcomes among patients with OL is unknown. We aim at establishing the effect of a single dose preoperative infusion of sodium bicarbonate on maternal and fetal lactate levels and clinical outcomes among patients with OL.

Methods and analysis

This will be a double blind, randomised controlled clinical phase IIb trial. We will randomize 478 patients with OL to receive either 50 mls of placebo with standard preoperative infusion of Normal Saline (1.5 L) or 4.2 g of sodium bicarbonate solution (50 mls of 50 mmol/L) with the preoperative infusion of Normal Saline (1.5 L). The primary outcome will be mean lactate levels in maternal capillary blood at one hour after study drug administration and in the arterial cord blood at birth. We will use the intention to treat analysis approach. Secondary outcomes will include safety, maternal and fetal morbidity and mortality up to 14 days postpartum.

Ethics and Dissemination

Makerere University School of Medicine Research and Ethics Committee and Uganda National Council for Science and Technology have approved the protocol. Each participant will give informed consent at enrollment. The trial registration number is PACTR201805003364421.

Strengths and limitations of this study;

Strengths.

i. This is among the first studies to investigate the effect of preoperative bicarbonate infusion on maternal and fetal outcomes among patients with OL, using a randomized control design.
ii. Measurement of maternal lactate levels and fetal cord blood lactate at the bedside using a hand-held device (Lactate Pro 2), instead of a blood gas analyser that is expensive to acquire and operate; in a resource-limited setting.

Limitations.

i. This study will only ascertain the efficacy and not the effectiveness of the preoperative sodium bicarbonate infusion
ii. Given the short duration of follow up, we will not have any information regarding the long term effects of sodium bicarbonate on maternal and perinatal outcomes.
iii. Improving maternal and fetal lactate levels may not improve the fetal outcome in OL, as the tocolytic effect of the lactate may be a fetal protective mechanism.

Introduction

Globally, the annual number of maternal deaths (MD) has decreased from 532,000 in 1990 to 303,000 in 2015.[1,2] But almost all of them (99.6%) occur in Sub Saharan Africa (66.3%) and South Central Asia,[1] where it is estimated that the lifetime risk of MD is as high as 1 in 16 and 1 in 46 respectively, compared to 1 in 2,800 in developed regions.[1,2] Although, primary postpartum haemorrhage (PPH) and sepsis are the leading causes of MD, obstructed labour (OL) indirectly contributes to more than 70% of these deaths.[3] Directly, OL causes 8% of all the MD[4,5] and up to 90% of the perinatal deaths due to birth asphyxia.[6] In the 2015/16 financial year, of the 246 maternal deaths reported to the Uganda Ministry of Health (MOH), 9% were due to OL, 39% were due to haemorrhage and 20% were due to sepsis.[7] In addition,

69.3% of 411 perinatal deaths were due to birth asphyxia although the contribution of OL was not specified.

The prevalence of OL varies from 2– 8 % worldwide. It is highest in low and middle income countries (LMICs) and is almost none-existent in developed countries. [4,5] In LMICs many patients experience delays in accessing quality emergency obstetric and neonatal care services, so they end up with neglected OL which causes significant maternal morbidity (dehydration, uterine rupture, sepsis, vesicovaginal/rectovaginal fistulae and postpartum haemorrhage) and neonatal morbidity (asphyxia and sepsis).[3,8] Obstructed labour occurs when the fetal presenting part does not descend into the maternal pelvis despite adequate uterine contractions. [4] Usually, the obstruction can only be safely relieved by an operative delivery.[6] In fact OL is the commonest indication for primary caesarean section and a major risk factor for infective morbidity (puerperal and neonatal sepsis) especially in LMICs.[3,9]

Obstructed Labour is associated with higher levels of lactate in blood and amniotic fluid compared to normal labour, and this correlates directly with perinatal outcomes.[10] Lactate is a byproduct of anaerobic respiration that is produced by both the fetus and the myometrium in response to intermittent hypoxia during labour.[11] In OL, the episodes of hypoxia are prolonged leading to accumulation of lactic acid (metabolic acidosis) from anaerobic break down of glucose. Although impaired uterine contractility caused by myometrial acidosis increases the risk of primary PPH, it is beneficial to the fetus because it increases fetal placental circulation (oxygenation) which is protective against intrapartum birth asphyxia.[10,12] The transfer of excess hydrogen ions across the placenta to the fetus is associated with low fetal PH, fetal distress and poor APGAR. [13]

Oral bicarbonate is a widely used acid buffer in sports science, to improve physical performance in vigorous exercises because it can reverse lactic acidosis.[14] Bicarbonate does not cross the placental barrier,[15] but it plays a key role in regulating the maternal and fetal acid-base chemistry.[13] There are

conflicting reports regarding its benefits in labour. Earlier studies involving the use of Bicarbonate in normal labour showed improvements in pH, base excess and plasma bicarbonate, but none reported APGAR scores. A recent RCT involving the use of oral bicarbonate solution in abnormal (dystocic) labour reported a significant improvement in both maternal and perinatal outcomes. [14] Significantly, none of these studies reported adverse maternal and perinatal effects or included participants with OL. Currently, preoperative intravenous infusion with at least 1.5 L of fluid is recommended as a key element of the standard care. This is adequate to correct the dehydration and electrolyte imbalance but it probably doesn't completely reverse the associated metabolic acidosis.[16,17]

Various formulations and doses of sodium bicarbonate have been safely used for both clinical indications and research purposes with no reported adverse clinical reactions. A single preoperative infusion of 4.2 g of sodium bicarbonate solution (50 mls of 50 mmol/L) will be given as a single dose at enrolment, since OL is an obstetric emergency that requires urgent intervention. [18] The same dose was used orally in the recent trial in which bicarbonate solution was administered to women with dystocia in labour. [14] The main outcome of this study will be to assess whether bicarbonate changes the maternal and fetal lactate levels among patients with OL. Lactate is easier to measure than full blood gas analysis using maintenance free, battery operated pocket size devices like the lactate Pro2 (Arkray). This device produces accurate results in a short time with a high intraclass correlation coefficient (ICC) which is comparable to that of gold standard in a given population i.e. 0.90 versus 0.92.[18]Lactate is comparable to pH and base deficit with respect to sensitivity, specificity and predictive values of various perinatal complications.[13]

We hypothesize that supplementation with preoperative sodium bicarbonate infusion as an acid buffer among patients with OL can reduce maternal acidosis at one hour after administration, while their newborns in the bicarbonate group will have less acidosis in cord blood at birth. Bicarbonate is safe, effective, cheap and already widely used.[19] Establishing its effect on maternal and fetal outcomes following OL is necessary because it could be added to the standard preoperative care package as a form

of tertiary prevention. This study aims to establish the effect of a single dose preoperative infusion of sodium bicarbonate on maternal and fetal lactate levels and clinical outcomes among patients with OL.

Methods/Design

Study design

This will be a superiority, double blind, randomised controlled clinical phase IIb trial. Half of the 478 patients with OL will receive the intervention (sodium bicarbonate infusion) with preoperative normal saline infusion, and the other half will receive the standard of care (preoperative saline infusion) alone.

Study setting

We will conduct this study in Mbale Regional Referral Hospital located at the heart of Mbale Municipality, 214 km to the East of the capital city, Kampala. It is the main referral hospital, serving 14 districts in the Elgon zone, bordering western Kenya. This is a government run, not-for-profit, charge-free, 470-bed hospital with 52 maternity beds. The Department of Obstetrics and Gynaecology has one consultant, two specialists, three medical officers and 21 Midwives. In terms of outputs, the labour and delivery suite is only second to the Mulago National Referral Hospital labour suite. Annually, about 12,000 childbirths occur in this hospital with a caesarean section rate of 35% and nearly 500 mothers have OL. The Ministry of Health has ranked it as the best performing Regional Referral Hospital in Uganda for the last four years.

Participants

This study will be carried out among patients with OL admitted to the labour suite in Mbale Regional Referral Hospital for emergency cesarean section during the period of the study. Either a Medical Officer or specialist on duty using the ACOG definition will make the diagnosis of OL. In the first stage of labour she should have cervical dilatation >6cm with ruptured membranes, adequate contractions lasting > 4hrs with no change in cervical dilatation, OR, delay in the second active stage of labour (nullipara > 2hrs,

multipara > 1 hr.) with adequate uterine contractions. IN ADDITION, ANY TWO OF: the obvious signs of severe obstruction such as caput formation, severe moulding, Bandl's ring, sub-conjunctival hemorrhages, or an oedematous vulva.

We will include patients with OL carrying singleton, term pregnancies (≥37 weeks of gestation) in cephalic presentation. We will exclude patients with other obstetric emergencies such as (antepartum haemorrhage, Pre-eclampsia and eclampsia (defined as elevated blood pressure of at least 140/90 mmHg, urine protein of at least 2+, any of the danger signs and fits), premature rupture of membranes and intrauterine fetal death. Patients with comorbidities such as diabetes mellitus, Sickle cell disease, renal disease, liver disease & heart disease. We will also exclude those patients with hypokalemia (<3.3 mmol/L), hypocalcaemia (<8.2 mmol/L), hypernatraemia (> 148 mmol/L) and alkalosis (bicarbonate > 22 mmol/L) because they are more likely to develop adverse drug reactions.

Randomization

An independent biostatician will generate a sequence of random numbers using the online randomisation service of www.sealedenvelope.com in permuted block sizes of four, six and eight. Based on this sequence, OL patients will be randomly allocated to either intervention or control arms in a 1:1 ratio. An independent pharmacist who is not involved in the recruitment of study participants, will conceal the randomization sequence by preparing new labels with sequential numbers to be placed on identical study drug packages each containing five similar 10 ml glass vials without the original labels. After consent for inclusion is confirmed, a study nurse will take the next study drug package and administer its contents to the participant.

Intervention;

The intervention will be a preoperative infusion of 50 mls of sodium bicarbonate 8.4% solution equivalent to 4.2 g or 50 mmol/L of bicarbonate (Martindale Pharma, Essex) in 10 ml glass vials. The sodium

bicarbonate will be administered intravenously as a bolus immediately after recruitment by trained research assistants who are all experienced midwives working in the labour suite, followed by 1.5 L of Normal Saline over the next hour.

Comparator;

Participants in the control arm will receive a preoperative infusion of Normal Saline, which is part of the current standard of care. Fifty mls of sodium chloride 0.9% in identical 10 ml glass vials (AccuHealth Care, Gujarat) will be administered intravenously as a bolus immediately after recruitment by trained research assistants, who are all experienced midwives working in the labour suite, followed by 1.5 L Normal Saline over the next hour.

In addition, recruits will receive the standard pre-operative care which includes pre-operative antibiotic prophylaxis, at least 1.5 L of intravenous fluids pre-operatively, bladder emptying, administration of oxygen, and lying in left lateral position.[16]

Measurements;

The primary outcomes in this study will be the mean lactate levels in maternal capillary blood at one hour after the onset of study drug administration and in arterial cord blood within 1 minute of birth. We will measure Lactate at the bedside using a hand-held Lactate Pro 2 device (Arkray Factory Inc. Shiga).

The Secondary maternal outcomes will include myometrial lactate levels at caesarean section, maternal mortality up to 14 days postpartum. Other morbidities such as primary PPH, birth canal injuries, duration of admission, puerperal sepsis (Persistent fever >38°C,Chills and general malaise, Pain in the lower abdomen, Persistent bloody/pus discharge (lochia) from genital tract, which may have an unpleasant smell, Tenderness on palpating the uterus Uterine sub-involution, wound dehiscence/ burst abdomen),[16] fistulae and readmissions. Secondary perinatal outcomes will include mean lactate in

venous cord blood, Apgar score, admission to the NICU, asphyxia, neonatal sepsis (irritability, poorly breastfeeding, bulging anterior fontanelle)[16] and perinatal death up to 7 days postpartum.

For the secondary safety outcomes, we will monitor for the following drug reactions throughout the period of the study. Frequent urge to urinate, continuing headache, continuing loss of appetite, mood or mental changes, muscle pain or twitching, nausea or vomiting, stomach crumps, slow breathing, swelling of feet or lower limbs, unpleasant taste, increased thirst, unusual tiredness or weakness, venous irritation, cellulitis and IV site pain.[20–22]

Sociodemographic, clinical and laboratory characteristics;

Using an interviewer administered questionnaire and available records (antenatal cards, facility registers and case report files), sociodemographic and clinical characteristics will be collected by trained research assistants. At baseline, five mls of blood will be collected in the appropriate vacutainers for a complete blood count, renal function tests, liver function tests and electrolytes. Ten mls of fresh urine will be collected in a sterile container for analysis. All these specimens will be delivered to MBN clinical laboratories within 1 hour of collection for analysis. Figure 1 shows the CONSORT flow diagram for this study. We will follow up patients for up to 14 days postpartum either by phone call if they are discharged or by direct visits if they are still admitted according to the current standard of care for patients with OL in Uganda.

Sample size and power calculation;

We used the formula, $n <= (Z_{1-\frac{\alpha}{2c}} + Z_{1-\beta})^2 2(\frac{SD}{\Delta})^2$ [23] and Open Epi [24] to detect a $\Delta = 15\%$ difference in mean lactate levels between the intervention and control arms. Assuming an equal number of participants in each group, a two-sided significance level α of 0.05 for a 95% confidence interval, a

power (1- β) of 80%, an allowance of c = two multiple comparisons and a Bonferroni-Holm method for comparison of means.

The mean and standard deviation (SD) of the maternal venous lactate at the end of second stage of labour is 2.6 ± 1.0 mmol/L[25] without any use of bicarbonate. To detect a difference of 15% (0.39 mmol/L) at one hour and assuming the same S.D. of ±1 in both arms, 326 participants will be required. Correcting for an attrition rate of 10%,[14] gives a total sample size of 364.

The mean arterial umbilical cord blood lactate at 37 weeks of gestation is 4.3 ± 1.9 mmol/L[26] without any use of bicarbonate. In order to detect a difference of 15% (0.645 mmol/L) at birth and assuming the same S.D of ±1.9 in both groups, 432 participants will be recruited. Correcting for an attrition rate of 10%,[14] gives a total sample size of 478. We therefore, chose a sample size of 478 to provide adequate power for both hypotheses.

Data collection and management;

Well trained RAs will collect data using a pretested interviewer administered electronic questionnaire on password protected smart phones using the Open Data Kit software.[27] To increase accuracy, the data will be triangulated with a review of relevant health facility records such as the antenatal cards, the maternity and theatre registers, and the participants' case notes. The questionnaire will be coded with checks for internal consistency. Data on sociodemographic, clinical and laboratory parameters will be collected at baseline, at one hour after onset of study drug administration for the primary maternal outcome, at the time of childbirth for the primary neonatal outcome, and at 7 and 14 days postpartum for the secondary perinatal and maternal outcomes as summarised in table 1. The PI will review the entries from the Google aggregate server every 24 hours to ensure data quality and completeness.

Table 1; Summary of the study procedures and timelines

Procedure	At admission (Baseline)	1 hour after onset of study drug administration	At birth	At 7 days postpartum	At 14 days postpartum
Assessment of eligibility	x				
Randomisation	x				
Data collection for baseline parameters	x				
Study drug administration	x				
Questionnaire administration	x	x	x	x	x
Data collection for primary outcome		x	x		
Data collection for secondary outcome			x	x	x

Statistical analysis;

This will be conducted using STATA version 14 software or higher using the principle of 'intention to treat'. Descriptive statistics will be used to summarise baseline characteristics of the study participants and assess if randomisation was successful. The primary maternal outcome will be the difference in capillary blood lactate levels at one hour after onset of study drug administration. The Bonferroni-Holm method[28,29] will be used to compare the difference in means at baseline and one hour after onset of study drug administration both within and between each of the two arms.

For the primary fetal outcome of mean arterial cord blood lactate at birth, The Bonferroni-Holm method will be used to compare the mean lactate levels in the two arms within 1 minute of childbirth.

The secondary outcomes will be reported as proportions in each of the two arms. Categorical variables will be compared using the Chi-square and Fishers exact tests. Potential confounders and effect modifiers unbalanced at baseline and associated with the outcome ($p< 0.05$) will be adjusted for using multivariable

linear or/and logistic regression. Proportions and the number needed to treat/harm (NNT/NNH) will be reported for the secondary maternal and fetal outcomes.

We will do a sub-group analysis of patients admitted as referrals with a diagnosis of OL (to represent patients most likely to have neglected OL) to compare them with those that are diagnosed with OL within the referral hospital. A second sub-group analysis will be for those patients that give birth more than two hours after administration of the study drug, when we expect the effect of the intervention to have worn off.

Quality control;

We will conduct a dry run for a period of one month before introducing the intervention. To facilitate the training of all the research assistants in the study protocol procedures, filling of study questionnaires using the ODK software,[27] accurate measurement of lactate at the bedside using the Lactate Pro 2 device and the ideal technique for collection of samples especially blood to avoid haemolysis. The MBN clinical laboratories are internationally accredited and they are involved in regular internal and external quality control checks.

The sponsor of this study (Makerere University) does not formally monitor studies to ensure compliance and adherence to the standard operating procedures (SOP's) of the study protocol. The PI will check each case report form (CRF) on submission for completeness and undertake regular interviews with study staff and a sample of the study participants to check on the adherence. In addition, the regulatory bodies such as the IRB, UNCST and National Drug Authority (NDA) also carry out regular scheduled and unscheduled spot checks to monitor adherence of the study to the approved protocol.

Ethics and dissemination;

The protocol is approved by the Makerere University School of Medicine Research and Ethics Committee (#REC REF 2017-103), the Uganda National Council for Science and Technology (HS217ES) and the Mbale Regional Referral Research and Ethics Committee(MRRH-REC IN-COM 00/2018). Participant safety;

During the study, all the serious adverse events will be actively identified and reported to the IRB within 24 hours of occurrence. We will adopt and use the School of Medicine Research Ethics Committee reporting form. Only qualified health workers will be recruited and trained in the protocol to work as Research Assistants on this trial. The independent data monitoring committee will review unblinded data when 1/3 of the participants have been enrolled and followed up to completion and report to the sponsor of the study. If need arises such as patient safety, the study Steering Committee and the IDMC will request the independent study biostatistician to unblind the treatment allocation for a specific patient or group of patients without compromising the allocation concealment for the rest of the participants.

Dissemination plan;

Results will be disseminated to the study participants through the local radio stations and local council community meeting at the village level. Findings will be shared with colleagues and administrators in Mbale Regional Referral Hospital/Busitema University Faculty of Health Sciences and the Uganda Ministry of Health through workshops and seminars. To reach the wider scientific community, the findings will be published in open access peer reviewed journals and presented at both local and international conferences. The data sets will be provided free of charge by the primary author on request.

Patient and Public involvement;

The patients and public were not involved in the design and conceptualisation of this study.

Discussion;

If the preoperative infusion of sodium bicarbonate is safe and effective in reducing maternal and fetal lactatemia (acidosis) among patients with OL, then the data from this trial will inform the design of future trials that will facilitate the inclusion of sodium bicarbonate infusion in the standard preoperative care for patients with OL in low resource settings. Its adoption will help to mitigate adverse maternal and perinatal outcomes associated with OL as a tertiary preventive measure for intrauterine maternal and fetal resuscitation. Obstructed labour is still an important clinical and public health problem in low resource settings because of the associated maternal and perinatal morbidity and mortality caused by the accompanying electrolyte and metabolic changes. Therefore, identifying an effective, cheap, safe and readily available acid buffer like sodium bicarbonate might offer immense health benefits.

In obstructed labour, lactatemia might be a protective mechanism to prevent uterine rupture especially in the multiparous patients and fetal hypoxia by causing relaxation of the myometrium in order to improve fetal placental circulation.[10–12] Therefore, reversal of lactic acidosis might result in stronger uterine contractions and increase the degree of fetal hypoxia or risk of uterine rupture especially if the surgical intervention is delayed. Thus, although this study will help us to understand whether 50 mmol of bicarbonate is effective at reversing lactic acidosis; further studies will be required to ascertain its effects on maternal and fetal morbidity.

In the body, sodium bicarbonate ($NaHCO_3$) rapidly disintegrates into sodium and bicarbonate ions and its effects wear off in 60-90 minutes. It does not cross the placenta, it is unknown if $NaHCO_3$ is excreted in breast milk and its effects on lactation are unknown. Since we are administering a single low dose preoperatively, we believe that it will have no effect on lactation. This will need further study in the future even if past studies have not reported any adverse effects.[20–22]

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Author contributions;

Musaba Milton Wamboko (MMW) conceptualised, designed, developed the protocol and drafted the manuscript. Justus K Barageine (JKB), Julius N Wandabwa (JNW), Grace Ndeezi (GN) and Andrew Weeks (AW) all participated in the conceptualization, design, development of the protocol and writing of the manuscript by providing critical review and refinement of the research idea as supervisors of my PhD studies. All the authors reviewed and approved the final draft of the manuscript for submission.

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Competing interests statement; None declared

Patients consent; Required

Ethics approval;

Provenance and peer review; Not commissioned; externally peer reviewed.

Open Access;

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Figure1 Flow diagram of study participants in the trial

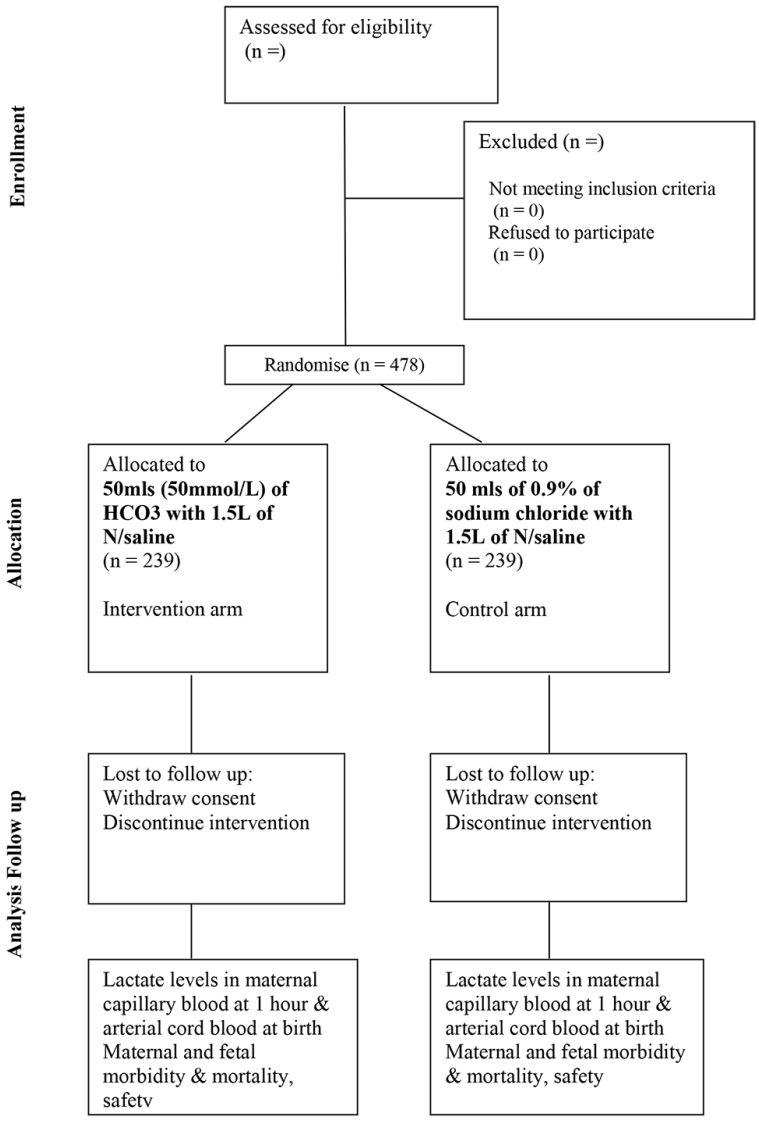

Figure1; Flow chart of study participants

SPIRIT

STANDARD PROTOCOL ITEMS: RECOMMENDATIONS FOR INTERVENTIONAL TRIALS

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	Item No	Description
Administrative information		
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym **YES on the title page**
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry **YES at the end of the abstract**
	2b	All items from the World Health Organization Trial Registration Data Set
Protocol version	3	Date and version identifier **Yes**
Funding	4	Sources and types of financial, material, and other support **Yes on page 14**
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors **Yes on the title page**
	5b	Name and contact information for the trial sponsor **Yes page 14**
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities **Yes page 14**
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee) **NA**
Introduction		
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention **Yes page 3 to 5**
	6b	Explanation for choice of comparators **Yes 6&7**
Objectives	7	Specific objectives or hypotheses **Yes page 5**

Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory) **Yes page 6**
Methods: Participants, interventions, and outcomes		
Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained **Yes page 6**
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists) **Yes Page 6&7**
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered **Yes page 7 & 8**
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease) **NA**
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests) **NA**
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial **NA**
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended **Yes page 8**
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (**see Figure 2**)
Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations **Yes page 11&10**
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size **NA**
Methods: Assignment of interventions (for controlled trials)		
Allocation:		

Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions **Yes see page 7 under randomisation**
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned **Yes see page 7 under randomisation**
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions **Yes see page 7 under randomisation**
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how **Yes see page 7 under randomisation**
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial **Yes see page 7 under randomisation**
Methods: Data collection, management, and analysis		
Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol **Yes see page 11**
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols **NA**
Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol **Yes see page 11**
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol **Yes see page 12**
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses) **NA**

	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation) **NA**
Methods: Monitoring		
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed **Yes see page 13**
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial **Yes see page 13**
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct **Yes see page 13**
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor **Yes see page 13**
Ethics and dissemination		
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval **Yes see page 11**
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators) **NA**
Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how **(see attached consent)**
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable **NA**
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial **Yes see page 11**
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site **see page 14**
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators **NA**

Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation **(see attached consent form)**
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions **Yes see page 13**
	31b	Authorship eligibility guidelines and any intended use of professional writers **NA**
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code **NA**
Appendices		
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates **(Attached to submission)**
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable **(Yes see attached consent)**

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.

BMJ Open

Effect of preoperative bicarbonate infusion on Maternal and Perinatal outcomes of obstructed labour in Mbale Regional Referral Hospital; A study protocol for a Randomised Controlled Trial

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Title:

Effect of preoperative bicarbonate infusion on Maternal and Perinatal outcomes of obstructed labour in Mbale Regional Referral Hospital; A study protocol for a Randomised Controlled Trial

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ABSTRACT

Introduction

To improve maternal and fetal outcomes among patients with obstructed labour (OL) in low resource settings, the associated electrolyte and metabolic derangements must be adequately corrected. Oral fluid intake during labour and preoperative intravenous fluid replacement following OL corrects the associated dehydration and electrolyte changes, but it does not completely reverse the metabolic acidosis that is a cause of intrapartum birth asphyxia and a risk factor for primary postpartum haemorrhage due to uterine atony.

Sodium bicarbonate is a safe, effective, cheap and readily available acid buffer that is widely used by sportspeople to improve performance. It also appears to improve fetal and maternal outcomes in abnormally progressing labour. However, its effects on maternal and fetal outcomes among patients with OL is unknown. We aim at establishing the effect of a single dose preoperative infusion of sodium bicarbonate on maternal and fetal lactate levels and clinical outcomes among patients with OL.

Methods and analysis

This will be a double blind, randomised controlled clinical phase IIb trial. We will randomize 478 patients with OL to receive either 50 mls of placebo with standard preoperative infusion of Normal Saline (1.5 L) or 4.2 g of sodium bicarbonate solution (50 mls of 50 mmol/L) with the preoperative infusion of Normal Saline (1.5 L). The primary outcome will be mean lactate levels in maternal capillary blood at one hour after study drug administration and in the arterial cord blood at birth. We will use the intention to treat analysis approach. Secondary outcomes will include safety, maternal and fetal morbidity and mortality up to 14 days postpartum.

Ethics and Dissemination

Makerere University School of Medicine Research and Ethics Committee and Uganda National Council for Science and Technology have approved the protocol. Each participant will give informed consent at enrollment. The trial registration number is PACTR201805003364421.

Strengths and limitations of this study;

Strengths.

i. This is among the first studies to investigate the effect of preoperative bicarbonate infusion on maternal and fetal outcomes among patients with OL, using a randomized control design.
ii. Measurement of maternal lactate levels and fetal cord blood lactate at the bedside using a hand-held device (Lactate Pro 2), instead of a blood gas analyser that is expensive to acquire and operate; in a resource-limited setting.

Limitations.

i. This study will only ascertain the efficacy and not the effectiveness of the preoperative sodium bicarbonate infusion
ii. Given the short duration of follow up, we will not have any information regarding the long term effects of sodium bicarbonate on maternal and perinatal outcomes.
iii. Improving maternal and fetal lactate levels may not improve the fetal outcome in OL, as the tocolytic effect of the lactate may be a fetal protective mechanism.

Introduction

Globally, the annual number of maternal deaths (MD) has decreased from 532,000 in 1990 to 303,000 in 2015.[1,2] But almost all of them (99.6%) occur in Sub Saharan Africa (66.3%) and South Central Asia,[1] where it is estimated that the lifetime risk of MD is as high as 1 in 16 and 1 in 46 respectively, compared to 1 in 2,800 in developed regions.[1,2] Although, primary postpartum haemorrhage (PPH) and sepsis are the leading causes of MD, obstructed labour (OL) indirectly contributes to more than 70% of these deaths.[3] Directly, OL causes 8% of all the MD[4,5] and up to 90% of the perinatal deaths due to birth asphyxia.[6] In the 2015/16 financial year, of the 246 maternal deaths reported to the Uganda Ministry of Health (MOH), 9% were due to OL, 39% were due to haemorrhage and 20% were due to sepsis.[7] In addition,

69.3% of 411 perinatal deaths were due to birth asphyxia although the contribution of OL was not specified.

The prevalence of OL varies from 2– 8 % worldwide. It is highest in low and middle income countries (LMICs) and is almost none-existent in developed countries. [4,5] In LMICs many patients experience delays in accessing quality emergency obstetric and neonatal care services, so they end up with neglected OL which causes significant maternal morbidity (dehydration, uterine rupture, sepsis, vesicovaginal/rectovaginal fistulae and postpartum haemorrhage) and neonatal morbidity (asphyxia and sepsis).[3,8] Obstructed labour occurs when the fetal presenting part does not descend into the maternal pelvis despite adequate uterine contractions. [4] Usually, the obstruction can only be safely relieved by an operative delivery.[6] In fact OL is the commonest indication for primary caesarean section and a major risk factor for infective morbidity (puerperal and neonatal sepsis) especially in LMICs.[3,9]

Obstructed Labour is associated with higher levels of lactate in blood and amniotic fluid compared to normal labour, and this correlates directly with perinatal outcomes.[10] Lactate is a byproduct of anaerobic respiration that is produced by both the fetus and the myometrium in response to intermittent hypoxia during labour.[11] In OL, the episodes of hypoxia are prolonged leading to accumulation of lactic acid (metabolic acidosis) from anaerobic break down of glucose. Although impaired uterine contractility caused by myometrial acidosis increases the risk of primary PPH, it is beneficial to the fetus because it increases fetal placental circulation (oxygenation) which is protective against intrapartum birth asphyxia.[10,12] The transfer of excess hydrogen ions across the placenta to the fetus is associated with low fetal PH, fetal distress and poor APGAR. [13]

Oral bicarbonate is a widely used acid buffer in sports science, to improve physical performance in vigorous exercises because it can reverse lactic acidosis.[14] Bicarbonate does not cross the placental barrier,[15] but it plays a key role in regulating the maternal and fetal acid-base chemistry.[13] There are

conflicting reports regarding its benefits in labour. Earlier studies involving the use of Bicarbonate in normal labour showed improvements in pH, base excess and plasma bicarbonate, but none reported APGAR scores. A recent RCT involving the use of oral bicarbonate solution in abnormal (dystocic) labour reported a significant improvement in both maternal and perinatal outcomes. [14] Significantly, none of these studies reported adverse maternal and perinatal effects or included participants with OL. Currently, preoperative intravenous infusion with at least 1.5 L of fluid is recommended as a key element of the standard care. This is adequate to correct the dehydration and electrolyte imbalance but it probably doesn't completely reverse the associated metabolic acidosis.[16,17]

Various formulations and doses of sodium bicarbonate have been safely used for both clinical indications and research purposes with no reported adverse clinical reactions. A single preoperative infusion of 4.2 g of sodium bicarbonate solution (50 mls of 50 mmol/L) will be given as a single dose at enrolment, since OL is an obstetric emergency that requires urgent intervention. [18] The same dose was used orally in the recent trial in which bicarbonate solution was administered to women with dystocia in labour. [14] The main outcome of this study will be to assess whether bicarbonate changes the maternal and fetal lactate levels among patients with OL. Lactate is easier to measure than full blood gas analysis using maintenance free, battery operated pocket size devices like the lactate Pro2 (Arkray). This device produces accurate results in a short time with a high intraclass correlation coefficient (ICC) which is comparable to that of gold standard in a given population i.e. 0.90 versus 0.92.[18]Lactate is comparable to pH and base deficit with respect to sensitivity, specificity and predictive values of various perinatal complications.[13]

We hypothesize that supplementation with preoperative sodium bicarbonate infusion as an acid buffer among patients with OL can reduce maternal acidosis at one hour after administration, while their newborns in the bicarbonate group will have less acidosis in cord blood at birth. Bicarbonate is safe, effective, cheap and already widely used.[19] Establishing its effect on maternal and fetal outcomes following OL is necessary because it could be added to the standard preoperative care package as a form

of tertiary prevention. This study aims to establish the effect of a single dose preoperative infusion of sodium bicarbonate on maternal and fetal lactate levels and clinical outcomes among patients with OL.

Methods/Design

Study design

This will be a superiority, double blind, randomised controlled clinical phase IIb trial. Half of the 478 patients with OL will receive the intervention (sodium bicarbonate infusion) with preoperative normal saline infusion, and the other half will receive the standard of care (preoperative saline infusion) alone.

Study setting

We will conduct this study in Mbale Regional Referral Hospital located at the heart of Mbale Municipality, 214 km to the East of the capital city, Kampala. It is the main referral hospital, serving 14 districts in the Elgon zone, bordering western Kenya. This is a government run, not-for-profit, charge-free, 470-bed hospital with 52 maternity beds. The Department of Obstetrics and Gynaecology has one consultant, two specialists, three medical officers and 21 Midwives. In terms of outputs, the labour and delivery suite is only second to the Mulago National Referral Hospital labour suite. Annually, about 12,000 childbirths occur in this hospital with a caesarean section rate of 35% and nearly 500 mothers have OL. The Ministry of Health has ranked it as the best performing Regional Referral Hospital in Uganda for the last four years.

Participants

This study will be carried out among patients with OL admitted to the labour suite in Mbale Regional Referral Hospital for emergency cesarean section during the period of the study. Either a Medical Officer or specialist on duty using the ACOG definition will make the diagnosis of OL. In the first stage of labour she should have cervical dilatation >6cm with ruptured membranes, adequate contractions lasting > 4hrs with no change in cervical dilatation, OR, delay in the second active stage of labour (nullipara > 2hrs,

multipara > 1 hr.) with adequate uterine contractions. IN ADDITION, ANY TWO OF: the obvious signs of severe obstruction such as caput formation, severe moulding, Bandl's ring, sub-conjunctival hemorrhages, or an oedematous vulva.

We will include patients with OL carrying singleton, term pregnancies (≥37 weeks of gestation) in cephalic presentation. We will exclude patients with other obstetric emergencies such as (antepartum haemorrhage, Pre-eclampsia and eclampsia (defined as elevated blood pressure of at least 140/90 mmHg, urine protein of at least 2+, any of the danger signs and fits), premature rupture of membranes and intrauterine fetal death. Patients with comorbidities such as diabetes mellitus, Sickle cell disease, renal disease, liver disease & heart disease. We will also exclude those patients with hypokalemia (<3.3 mmol/L), hypocalcaemia (<8.2 mmol/L), hypernatraemia (> 148 mmol/L) and alkalosis (bicarbonate > 22 mmol/L) because they are more likely to develop adverse drug reactions.

Randomization

An independent biostatician will generate a sequence of random numbers using the online randomisation service of www.sealedenvelope.com in permuted block sizes of four, six and eight. Based on this sequence, OL patients will be randomly allocated to either intervention or control arms in a 1:1 ratio. An independent pharmacist who is not involved in the recruitment of study participants, will conceal the randomization sequence by preparing new labels with sequential numbers to be placed on identical study drug packages each containing five similar 10 ml glass vials without the original labels. After consent for inclusion is confirmed, a study nurse will take the next study drug package and administer its contents to the participant.

Intervention;

The intervention will be a preoperative infusion of 50 mls of sodium bicarbonate 8.4% solution equivalent to 4.2 g or 50 mmol/L of bicarbonate (Martindale Pharma, Essex) in 10 ml glass vials. The sodium

bicarbonate will be administered intravenously as a bolus immediately after recruitment by trained research assistants who are all experienced midwives working in the labour suite, followed by 1.5 L of Normal Saline over the next hour.

Comparator;

Participants in the control arm will receive a preoperative infusion of Normal Saline, which is part of the current standard of care. Fifty mls of sodium chloride 0.9% in identical 10 ml glass vials (AccuHealth Care, Gujarat) will be administered intravenously as a bolus immediately after recruitment by trained research assistants, who are all experienced midwives working in the labour suite, followed by 1.5 L Normal Saline over the next hour.

In addition, recruits will receive the standard pre-operative care which includes pre-operative antibiotic prophylaxis, at least 1.5 L of intravenous fluids pre-operatively, bladder emptying, administration of oxygen, and lying in left lateral position.[16]

Measurements;

The primary outcomes in this study will be the mean lactate levels in maternal capillary blood at one hour after the onset of study drug administration and in arterial cord blood within 1 minute of birth. We will measure Lactate at the bedside using a hand-held Lactate Pro 2 device (Arkray Factory Inc. Shiga).

The Secondary maternal outcomes will include myometrial lactate levels at caesarean section, maternal mortality up to 14 days postpartum. Other morbidities such as primary PPH, birth canal injuries, duration of admission, puerperal sepsis (Persistent fever >38°C,Chills and general malaise, Pain in the lower abdomen, Persistent bloody/pus discharge (lochia) from genital tract, which may have an unpleasant smell, Tenderness on palpating the uterus Uterine sub-involution, wound dehiscence/ burst abdomen),[16] fistulae and readmissions. Secondary perinatal outcomes will include mean lactate in

venous cord blood, Apgar score, admission to the NICU, asphyxia, neonatal sepsis (irritability, poorly breastfeeding, bulging anterior fontanelle)[16] and perinatal death up to 7 days postpartum.

For the secondary safety outcomes, we will monitor for the following drug reactions throughout the period of the study. Frequent urge to urinate, continuing headache, continuing loss of appetite, mood or mental changes, muscle pain or twitching, nausea or vomiting, stomach crumps, slow breathing, swelling of feet or lower limbs, unpleasant taste, increased thirst, unusual tiredness or weakness, venous irritation, cellulitis and IV site pain.[20–22]

Sociodemographic, clinical and laboratory characteristics;

Using an interviewer administered questionnaire and available records (antenatal cards, facility registers and case report files), sociodemographic and clinical characteristics will be collected by trained research assistants. At baseline, five mls of blood will be collected in the appropriate vacutainers for a complete blood count, renal function tests, liver function tests and electrolytes. Ten mls of fresh urine will be collected in a sterile container for analysis. All these specimens will be delivered to MBN clinical laboratories within 1 hour of collection for analysis. Figure 1 shows the CONSORT flow diagram for this study. We will follow up patients for up to 14 days postpartum either by phone call if they are discharged or by direct visits if they are still admitted according to the current standard of care for patients with OL in Uganda.

Sample size and power calculation;

Since the multiple testing in this study will be corrected for at analysis, we estimated the sample size to cater for that. The testing will take place c=two times, the final analysis will use a Bonferroni-Holm correction to adjust for multiplicity and the critical value will divide the α level by c.

To detect a $\Delta = 15\%$ difference in mean lactate levels between the intervention and control arms. Assuming an equal number of participants in each group, a two-sided significance level α of 0.05 for a 95% confidence interval, a power (1- β) of 90%, an allowance of c = two multiple comparisons and a Bonferroni-Holm method for comparison of means, we used the formula, $n >= (Z_{1-\frac{\alpha}{2c}} + Z_{1-\beta})^2 2(\frac{SD}{\Delta})^2$ [23] and Open Epi [24] to determine the sample size. Where $Z_{1-\frac{\alpha}{2c}} = Z_{1-\frac{0.05}{2*2}} = Z_{1-0.0125} = 2.24$ and $Z_{1-\beta} = Z_{1-0.1} = Z_{0.9} = 1.28$ using standard normal tables.

The mean and standard deviation (SD) of the maternal venous lactate at the end of second stage of labour is 2.6 ± 1.0 mmol/L[25] without any use of bicarbonate. To detect a difference of 15% (0.39 mmol/L) at one hour and assuming the same S.D. of ±1 in both arms, 326 participants will be required. Correcting for an attrition rate of 10%,[14] gives a total sample size of 364.

The mean arterial umbilical cord blood lactate at 37 weeks of gestation is 4.3 ± 1.9 mmol/L[26] without any use of bicarbonate. In order to detect a difference of 15% (0.645 mmol/L) at birth and assuming the same S.D of ±1.9 in both groups, 432 participants will be recruited. Correcting for an attrition rate of 10%,[14] gives a total sample size of 478. We therefore, chose a sample size of 478 to provide adequate power for both hypotheses.

Data collection and management;

Well trained RAs will collect data using a pretested interviewer administered electronic questionnaire on password protected smart phones using the Open Data Kit software.[27] To increase accuracy, the data will be triangulated with a review of relevant health facility records such as the antenatal cards, the maternity and theatre registers, and the participants' case notes. The questionnaire will be coded with checks for internal consistency. Data on sociodemographic, clinical and laboratory parameters will be collected at baseline, at one hour after onset of study drug administration for the primary maternal

outcome, at the time of childbirth for the primary neonatal outcome, and at 7 and 14 days postpartum for the secondary perinatal and maternal outcomes as summarised in table 1. The PI will review the entries from the Google aggregate server every 24 hours to ensure data quality and completeness.

Table 1; Summary of the study procedures and timelines

Procedure	**At admission (Baseline)**	**1 hour after onset of study drug administration**	**At birth**	**At 7 days postpartum**	**At 14 days postpartum**
Assessment of eligibility	x				
Randomisation	x				
Data collection for baseline parameters	x				
Study drug administration	x				
Questionnaire administration	x	x	x	x	x
Data collection for primary outcome		x	x		
Data collection for secondary outcome			x	x	x

Statistical analysis;

This will be conducted using STATA version 14 software or higher using the principle of 'intention to treat'. Descriptive statistics will be used to summarise baseline characteristics of the study participants and assess if randomisation was successful. The primary maternal outcome will be the difference in capillary blood lactate levels at one hour after onset of study drug administration. The Bonferroni-Holm method[28,29] will be used to compare the difference in means at baseline and one hour after onset of study drug administration both within and between each of the two arms.

For the primary fetal outcome of mean arterial cord blood lactate at birth, The Bonferroni-Holm method will be used to compare the mean lactate levels in the two arms within 1 minute of childbirth.

The secondary outcomes will be reported as proportions in each of the two arms. Categorical variables will be compared using the Chi-square and Fishers exact tests. Potential confounders and effect modifiers unbalanced at baseline and associated with the outcome ($p< 0.05$) will be adjusted for using multivariable linear or/and logistic regression. Proportions and the number needed to treat/harm (NNT/NNH) will be reported for the secondary maternal and fetal outcomes.

We will do a sub-group analysis of patients admitted as referrals with a diagnosis of OL (to represent patients most likely to have neglected OL) to compare them with those that are diagnosed with OL within the referral hospital. A second sub-group analysis will be for those patients that give birth more than two hours after administration of the study drug, when we expect the effect of the intervention to have worn off.

Quality control;

We will conduct a dry run for a period of one month before introducing the intervention. To facilitate the training of all the research assistants in the study protocol procedures, filling of study questionnaires using the ODK software,[27] accurate measurement of lactate at the bedside using the Lactate Pro 2 device and the ideal technique for collection of samples especially blood to avoid haemolysis. The MBN clinical laboratories are internationally accredited and they are involved in regular internal and external quality control checks.

The sponsor of this study (Makerere University) does not formally monitor studies to ensure compliance and adherence to the standard operating procedures (SOP's) of the study protocol. The PI will check each case report form (CRF) on submission for completeness and undertake regular interviews with study staff and a sample of the study participants to check on the adherence. In addition, the regulatory bodies such as the IRB, UNCST and National Drug Authority (NDA) also carry out regular scheduled and unscheduled spot checks to monitor adherence of the study to the approved protocol.

Ethics and dissemination;

The protocol is approved by the Makerere University School of Medicine Research and Ethics Committee (#REC REF 2017-103), the Uganda National Council for Science and Technology (HS217ES) and the Mbale Regional Referral Research and Ethics Committee(MRRH-REC IN-COM 00/2018). Participant safety;

During the study, all the serious adverse events will be actively identified and reported to the IRB within 24 hours of occurrence. We will adopt and use the School of Medicine Research Ethics Committee reporting form. Only qualified health workers will be recruited and trained in the protocol to work as Research Assistants on this trial. The independent data monitoring committee will review unblinded data when 1/3 of the participants have been enrolled and followed up to completion and report to the sponsor of the study. If need arises such as patient safety, the study Steering Committee and the IDMC will request the independent study biostatistician to unblind the treatment allocation for a specific patient or group of patients without compromising the allocation concealment for the rest of the participants.

Dissemination plan;

Results will be disseminated to the study participants through the local radio stations and local council community meeting at the village level. Findings will be shared with colleagues and administrators in Mbale Regional Referral Hospital/Busitema University Faculty of Health Sciences and the Uganda Ministry of Health through workshops and seminars. To reach the wider scientific community, the findings will be published in open access peer reviewed journals and presented at both local and international conferences. The data sets will be provided free of charge by the primary author on request.

Patient and Public involvement;

The patients and public were not involved in the design and conceptualisation of this study.

Discussion;

If the preoperative infusion of sodium bicarbonate is safe and effective in reducing maternal and fetal lactatemia (acidosis) among patients with OL, then the data from this trial will inform the design of future trials that will facilitate the inclusion of sodium bicarbonate infusion in the standard preoperative care for patients with OL in low resource settings. Its adoption will help to mitigate adverse maternal and perinatal outcomes associated with OL as a tertiary preventive measure for intrauterine maternal and fetal resuscitation. Obstructed labour is still an important clinical and public health problem in low resource settings because of the associated maternal and perinatal morbidity and mortality caused by the accompanying electrolyte and metabolic changes. Therefore, identifying an effective, cheap, safe and readily available acid buffer like sodium bicarbonate might offer immense health benefits.

In obstructed labour, lactatemia might be a protective mechanism to prevent uterine rupture especially in the multiparous patients and fetal hypoxia by causing relaxation of the myometrium in order to improve fetal placental circulation.[10–12] Therefore, reversal of lactic acidosis might result in stronger uterine contractions and increase the degree of fetal hypoxia or risk of uterine rupture especially if the surgical intervention is delayed. Thus, although this study will help us to understand whether 50 mmol of bicarbonate is effective at reversing lactic acidosis; further studies will be required to ascertain its effects on maternal and fetal morbidity.

In the body, sodium bicarbonate ($NaHCO_3$) rapidly disintegrates into sodium and bicarbonate ions and its effects wear off in 60-90 minutes. It does not cross the placenta, it is unknown if $NaHCO_3$ is excreted in breast milk and its effects on lactation are unknown. Since we are administering a single low dose preoperatively, we believe that it will have no effect on lactation. This will need further study in the future even if past studies have not reported any adverse effects.[20–22]

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Author contributions;

Musaba Milton Wamboko (MMW) conceptualised, designed, developed the protocol and drafted the manuscript. Justus K Barageine (JKB), Julius N Wandabwa (JNW), Grace Ndeezi (GN) and Andrew Weeks (AW) all participated in the conceptualization, design, development of the protocol and writing of the manuscript by providing critical review and refinement of the research idea as supervisors of my PhD studies. All the authors reviewed and approved the final draft of the manuscript for submission.

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Competing interests statement; None declared

Patients consent; Required

Ethics approval;

Provenance and peer review; Not commissioned; externally peer reviewed.

Open Access;

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Figure1 Flow diagram of study participants in the trial

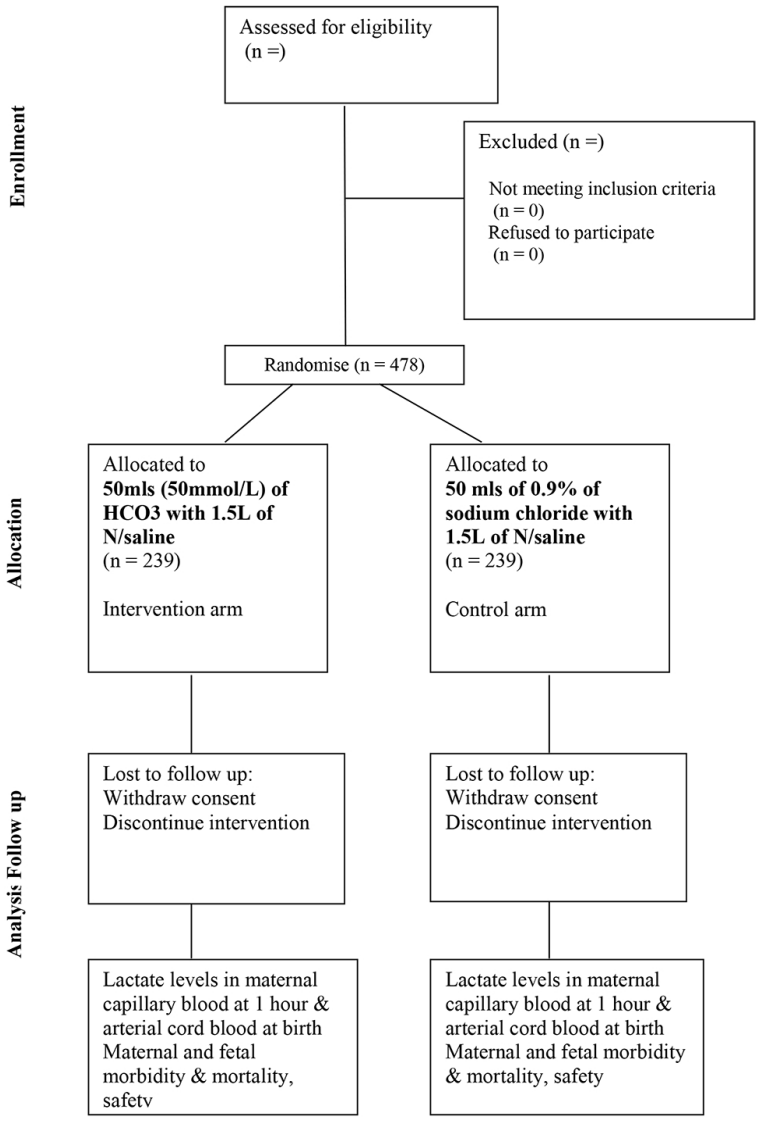

Figure1; Flow chart of study participants

SPIRIT

STANDARD PROTOCOL ITEMS: RECOMMENDATIONS FOR INTERVENTIONAL TRIALS

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	Item No	Description
Administrative information		
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym **YES on the title page**
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry **YES at the end of the abstract**
	2b	All items from the World Health Organization Trial Registration Data Set
Protocol version	3	Date and version identifier **Yes**
Funding	4	Sources and types of financial, material, and other support **Yes on page 14**
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors **Yes on the title page**
	5b	Name and contact information for the trial sponsor **Yes page 14**
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities **Yes page 14**
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee) **NA**
Introduction		
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention **Yes page 3 to 5**
	6b	Explanation for choice of comparators **Yes 6&7**
Objectives	7	Specific objectives or hypotheses **Yes page 5**

Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory) **Yes page 6**
Methods: Participants, interventions, and outcomes		
Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained **Yes page 6**
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists) **Yes Page 6&7**
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered **Yes page 7 & 8**
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease) **NA**
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests) **NA**
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial **NA**
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended **Yes page 8**
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (**see Figure 2**)
Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations **Yes page 11&10**
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size **NA**
Methods: Assignment of interventions (for controlled trials)		
Allocation:		

Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions **Yes see page 7 under randomisation**
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned **Yes see page 7 under randomisation**
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions **Yes see page 7 under randomisation**
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how **Yes see page 7 under randomisation**
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial **Yes see page 7 under randomisation**
Methods: Data collection, management, and analysis		
Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol **Yes see page 11**
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols **NA**
Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol **Yes see page 11**
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol **Yes see page 12**
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses) **NA**

	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation) **NA**
Methods: Monitoring		
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed **Yes see page 13**
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial **Yes see page 13**
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct **Yes see page 13**
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor **Yes see page 13**
Ethics and dissemination		
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval **Yes see page 11**
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators) **NA**
Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how **(see attached consent)**
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable **NA**
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial **Yes see page 11**
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site **see page 14**
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators **NA**

Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation **(see attached consent form)**
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions **Yes see page 13**
	31b	Authorship eligibility guidelines and any intended use of professional writers **NA**
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code **NA**
Appendices		
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates **(Attached to submission)**
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable **(Yes see attached consent)**

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.