PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	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
AUTHORS	Musaba, Milton; Barageine, Justus; Ndeezi, Grace; Wandabwa, Julius; Weeks, Andrew

VERSION 1 - REVIEW

REVIEWER	Prof Ishag Adam University of Khartoum, Sudan
REVIEW RETURNED	27-Oct-2018

GENERAL COMMENTS	I suggest accepting this work

REVIEWER	Tomoko Fujii Monash University, Australia
REVIEW RETURNED	04-Nov-2018

GENERAL COMMENTS	Musaba et al. have planned a phase 3 randomised controlled trial to assess the efficacy of intravenous sodium bicarbonate on maternal and fetal lactate levels that are surrogate to perinatal complications. The research question is very important to be examined, and the protocol is generally well written. I have several comments. Major comments 1. The trial adopts maternal and fetal lactate levels as the primary outcomes. Please add some explanations why the investigators did not choose a 'hard' outcome which is more relevant to mothers or neonates, such as maternal and/or fetal death. I acknowledge that lactate may predict the perinatal outcomes; however, it does not mean reversing lactatemia is equal to improving the outcome (it may not be a causal inference). Lactatemia may be just an epiphenomenon of the severity of the condition. If there is a paucity of evidence to conduct a pivotal phase 3 trial to assess the effect of NaHCO3 on maternal/fetal survival, I would suggest the investigators conduct this trial as a phase IIb trial and further examine whether the NaHCO3 treatment is an effective treatment for the clinically relevant outcome (i.e. mortality). 2. The primary outcomes are maternal AND fetal lactate levels. This means this trial has two hypothesis and the two outcomes are

	not independent of each other. Please clarify (i) how the investigators address an issue of multiple comparisons (it seems they do not consider it in the current protocol), and (ii) how they interpret the result if only one of the two results seems effective or if the two results show a different direction of the effectiveness. 3. As NaHCO3 may decrease blood ionised calcium and increase PaCO2 (Jaber et al. Lancet 2018, Viallon 1999), but it seems blood gas analysis is not accessible in the trial settings. Please refer to these possible side effects. If the investigators are not going to monitor these values, please provide the rationale and/or add this as a limitation of this trial. 4. Does intravenous NaHCO3 affect breastfeeding after the delivery? Please provide some information. 5. Please include a plan to monitor adherence of the study intervention protocols as obtaining informed consent, randomising and infusing the 50ml of study drug in a limited pre-operative time would be difficult in some cases of obstructed labour. 6. The consent form was not attached. 7. Figure 2 (or Table 2?) was not attached also. Minor comments 1. Please add a reference that provides evidence of the accuracy of Lactate Pro 2 (Arkray). 2. Please cite 'Open Epi' and 'Open Data Kit' with a full reference.

REVIEWER	Eckhart Buchmann Department of Obstetrics and Gynaecology, University of the Witwatersrand, Johannesburg, South Africa.
REVIEW RETURNED	19-Nov-2018

GENERAL COMMENTS	This is a protocol for a double-blind randomised placebo-controlled trial to investigate the effect of giving an intravenous bolus of sodium bicarbonate to women with obstructed labour in a Ugandan referral hospital. The concept is soundly based and explained in the introduction. The method is reasonably rigorous and the trial has ethical approval and has been registered. The authors do not clearly distinguish between, on the one hand, neglected obstructed labour and on the other, obstructed labour (cephalopelvic disproportion) commonly found in hospitals all around the world. The former condition is, I believe, becoming a rarity even in the lowest resource settings. The introduction emphasises neglected obstructed labour, but the study inclusion criteria describe hospital patients who are not necessarily neglected. The design will need to record which of the included patients qualify as neglected obstructed labour, with explicit criteria for this category. Subgroup analysis will therefore be possible for women with neglected obstructed labour. A more pure characterisation of obstructed labour for this trial would be one that includes only nulliparous women who have failed oxytocin augmentation or who have evidence of neglected obstructed labour as the authors might like to define. A less stringent definition as proposed by the authors brings in a group of

	women with dystocia, but not necessarily obstruction. The presence of moulding and caput are not specific for obstructed labour. Is the trial actually about obstruction or about difficult labour? Does it matter? If it's more about difficult labour, a less stringent definition would be acceptable. Whatever the case, the use of less stringent criteria (including multiparas and primigravidas not necessarily on oxytocin) should be justified by scientific considerations and not be driven by the need to collect an adequate sample in as little time as possible. The trial protocol should state clearly that a participant will be randomised when obstructed labour is diagnosed AND caesarean delivery is decided upon. The latter addition makes the inclusion criterion 'hard'. Correctly, the authors will use the principle of 'intention to treat'. It should be expected that some of the women who have been randomised will give birth vaginally while awaiting caesarean delivery, especially if less stringent inclusion criteria are applied. What will the procedure be in such cases? Will all trial procedures (except perhaps myometrial lactate measurement) still be applicable and feasible? In the discussion, the authors' last thought is that 'sodium bicarbonate might offer immense health benefits'. Sure, but that is a very long view. The idea is eventually to help reduce severe maternal and perinatal morbidity and death, as well as cerebral palsy. This trial will not be powered to show any such benefits. The primary outcomes for which the study is powered are useful proxies only. Let us not get ahead of ourselves. Much work remains to be done even if the authors find that this intervention shows promise.

VERSION 1 – AUTHOR RESPONSE

Reviewer: 1
I suggest accepting this work Thank you for the suggestion
Reviewer: 2
Major comments; 1. The trial adopts maternal and foetal lactate levels as the primary outcomes. Please add some explanations why the investigators did not choose a 'hard' outcome, which is more relevant to mothers or neonates, such as maternal and/or fetal death. I acknowledge that lactate may predict the perinatal outcomes; however, it does not mean reversing lactatemia is equal to improving the outcome (it may not be a causal inference). Lactatemia may be just an epiphenomenon of the severity of the condition. If there is a paucity of evidence to conduct a pivotal phase 3 trial to assess the effect of NaHCO3 on maternal/fetal survival, I would suggest the investigators conduct this trial as a phase IIb trial and further examine whether the NaHCO3 treatment is an effective treatment for the clinically relevant outcome (i.e. mortality). - We agree that our primary indicator is not a hard outcome but a good a proxy indicator of the severity of maternal and fetal acidosis which may predict outcomes. Maternal and neonatal mortality will be considered as secondary outcomes, together with fetal morbidities (sepsis, admission to neonatal unit) up to 7 days and maternal morbidities (primary PPH, puerperal sepsis, ruptured uterus and fistulae) up to 14 days postpartum.

- NaHCO3 has been tested among patients with normal and prolonged labour and there were no serious adverse events reported including death. None of these studies included women with obstructed labour because they were conducted in developed countries where this condition is a very rare event.
The current study will examine the effect of bicarbonate on blood lactate among a subset of patients with obstructed labour, who might benefit more from the intervention.
The results of this trial will inform the design of future pivotal phase 3 trials to assess the effect of NaHCO3 on maternal and neonatal survival in low income countries.

2. The primary outcomes are maternal AND foetal lactate levels. This means this trial has two hypothesis and the two outcomes are not independent of each other. Please clarify (i) how the investigators address an issue of multiple comparisons (it seems they do not consider it in the current protocol),
-In order to take care of the two dependent measurements of maternal and foetal lactate, we will use the Holm-Bonferroni method to compute an adjusted P value for hypothesis testing. (Bland &Altman,1995; Chen et al,2017. We thank the reviewer for this comment. We have now clarified the protocol and the two hypotheses have been written as follows:
1. We hypothesize that supplementation with preoperative sodium bicarbonate infusion as an acid buffer can reduce maternal acidosis among patients with OL.
2. Among newborns of mothers with OL we hypothesise that those in the intervention group will have a lower level of cord blood lactate compared to the placebo arm.

and (ii) how they interpret the result if only one of the two results seems effective or if the two results show a different direction of the effectiveness.
-We intend to individually analyse, interpret and report the effects of pre-operative sodium bicarbonate infusion on maternal blood lactate levels before and after the intervention.
-The fetal arterial cord blood lactate levels at birth will be compared between the intervention and the control arms.

3. As NaHCO3 may decrease blood ionised calcium and increase PaCO2 (Jaber et al. Lancet 2018, Viallon 1999), but it seems blood gas analysis is not accessible in the trial settings. Please refer to these possible side effects. If the investigators are not going to monitor these values, please provide the rationale and/or add this as a limitation of this trial.
- Not having access to a blood gas analyser is one of the limitations in this study. But we have taken a number of precaution's to mitigate any side effects;
1. At baseline, we are excluding patients with metabolic alkalosis, hypokaelmia, hypocalcaemia and hypernatremia who are more likely to develop these side effects.
2. We have chosen the lowest dose (50mmol), that was used in the most recent trial (Wieberg-itzel, 2017). In addition, this will be administered as a single as opposed to a continuous infusion to achieve a certain target PH which is associated with a higher risk of side effects and therefore requires a blood gas analyser.
3. The studies published have not reported any life threatening episodes or adverse maternal foetal outcomes. So the NaHCO3 is a very safe drug as long as there is no over dose. (Clark et al 1971, Beveridge CJE, 2005)

4. Does intravenous NaHCO3 affect breastfeeding after the delivery? Please provide some information.
It is not known if NaHCO3 is excreted in breast milk so the effects on lactation are unknown. It is readily absorbed as Sodium and Bicarbonate ions in the body and the effects wear off in 60-90 minutes. It does not cross the placenta and since it is to be administered preoperatively as a low single dose of 50mmol, we think it will not have any adverse effects on lactation. This is something

that needs to be studied in future, although the most recent trial did not report any effects on lactation (Wieberg-itzel, 2017).https://www.medicines.org.uk/emc/product/3697/smpc https://www.glowm.com/resources/glowm/cd/pages/drugs/s014.html

5. Please include a plan to monitor adherence of the study intervention protocols as obtaining informed consent, randomising and infusing the 50ml of study drug in a limited pre-operative time would be difficult in some cases of obstructed labour.

- Makerere University as a sponsor of the study does not formally monitor studies. However, compliance will be monitored by the PI, by checking each CRF on submission, interviewing staff and patients after recruitment to check on adherence.
- The regulatory bodies such as the IRB also carry out regular scheduled and unscheduled spot checks to monitor adherence of the study to the approved protocol.

6. The consent form was not attached
Sorry for the omission this has now been attached
7. Figure 2 (or Table 2?) was not attached also.
-We have only one figure and table in the manuscript. Thank you, this has been updated accordingly.

Minor comments;
1. Please add a reference that provides evidence of the accuracy of Lactate Pro 2 (Arkray).
-This has been added please see the track changes. (Gaieski et al, 2013). But we are also aware the accuracy of device is dependent on the population under study i.e. the intraclass correlation coefficient (ICC) is not uniform across all populations. So this is one of the limitations of the method

2. Please cite 'Open Epi' and 'Open Data Kit' with a full reference.
- We have added both references in the manuscript.

Reviewer: 3

-The authors do not clearly distinguish between, on the one hand, neglected obstructed labour and on the other, obstructed labour (cephalopelvic disproportion) commonly found in hospitals all around the world. The former condition is, I believe, becoming a rarity even in the lowest resource settings. The introduction emphasises neglected obstructed labour, but the study inclusion criteria describe hospital patients who are not necessarily neglected. The design will need to record which of the included patients qualify as neglected obstructed labour, with explicit criteria for this category. Subgroup analysis will therefore be possible for women with neglected obstructed labour. A more pure characterisation of obstructed labour for this trial would be one that includes only nulliparous women who have failed oxytocin augmentation or who have evidence of neglected obstructed labour as the authors might like to define. A less stringent definition as proposed by the authors brings in a group of women with dystocia, but not necessarily obstruction. The presence of moulding and caput are not specific for obstructed labour. Is the trial actually about obstruction or about difficult labour? Does it matter? If it's more about difficult labour, a less stringent definition would be acceptable. Whatever the case, the use of less stringent criteria (including multiparas and primigravidas not necessarily on oxytocin) should be justified by scientific considerations and not be driven by the need to collect an adequate sample in as little time as possible.

There is no clear definition for obstructed labour and so the guidelines for its diagnosis also vary, the presence of a caput is just one of the parameters used in conjunction with many other clinical signs. The main difference between prolonged labour and obstructed labour is absence of adequate contractions in prolonged labour, which can be corrected augmentation with oxytocin. So this study is about patients with OL and not just difficult /prolonged. Our thinking is that a

preoperative infusion of bicarbonate can be used as a form of intrauterine maternal/foetal resuscitation before caesarean section and not to achieve a vaginal delivery (Wieberg-itzel E, 2017). Actually, NaHCO3 has been shown to improve the success rates of vaginal birth after augmentation with oxytocin.

We see two subsets of patients with obstructed labour; those referred from the lower health facilities (the ones most likely to qualify have neglected OL); and those diagnosed within the facility with obstructed labour. Therefore, both subsets of patients will be included in this trial because they are just variants of the same situation. We will do sub group analysis of referred patients with OL as a proxy for those with neglected obstructed labour

We will include both nulliparous and multiparous patients because they are all at risk of OL due to many other causes such as malposition/malpresentation besides cephalopelvic disproportion which is the common cause in prim parous patients (Kabakyega et al, 2011).

-The trial protocol should state clearly that a participant will be randomised when obstructed labour is diagnosed AND caesarean delivery is decided upon. The latter addition makes the inclusion criterion 'hard'.
Each patient diagnosed with OL is prepared for emergency caesarean section especially if the baby is alive, but because of un avoidable delays in accessing theatre, some of them end up giving birth vaginally. This is actually our main inclusion criteria and the suggestion has been added in the main text (see track changes).
In this trial, every effort will be made to ensure that the decision to incision time is reduced significantly by arranging for extra theatre space and providing some of the missing supplies. We have also planned to do a sub group analysis for patients who give birth beyond two hours after study drug administration, when we expect its effects to have worn off.

-Correctly, the authors will use the principle of 'intention to treat'. It should be expected that some of the women who have been randomised will give birth vaginally while awaiting caesarean delivery, especially if less stringent inclusion criteria are applied. What will the procedure be in such cases? Will all trial procedures (except perhaps myometrial lactate measurement) still be applicable and feasible?
About 90% of patients with OL deliver by emergency caesarean section and all the planned study procedures as indicated in table 1 will be possible. As you correctly pointed out, myometrial lactate measurement will be missed out in only 10% of the patients with OL who give birth vaginally with some assistance (Usharani N, Bendigeri M, 2017).

-In the discussion, the authors' last thought is that 'sodium bicarbonate might offer immense health benefits'. Sure, but that is a very long view. The idea is eventually to help reduce severe maternal and perinatal morbidity and death, as well as cerebral palsy. This trial will not be powered to show any such benefits. The primary outcomes for which the study is powered are useful proxies only. Let us not get ahead of ourselves. Much work remains to be done even if the authors find that this intervention shows promise.
Thank you for this observation, the wording in that section has been changed accordingly (see track changes).

VERSION 2 – REVIEW

REVIEWER	Tomoko Fujii Monash University, Australia

REVIEW RETURNED	16-Dec-2018

GENERAL COMMENTS	Thank you for responding to my comments. However, some comments are not reflected in the protocol. Also, some concerns have remained. 1. The Holm-Bonferroni method is not to adjust p-value. It is a method to adjust the alpha level. If the authors use the HB correction, then the sample size calculation should be changed in line with the analysis for the primary outcomes. If the authors are not confident with statistical analysis in clinical trials, please consult a statistician. 2. The authors acknowledged that the proposed trial is to inform the future phase 3 trial by providing information about the effect of NaHCO3 on the surrogate endpoints. Then I would suggest authors place this trial as phase 2b trial, and safety outcomes should be included in secondary outcomes. 3. The authors mentioned unblinding treatment allocation to monitor safety issues by the independent data monitoring committee. However, the logistics to keep the trial integrity (allocation concealment) are not written. 4. The authors replied, "At baseline, we are excluding patients with metabolic alkalosis, hypokaelmia, hypocalcaemia and hypernatremia who are more likely to develop these side effects." However, this is not written in the protocol. Also, the authors mentioned, "Not having access to a blood gas analyser is one of the limitations in this study." Then how those patients will be excluded in this trial setting? Please explain in the manuscript. 5. Regarding the effect on lactation, authors' response should be written in the manuscript. 6. The authors' response as for monitoring and protocol adherence should be written in the manuscript. 7. "alkalosis >22mmol/L" is unclear. Please indicate clearly which variable you are measuring.

REVIEWER	Eckhart Buchmann Department of Obstetrics and Gynaecology University of the Witwatersrand Johannesburg South Africa
REVIEW RETURNED	20-Dec-2018

GENERAL COMMENTS	No further comments.

VERSION 2 – AUTHOR RESPONSE

Reviewer: 2
Thank you for responding to my comments. However, some comments are not reflected in the protocol. Also, some concerns have remained.

1. The Holm-Bonferroni method is not to adjust p-value. It is a method to adjust the alpha level. If the authors use the HB correction, then the sample size calculation should be changed in line with the analysis for the primary outcomes. If the authors are not confident with statistical analysis in clinical trials, please consult a statistician.
-Thank you for the suggestion, we have adjusted the sample size and analysis plan accordingly on pages 10 and 12 of the manuscript.

2. The authors acknowledged that the proposed trial is to inform the future phase 3 trial by providing information about the effect of NaHCO3 on the surrogate endpoints. Then I would suggest authors place this trial as phase 2b trial, and safety outcomes should be included in secondary outcomes.
- Thank you for the suggestion, this has been adopted and updated accordingly in the manuscript on pages 6& 9.

3. The authors mentioned unblinding treatment allocation to monitor safety issues by the independent data monitoring committee. However, the logistics to keep the trial integrity (allocation concealment) are not written.
- We have an independent biostatistician who is not involved in the conduct of the study. When the need arises to unblind the treatment for safety concerns or otherwise, the biostatistician will be requested to reveal the treatment allocation for a specified patient or group of patients without compromising the allocation for the rest of the participants. In addition, the study team staff will not be involved in this process of unblinding before the study ends. This will only be done by the study steering committee and the IDMC. This has been updated accordingly on page 13 under the ethics and dissemination section.

4. The authors replied, "At baseline, we are excluding patients with metabolic alkalosis, hypokaelmia, hypocalcaemia and hypernatremia who are more likely to develop these side effects." However, this is not written in the protocol. Also, the authors mentioned, "Not having access to a blood gas analyser is one of the limitations in this study." Then how those patients will be excluded in this trial setting? Please explain in the manuscript.

- Thank you for the suggestion, we have updated the manuscript accordingly on page 6.
-To overcome this limitation of not having reliable and full time access to a blood gas analyser in the government hospital, we have sourced the services of MBN clinical laboratories to provide all the laboratory services for this trial. Since it is a privately run laboratory, we believe that it will be more reliable. In case of an abnormal laboratory test they will be able to quickly inform the study team by mobile to halt the recruitment.

5. Regarding the effect on lactation, authors' response should be written in the manuscript.
- Thank you for the suggestion this has been adopted and updated accordingly in the manuscript on page 14.

6. The authors' response as for monitoring and protocol adherence should be written in the manuscript.
- Thank you for the suggestion this has been adopted and updated accordingly in the manuscript on page 11.

7. "alkalosis >22mmol/L" is unclear. Please indicate clearly which variable you are measuring.
- Thank you, this has been up dated

VERSION 3 - REVIEW

REVIEWER	Tomoko Fujii Monash University, Australia
REVIEW RETURNED	05-Feb-2019

GENERAL COMMENTS	Thank you for addressing my comments. The manuscript has been improved largely, although it was difficult to follow how the authors calculated the sample size.

VERSION 3 – AUTHOR RESPONSE

Reviewer: 2
The manuscript has been improved largely, although it was difficult to follow how the authors calculated the sample size. - The section has been written afresh to make clearer and easy to follow